trichloropyridinol (TCP), based on anodic stripping voltammetry and bioelectrochemical magnetic immunosensing, respectively. These systems demonstrate good linear response over broad concentration ranges (1 - 2000 ppb). Pharmacokinetic studies have been conducted in rats to assess the relationship between saliva and blood (plasma & RBC) Pb and TCP concentrations as a function of dose and time. For both chemicals, the pharmacokinetics provides a framework for quantifying dosimetry based on a saliva measurement. Physiologically based pharmacokinetic (PBPK) models for Pb and chlorpyrifos can then be used to simulate blood and saliva concentrations. These results suggest that technology developed for non-invasive biomonitoring provides a sensitive, and portable analytical tool capable of assessing exposure in real-time. By coupling these non-invasive technologies with PBPK modeling it is feasible to quantify exposure to a broad range of chemical agents involving multiple routes of exposure (i.e. skin, ingestion, inhalation). In summary, it is envisioned that once fully validated, these monitoring and modeling approaches will be very useful for accessing human exposure and health risk. (CDC/NIOSH 1 R01 OH003629-03; NIEHS 1 R01 ES010976-02; and DOE contract DE-AC05-76RL01830)

1521 THERMOREGULATION AND ITS INFLUENCE ON TOXICITY ASSESSMENT

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Temperature is a fundamental factor influencing all aspects of biological systems. Perhaps because of its simplicity and ubiquitous nature, changes in body temperature are often overlooked, or minimized, when assessing the toxicity of chemicals, air pollutants, toxins and pharmacologic agents. Rodents in particular can respond to acute xenobiotic exposure with a regulated reduction in core body temperature (hypothermia) which can have a major impact on physiological and biochemical processes of the organism. This acute response is generally beneficial to the animal because supportive measures to prevent the drop in core body temperature can decrease survival. The impact of toxicant-induced hypothermia is not limited to acute toxicologic endpoints. Micronucleus formation is routinely used to establish the potential mutagenicity of a test material. However, hypothermia alone can increase micronucleus formation, confounding the interpretation of the mutagenic activity attributed directly to the toxicant from that of the toxicant-induced adaptive hypothermic response. While hypothermia is the predominant thermoregulatory response to toxicant-exposure in rodents, hyperthermia is a frequent observation in humans following acute exposure to a variety of toxicants. Because humans do not respond similarly to exposure to toxic agents data extrapolation can be confounded, increasing the uncertainty of the risk assessment process. Given the complexity and divergence of these physiologic responses, toxicity data derived from exposures in rodents should be considered in the context of any chemical-induced effects on thermoregulation in order to improve predictions of potential human toxicity. This workshop should be of interest to experimental toxicologists in all disciplines, as well as individuals involved with pharmaceutical development, human risk assessment, and product regulation and registration.

1522 INTEGRATED THERMOREGULATORY RESPONSES TO TOXICANTS

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Since all biochemical and physiological processes are directly affected by temperature, how can one be sure that a particular endpoint that is affected by the toxicant is not actually an indirect result of a toxicant-induced change in temperature? Many toxicologists and pharmacologists are cognizant of the temperature-dependency and may apply corrective measures, such as by raising ambient temperature or by placing the animal on a heating pad to block a toxicant-induced hypothermia. However, at the whole-animal level, the toxicity-temperature interactions are complex and cannot always be explained with simple thermal kinetic models. Many toxicants elicit a regulated reduction in body temperature, meaning that the animal actively increases heat dissipation by peripheral vasodilation and behaviorally seeking cooler temperatures to lower core temperature. This thermoregulatory response is beneficial and improves survival and/or recovery from the toxic insult. Preventing the drop in temperature by raising ambient temperature actually exacerbates the toxicity of most toxicants when given to rodents. An integrative approach to study the thermoregulatory response to toxicants is essential to understand the mechanisms of action of the toxicants on thermoregulatory and other physiological process.

1523 BODY TEMPERATURE CHANGES IN RODENT INHALATION STUDIES: INDICATOR OF ADVERSE EFFECT OR RODENT-SPECIFIC ADAPTIVE RESPONSE?

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In rodents, reflex reactions occur upon exposure to irritant agents and are considered to be of a protective nature both with regard to reduction of the inhaled dose and metabolism. The stimulation of sensory nerves located in the upper respiratory tract is often associated with effects that include changes in respiration, heart rate, blood pressure, and body temperature. When mice and rats are exposed to the same atmosphere, changes in respiration and body temperature observed in mice are generally more pronounced and more stable,compared to rats. Some of the uncertainty regarding the nature and magnitude of extrapulmonary toxicity observed in rodents following exposure to respiratory tract irritants may be attributable to the modulatory influence of factors affecting the core body temperature. Seemingly routine experimental procedures and fluctuations in ambient temperatures can produce striking changes in these parameters, independent of treatment effects. Despite the transient nature of the response of rats and mice to irritant exposures, these secondary physiological effects are important for a number of reasons. First, hypothermia is a common physiologic response of laboratory rodents to toxic insult. Second, the magnitude of changes in thermoregulatory function may be modulated by a number of experimental conditions or stresses which may differ from one laboratory to another, confounding the comparison of results across-species and between laboratories. Third, it is unclear whether this physiological response to xenobiotic agents is unique to rodents or if it also occurs in larger mammals and humans. However, humans have a greater thermal inertia due to a larger body mass and therefore may not exhibit this response to any measurable degree. Hence, in addition to the direct effects of such irritants on the function and the structure of the pulmonary system, there may be substantial indirect effects related to changes in extrapulmonary parameters which, in turn, may significantly modify the final toxic outcome as a result of rodent-specific adaptive effects.

1524 THERMOREGULATION: A KEY VARIABLE FOR INTERPRETING RESULTS FROM THE MOUSE MICRONUCLEUS TEST

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The impact of hypothermia on toxicological endpoints was historically restricted to those of acute toxicology studies. Only recently has hypothermia been identified as a cause of increased micronuclei (MN) formation where in mice, chemically-induced transient changes in body temperature were documented to result in an increased frequency of MN (Asanami *et al.*, 1998; Asanami & Shimono, 1997). Similarly, experience in our own laboratory, has demonstrated an association between transient hypothermia and increased frequencies of MN for a number of industrial chemicals administered at high dose levels. Several case studies will be highlighted in the context of the importance and challenges of isolating the direct effects of a chemical, from the indirect effects of the induced body temperature changes, on the formation of MN. Understanding the potential effects of transient body temperature changes on the micronucleus test (MNT) and its relevance for assessing risk to humans is critical since the MNT is an *in vivo* assay for which a high degree of confidence is placed in establishing the potential mutagenicity of a chemical.

1525 TEMPERATURE AND NEUROTOXICITY - LESSONS FROM THE AMPHETAMINES

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Toxicity is impacted by many factors - the nature of the agent, the exposure situation and the organism. How the agent or various aspects of testing impact body temperature are rarely considered when assessing toxicity or its mechanism(s); our work examining the neurotoxicity of the substituted amphetamines (SAs) (e.g., amphetamine, methamphetamine, MDMA, fenfluramine) illustrate how temperature factors may affect toxicity. Some SAs induce a profound hyperthermia and early work examined how body and ambient temperature contributed to the aggregate toxicity frequently found in rodents but rarely emphasized how altered temperature might affect other SA toxicities. Recently the neurotoxic potential of the SAs is a focus because of the popularity of MDMA within the Rave dance culture and interest in its use as a psychotherapy adjunct as well as treatment of ADHD with amphetamine. The SAs are dopaminergic neurotoxicants in the mouse and we showed how temperature factors contribute because manipulations that alter body or ambient temperature also alter their neurotoxicity. Test factors (strain/species, housing,

handling) profoundly impact SA neurotoxicity and confound its assessment. Restraint stress because of its ability to lower body temperature provided neuroprotection rather than the expected increased toxicity. NMDA receptor antagonists protect against SA neurotoxicity but the cause is lowered body temperature rather than reduced glutamatergic signaling. The SAs and extreme hyperthermia induce distinctly different brain insults suggesting an as yet unknown necessary link between the hyperthermia induced by the SAs and their other actions in their ability to cause dopaminergic neurotoxicity. Links between temperature and SA neurotoxicity are clearly established but no agreement exists as to how SA temperature modulating aspects figure in the mechanism(s) of toxicity. The relevance of these observations for assessing brain and liver toxicity of the SAs in man is subject to current debate because of the extreme differences in thermal mass and thermoregulatory characteristics between man and laboratory species.

1526 IMPACT OF THERMOREGULATION ON PHARMACOKINETIC PARAMETERS AND IMPLICATIONS FOR HUMAN TOXICITY ASSESSMENT

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Body temperature and thermoregulation can have an important role in interpreting pharmacokinetic data. Temperature variation can affect the absorption, distribution, metabolism and elimination (ADME) of xenobiotics. The body temperature change may be induced by the xenobiotic or may be a result of an externally applied stress. The effects of temperature on pharmacokinetics can be roughly grouped into two classes: physiological and biochemical. Physiological changes, such as ventilation and perfusion rates, can change the amount of xenobiotic absorbed via inhalation and dermal absorption. Temperature has long been known to be an important influence on chemical reactions, including enzymatically controlled metabolic processes. The optimal temperature range for enzymatic reactions can, in fact, be quite narrow and thus be influenced by xenobiotic-induced thermoregulation. In addition, transport processes, such as active transport in the gut can be temperature dependent. Rodents and humans respond differently to xenobiotics and have differing thermoregulatory processes which can complicate the usage of rodent data in human risk assessment. Rodent thermoregulation may provide a protective effect that humans are not capable of producing or may change the xenobiotic pharmacokinetics. Thus, understanding species differences in thermoregulation, as specifically related to pharmacokinetics, may change the interpretation of studies where temperature or thermoregulation effects were noted.

1527 THE RAT H9C2 EMBRYONIC VENTRICULAR MYOCYTE CELL LINE: AN *IN VITRO* MODEL FOR EXAMINING STRIATED MUSCLE TOXICITY

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Compound induced muscle toxicity continues to be an issue in drug development. Detection of skeletal and cardiac muscle injury often does not occur until longer-term in vivo studies have been undertaken. Therefore an in vitro model and screen which could be used to evaluate compounds for their potential to induce muscle injury would allow drug development teams to filter large numbers of compounds and proceed with molecules with the lowest liability for muscle toxicity. Herein, we describe the use of the rat H9c2 embryonic ventricular myocyte cell line as an in vitro model for evaluating cardiac and skeletal muscle toxicity. By altering culturing conditions H9c2 cells can be directed towards either a skeletal muscle (myotube) or cardiac myocyte phenotype. Using H9c2 cells, which we differentiated towards a cardiac phenotype, we were able to demonstrate that H9c2 cells underwent a hypertrophic response when treated with classical cardiac hypertrophy inducers (Vasopressin, Phenylephrine, Endothelin I and Angiotensin II). We were able to observe a hypertrophic response in treated H9c2 cells by demonstrating increased cell size, increased actin staining, and increased protein synthesis, all hallmarks of cardiac hypertrophy. To evaluate H9c2 cells for their potential use as an in vitro model for skeletal muscle injury, we differentiated the cells to a skeletal myotube phenotype and treated with compounds known to be positive or negative for muscle injury. By measuring release of LDH, creatine kinase, AST, and 8-isoprostanes, as well as selected transcript changes, we were able to bin compounds based on their potential to induce skeletal muscle injury. In conclusion, based on our pilot experiments we have demonstrated that the H9c2 rat embryonic ventricular myocyte cell model has potential utility as an in vitro screen for compound induced muscle toxicity.

1528 INTERPRETATION OF QT INTERVAL USING HEART RATE CORRECTION FORMULA IN PRE-CLINICAL TOXICOLOGY STUDIES

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The assessment of potential adverse effects of a drug on cardiac function is a requirement for pre-clinical studies. The effect of a drug on cardiac function can be determined by evaluating electrocardiogram QT interval prolongation. To interpret QT interval for drug-induced effects, various published heart rate (HR) correction formulas are employed across laboratories. These correction formulas are derived to assist with the interpretation of QT interval in human subjects, conscious dogs or anesthetized dogs. Since the choice of correction formula can alter the outcome, it is very important to select the most appropriate formula to evaluate QT interval in the dog. Data collected from six GLP studies with Beagle dogs (83/sex; 5-9 months old) were used to compare QT interval and HR correlation. Paired ECG and HR data from leads I, II, and III were recorded using an ECG Analyzer. Five published QTc formulas were used to correct the QT interval. Linear regression analysis for QT or QT (corrected)=HR was performed using SigmaPlot statistical analysis software to determine the percentage of the variability (R squared value; R2) for uncorrected QT and for each QTc interval. Regression analysis showed that for our laboratory, uncorrected QT interval has a superior correlation with HR for male and female dogs (R2 = 0.231 and 0.221 respectively), compared to the QTc v/s HR. The method of the QT interval correction suggested by Kawataki et al. or Van de Water had a statistically-significant correlation only in males (R2 = 0.072 and 0.073 respectively) and Bazett's method had a statistically-significant correlation only in females (R2 = 0.146). These results suggest that each laboratory should evaluate their own data to determine which, if any, correction formula should be used to evaluate QT data at their facility.

1529 USE OF A FAILING RABBIT HEART AS A MODEL TO PREDICT TORSADOGENICITY

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Because humans with cardiovascular disease have an increase predilection for developing torsade de pointes, this study was designed to determine if rabbits with failing hearts developed greater lengthening of QTc and have a greater tendency to develop torsade de pointes than normal rabbits. Twenty eight out of 28 rabbits developed significant reduction in left ventricular shortening fraction 4 weeks after ligation of coronary arteries ($p<0.01$). Studies were performed on rabbits anesthetized with ketamine (35 mg/kg) and xylazine (5 mg/kg). When exposed to escalating dose of dofetilide (5, 10, 20, 40 μg/kg/10min), clofilium (250, 600, 2000 nM/kg/10min), and cisapride (0.25, 0.5, 1.0mg/kg/10min), verapamil (0.25, 0.5, 1.0 mg/kg/10min), amiodarone (3, 10, 30 mg/kg/10min), and quinidine (3, 10, 30 mg/kg/10 min), QTc lengthened more for rabbits with heart failure than for normals. Rabbits with heart failure developed torsade de pointes when infuse with escalating doses of dofetilide (85%), clofilium (100%), and cisapride (50%) whereas fewer of the normal rabbits did 25%, 33% and 0%, respectively. None of rabbits develop TdP when expose to amiodarone, verapamil and quinidine. Thus this model of rabbits with a failing heart is useful for identifying not only lengthening of QTc but also predilection for developing torsade de pointes.

1530 RELIABILITY OF TELEMETRY IN COMMON MARMOSETS FOR EVALUATION OF DRUG-INDUCED QT INTERVAL PROLONGATION

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QT interval prolongation is recently one of the major concerns in drug development because it is generally considered to be a surrogate marker for increased risk of Torsades de Pointes. We have been evaluating telemetry in the common marmoset, similar in body weight to rat, in order to reduce the amount of compound required for studies using cynomolgus monkeys or dogs.

In the present study, in order to confirm the reliability of a telemetry system using the common marmoset for evaluating human risk, we examined QT interval and plasma concentration profiles in the common marmoset from both high-risk and low-risk drugs for human. We used 4 conscious marmosets (2 males and 2 females, 2–3 years of age, approx. 300–400 g in weight) with implanted transmitters (TL11M2-C-50 PXT, DSI).

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Preface

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An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 500.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 534.

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