1758 EVALUATING THE CYTOTOXICITY OF 181 CHEMICALS TO HELA CELLS USING SAR EXPERT SYSTEM.

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Cellular toxicity (CelTox) is often used as a surrogate for other toxicological endpoints ranging from ocular irritation to systemic toxicity. In order to explore the validity of this assumption, we developed an SAR model of toxicity of chemicals towards cultured Hela cells. Based upon a database of 181 chemicals assayed for their growth-inhibiting activity after 24 hours of exposure, an SAR model based upon CASE/MultiCASE was developed. For chemicals external to the learning set, the model displayed a concordance between experimental and predicted results of 74% (Sensitivity: 0.75; Specificity: 0.72). This suggests that CelTox is a complex phenomenon reflecting a series of independent and/or sequential actions. Yet the SAR model is robust and the chemicals used to build the models are a good representation of the universe of chemicals. Moreover, it is to be expected that the predictivity of the model will improve as the number of chemicals included is increased. The structure overlap between SAR models can be taken as a measure of mechanistic similarity. There was significant, but not complete, structural overlap between CelTox and maximum tolerate dose (mice and rats), LD_{50} in rats, toxicity to fish, eye irritation and phenomena associated with electrophilicity (mutagenicity in *Salmonella;* allergic contact dermatitis). There was only minimal structural overlap between CelTox and α 2μ - induced nephrotoxicity or binding to the Ah receptor. These findings indicate that while CelTox can be used as a surrogate for other toxicological endpoints, this should be done as part of a battery of assays.

1759 A METHOD FOR QUANTITATION OF TISSUE VINCLOZOLIN AND METABOLITES USING A BENCHMATE® AUTOMATED SPE WITH GC-MS.

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Vinclozolin (*Vin*, CAS 50471-44-8), a dicarboximide fungicide, has been reported be an antagonist of androgen receptor binding in rats, effects that could result in decreased fertility, defects in reproductive organs or cancer. It is thought that *Vin* activation to the metabolites 2-[[(3,5-dichloro-phenyl)carbamoyl]oxy]-2-methyl-3-butanoic acid (*M1*, CAS 119209-27-7), 3',5'-dichloro-phenyl-2-hydroxy-2-methylbut-3-enanilide (*M2*, CAS 83792-61-4), and 3,5-dichlorobenzenamine (*M3*, CAS 626-43-7) could induce similar toxicity in workers. A potential biomonitoring method was developed to measure tissue levels and evaluated using Dutch Belted rabbits after exposure to *Vin*, either as a single dermal dose or multiple dermal doses. *Vin* (100 mg/kg) was applied to the skin in 100 µL DMSO. Plasma samples were taken at 0, 6, 8, 12, 24, and 48 hr after a single dose or weekly during multiple dose exposure. Skin from dermal application sites and testes were excised at termination, homogenized and filtered. A BenchMate® robotic workstation was used for automation of sample preparation. Bond Elute® 500 mg C8 SPE columns were conditioned with acetone, MeOH and H_2O pH 7. Samples were loaded onto columns, rinsed twice with H_2O. A fraction containing >96% of *Vin* and *Vin* metabolites was collected in 1.5-mL acetone, and reduced to 1 mL for GC-MS SIM analysis (Hewlett-Packard quadruple using a 12 m X 0.2 mm Ultra 1 column). Chromatographic standards *M1* and *M2* were synthesized by alkaline hydrolysis of *Vin* and isolated by HPLC. *Vin*, *M1*, *M2*, and *M3* were detected in both plasma and tissues, but animal variation was problematic. After a single application *Vin* plasma levels were highest at 6 hr whereas levels of *M1*, *M2*, and *M3* were highest at 12 hr. After 4 weeks of dosing *Vin* levels in plasma were 162.2 ng/mL — consistent with testes levels. *M2* was detected in the testes and skin levels of *Vin* were ~10 fold that of plasma. Thus, *Vin* and *Vin* metabolite internal exposure levels can be rapidly quantified in a single assay using an automated system.

1760 A FLUORESCENCE PLATE READER ASSAY FOR MONITORING THE SUSCEPTIBILITY OF BIOLOGICAL SAMPLES TO LIPID PEROXIDATION.

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The susceptibility of biological samples to lipid peroxidation can be determined by exposing samples to a lipid peroxidation initiator and measuring the length of time prior to the onset of lipid peroxidation. Previous studies have shown that aldehydes generated by lipid peroxidation can react with amines to produce fluorescent products. We have utilized this principle to develop a fluorescence plate reader assay for measuring susceptibility to lipid peroxidation. In this assay, samples are placed in glycine/phosphate buffer and loaded into a 96 well plate. Lipid peroxidation initiators are added, and fluorescence is monitored over time at excitation and emission wavelengths of 360/430 nm. Samples were assayed for susceptibility to lipid peroxidation by both the thiobarbituric acid reactive substances assay and the fluorescence plate reader assay. We found good agreement between these two methods in assessing relative susceptibility to lipid peroxidation in liver microsomes and mitochondria. The fluorescence assay was also used to monitor lipid peroxidation in liposomes and rat liver homogenates. The addition of 4-hydroxy-2-nonenal but not malondialdehyde to glycine/phosphate buffer produced a fluorophore with similar excitation/emission maximums as liposomes peroxidized in glycine/phosphate buffer. Fluorescence was stable over an extended time period and could be induced by a variety of lipid peroxidation initiators. The fluorescence plate reader assay offers a rapid method for monitoring lipid peroxidation in a large number of samples. (This work was supported by NIEHS/NIH grant # R01ES 05452.)

1761 A RETROSPECTIVE ANALYSIS OF CLINICAL PATHOLOGY PARAMETERS IN DOMESTIC SWINE: A COMPARISON OF VALUES BEFORE AND AFTER JUGULAR VEIN CATHETERIZATION.

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Domestic swine are often utilized in preclinical safety and efficacy studies. We decided several years ago to surgically implant jugular catheters in domestic pigs to minimize stress and pain when multiple serial blood collections are required within a study. Animals arriving at our Test Facility are placed in quarantine for a minimum of seven days for observations (clinical and physical) and clinical pathology testing, including fecal samples for analysis of intestinal parasites and blood collection for analysis of hematology (red cells, white cells and platelets) and serum chemistry parameters. This blood collection requires tranquilization and/or physical restraint, and generally occurs 4-5 days after receipt of the animals into their new habitat. We compared the hematology and serum chemistry values obtained from this analysis with the same parameters from a sample collected in conscious, unrestrained pigs via a jugular catheter at least five days post-surgery. This analysis includes collation of clinical pathology data obtained from more than 200 castrated male and female Yorkshire pigs (*Suis sus*) approximately 2-3 months old. The pigs weighed between 25 and 40 kg at the post-surgical blood collection time point. Total white blood cell counts, moderately elevated at the quarantine blood collection, were decreased when collected via a jugular vein catheter. This was primarily due to a decrease in polymorphonuclear cells. In addition, there was often a small decrease in red blood cell values (total red cells, hematocrit, hemoglobin, MCV and MCH) post-surgically compared to values obtained from pigs without catheters. This retrospective analysis provides a set of baseline values for evaluation of treatments in future studies using domestic swine. (All animal studies at Primedica Corporation are conducted in compliance with USDA and NIH regulations, and reviewed by the Primedica Animal Care and Use Committee.)

1762 THE EFFECTS OF SODIUM NITRITE ON METHEMOGLOBIN FORMATION IN NONHUMAN PRIMATES.

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Methemoglobin (MHb) formers are protective against cyanide (CN) toxicity in multiple species. Sodium nitrite-produced MHb was studied in nonhuman primates as part of an anti-CN pre/treatment development program. The time-course of sodium nitrite ($NaNO_2$)-produced MHb formation and changes in related hematological parameters were measured in six rhesus monkeys (*Macaca mullata*) (two females and four males with mean weights of 5.3 and 9.7 kg, respectively). A surgical plane of anesthesia was produced and maintained with tiletamine HCl/zolazepam HCl (3 mg/kg, IM) and inhalation of 0.5 - 2.0% isoflurane in oxygen, respectively. Arterial blood was collected serially from a centrally placed catheter and analyzed to determine the animals capacity to form MHb following increasing concentrations of intravenous administration of $NaNO_2$ (total cumulative dose per animal ranged from 16.0 - 20.0 mg/kg). Total hemoglobin, oxyhemoglobin, reduced

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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 38th Annual Meeting of the Society of Toxicology, held at the Ernest N. Morial Convention Center, New Orleans, Louisiana, March 14-18, 1999.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 419.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 444.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

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