tissues and then measured by LC/MS/MS. The fullerene was detected in liver, kidney, spleen and lung in all injected rats. The highest concentration was 64.5 microg/g (wet weight) in the lung of the rat after injection one day. The average concentration in liver and spleen was a similar level to in lung, but in kidney the average concentration was much lower than in three tissues. After injection four days, the decrease in the concentration in lung, liver and spleen hardly could be recognized. In kidney, there was the significant lowering (Mann-Whitney's U-test, p=0.016). In the case of pregnancy rats, the fullerene was also distributed in lung, liver and spleen. However, the fullerene was very low in kidney and could not be observed in placenta and fetus. These results indicate the fullerene absorbed was distributed mainly in lung, liver and spleen and the fullerene in the blood flow was excreted rapidly as urine through kidney.

PL 1403 SHORT-TERM INHALATION TOXICITY STUDY WITH CD-BASED QUANTUM DOTS.

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Quantum Dots (QDs) are a new class of metal-based nanoscaled fluorescent particles. Their crucial physicochemical properties offer several advantages compared to other dyes, QDs are of great interest for histological, cellular and biomolecular imaging. The possibility to coat QDs with molecules for drug delivery, antibodies or tumor-targeting ligands also opens new opportunities in medical applications. However, little is known about the toxicological behavior of this material. We performed a short term (5 day) inhalation study to investigate the pulmonary and systemic toxicity as well as the distribution of Cd-based QDs after inhalation exposure. Male Wistar rats were head-nose exposed to clean air and maximal technically attainable concentration of QD on 5 consecutive days for 6 hours respectively. Shortly after the last exposure and 3 weeks thereafter animals were sacrificed for gross necropsy, histological examination as well as examinations of bronchoalveolar lavage fluid (BALF). Highly respirable aerosol (0.67 mg/m3 CdS/Cd(OH)2 QDs corresponding to 0.52 mg/m3 Cd with MMAD 1.7–2.9, GSD 6.5–4.3) was generated. A total of 5.3 % of inhaled materials was found in the lung. Cd was found excreted mainly in feces immediately after exposure, but not in urine. The exposure to CdS/Cd(OH)2 QDs induces a mild reaction in the animals' lungs indicated by increased lung weights (+16 %) and increased neutrophil count in BALF. The clearance of QD from the lung appeared to be low. No substantial translocation was observed.

PL 1404 AN *IN VITRO* ASSAY FOR THE PREDICITION OF CYTOKINE RELEASE SYNDROME.

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Acute cytokine release syndromes (CRS) are associated with some therapeutic antibodies in man, leading to a spectrum of clinical signs from nausea to serious hypotension and tachycardia. When anticipated this syndrome is typically manageable, however this adverse reaction recently became headline news when a massive and unexpected CRS occurred within a few hours of dosing six healthy volunteers with a therapeutic antibody (TGN1412) putting their lives at risk due to multiple organ failure. There are two potential mechanisms of antibody-induced cellular activation Type I which is dependent on the ligation of antigen by the V region of the antibody Type II which is dependent on the ligation of Fc receptors by the Fc portion of an antibody. In this work we have developed and In vitro assay using isolated leukocytes that dedifferentiates these two mechanisms and may be a useful test for predicting potential cytokine syndrome. Briefly, isolated leukocytes are incubated with either immobilised (type 1) or free (type II) antibody, spun, the supernatants collected and measured for CRA signature cytokines via cytokine bead array. In order to put the cytokine release induced by any test antibody into context, well-characterised clinical antibodies are also included in the assay. In this way the cytokine release induced by a test antibody can be translated into probable clinical outcome. The control antibodies generate a combined cytokine release in the expected hierarchy, with IgG4 (neg.con) being the lowest (usually <50pg./ml), followed by CD52 (approx 1000ng/ml) CD3 alone (approx. 5000ng/ml) or in combination with CD28 (approx 10,000ng/ml)The developed assay has intra and inter assay CV of <30%, dilutional linearity of 0.99-0.93 (depending on analyte), is highly specific and has sample stability of at least 6 months. Therefore this assay represents a useful too for the possible prediction of CRS in man.

PL 1405 USE OF THP-1 CELLS TO IDENTIFY PROHAPTENS.

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Animal based testing is currently used for screening of potential allergenic chemicals. Recent efforts have been directed at the development of non-animal based alternative tests for the identification of skin sensitizers including the use of in vitro cell activation assays. Upregulation of activation and costimulatory markers in antigen presenting cells are key events in the sensitization process and have been reported to serve as indicators of skin sensitization. Prohapten identification remains a limitation due to the lack of bioactivation of prohaptens in these cell lines. The present study evaluated the effect of hapten and prohapten exposure on cell surface marker expression (CD86, CD54, CD44 and CD40) on THP-1 cells. Cells were exposed to the prohaptens benzo(a)pyrene (BaP), 7,12-dimethylbenz(a)anthracene (DMBA) and carvone oxime (CVO) at concentrations ranging from 1-10 μM for 24 and 48 hours. The direct-binding hapten, dinitrochlorobenzene (DNCB), was used as a positive control. Bioactivation of prohaptens was achieved by addition of a rat liver microsomal (S9) cocktail to the cell cultures. Flow cytometry data demonstrated a consistent dose-dependent increase of surface expression of the T-cell costimulatory molecule CD86 when cells were dosed with a hapten or prohapten in the presence of S9. Expression of the adhesion molecule CD54 (ICAM-1) and the antigen presenting cell costimulatory molecule CD40 were also significantly elevated in both hapten and prohapten (+ S9) treated cells, however S9 alone also upregulated CD54. CVO and DMBA, but not BaP, induced inconsistent increases in the adhesion molecule CD44. In conclusion, modification of in vitro cell culture assays to include co-incubation with microsomes enhances identification of prohaptens and allows them to be clearly distinguished from haptens.

PL 1406 CYTOKINE LEVELS IN TISSUE AND MEDIUM OF PRECISION-CUT LUNG SLICES DURING PRODUCTION AND INCUBATION.

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Precision-cut lung slices (PCLS) provide a multicellular, 3D tissue model from which biochemical and histological data can be extracted, compared, and analyzed. We have examined the PCLS cytokine response to slice production and incubation and the effect of anti-inflammatory or pro-inflammatory stimuli. Lungs from adult male Fisher 344 rats were removed and processed for slicing in cold V7 solution. Using the roller method, slices were cultured in a serum-free, M199-based-medium (± 0.1 ng/ml hydroxycortisone) at 37oC with 5% CO2 for up to 6 days. Phortress (NSC710305), previously shown to elicit IL-1β and TNFα response in human PCLS, was added at day 0 (10 and 100 μM) and at days 1, 2, and 3 (100 μM) for 72 hrs. Medium and slices were collected every 24 hr, post-treatment. Cytokine (TNF-α, IFN-γ, IL-1β, IL-13, IL-4, IL-5, and CINC) quantities were measured using a multiplex rat cytokine-chemokine assay kit. Lysates and medium from untreated slices contained cytokine levels that spiked at day 0 and dropped to a steady state by day 3. Phortress at 100 μM (but not 10 μM) increased cytokine levels in both lysates and medium in a time-dependent manner. PCLS cultured for several days remained responsive to 100 μM Phortress treatment. Hydrocortisone inclusion did not prevent the cytokine surge that followed slice production. It did, however, reduce cytokine levels measured after post-surge (>day 3). Cell viability as determined histologically correlated with cytokine data. To conclude, observing the temporal cytokine response in this in vitro model allows for the proper timing for the application of toxicants. PCLS data obtained prior to the diminution of initial cytokine surge may be confounded by cytokine levels generated by slice production. Funded by NCI Contract No. HHSN261200800001E.

PL 1407 APPLICATION OF AN *IN SILICO* LIVER MODEL TO DETERMINE NUCLEAR RECEPTOR MEDIATED PATHWAYS IN LIVER CANCER.

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Nuclear receptors (NRs) are ligand-activated transcription factors that control diverse cellular processes. Chronic stimulation of some NRs in rodents can result in increased incidence of liver tumors. Tumors are thought to develop through non-genotoxic mechanisms with unclear relevance to humans. Human CAR, PXR,

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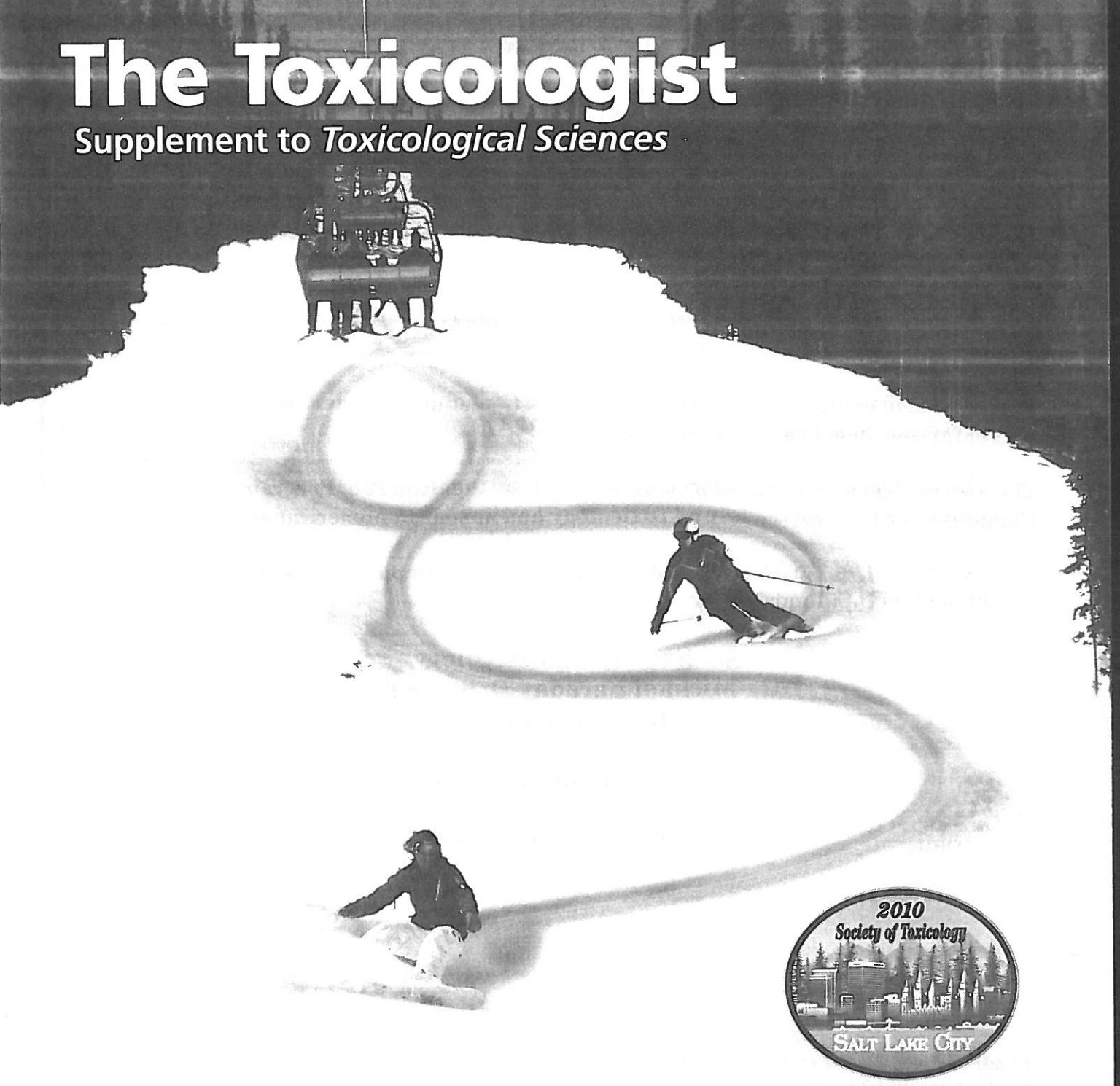

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Preface

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An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 473.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 496.

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

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