sorbed DBP in vivo was found excreted in urine. In vitro DBP absorption over 24 hr found 28.9 ± 2.1 %ADA in receptor fluid with approximately 21.8 % remaining in skin. Extended absorption studies for 72 hr found receptor fluid levels of 55.9 ± 3.9 %ADA with 17.3 %ADA remaining in skin. Charcoal impregnated filter paper attached (for 1 hr) to the top of the diffusion cell or to the top of the in vivo dosing chamber improved recovery by trapping the volatile DBP. These studies indicate there is considerable DBP absorption in skin. In conclusion, DBP tends to form a skin reservoir in vitro as shown by the increased receptor fluid levels found after 72 hr when compared to 24 hr. The 72 hr in vitro absorption values correlated most closely with the 24 hr in vivo results. These studies help determine the importance of including DBP remaining in the skin at the end of an in vitro study as potentially available for systemic absorption.

2096 ASSESSMENT OF DERMAL ABSORPTION BY THERMAL GRAVIMETRIC ANALYSIS – DEVELOPMENT OF A 2-COMPARTMENT DIFFUSION MODEL.

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Recent work in our laboratory shows that it is possible to register the dermal uptake of chemicals *in vitro* by thermal gravimetric analysis (TGA), i.e. by exposing a piece of skin to chemical vapour of known concentration while recording its weight in a high-precision scale during carefully controlled temperature and humidity conditions.
We have previously studied several organic solvents with the TGA technique using trypsinated porcine skin. The data indicate that the shape of the weight curve is related to the skin:air partition (P) and diffusion (D) coefficients of the chemical. To define the relations more precisely, a solution to Fick's second law of diffusion was derived, for the special case of recording total weight over time in the TGA setup. A good fit to observed data was obtained using a 2-compartment diffusion model. The parameters P and D were obtained by best fit to observed weight curves of butyl acetate, methanol, 2-propanol and toluene using the Berkeley Madonna software.
The same chemicals were also studied using conventional Franz' diffusion cells and dermatomed porcine skin. A good correlation was obtained between the diffusion coefficients derived from the Franz' cell experiments and those derived from the faster of the two compartments in the TGA diffusion model.
In conclusion, experiments with a limited number of chemicals indicate that skin:air partition and diffusion coefficients can be obtained by fitting a TGA-specific solution to Fick's second law to TGA weight curves and that the numerical values correlate well to the those obtained in conventional diffusion cell experiments. Further studies on several different types of chemicals are needed to confirm the usefulness of the method.
This study was supported by the Swedish Council for Working Life and Social Research (FAS).

2097 MARKOV CHAIN MODEL FOR QUANTITATING DERMAL ABSORPTION FROM COMPLEX MIXTURES.

C. S. Pitts[1, 2], C. E. Smith[2], R. E. Baynes[1], J. D. Brooks[1] and J. E. Riviere[1, 2]. *[1]Center for Chemical Toxicology Research and Pharmacokinetics, North Carolina State University, Raleigh, NC and [2]Biomathematics Program, North Carolina State University, Raleigh, NC.*

Exposure to pesticides dosed in complex chemical mixtures is a common environmental and occupational health concern. Risk assessors need to know the rate at which a pesticide is absorbed in to the skin in order to predict the toxicity of exposure to the pesticide. However, experimentally obtaining the absorption rates for even a small number of possible pesticide mixtures are expensive and time consuming. The objective of this study is to create a Markov chain model to predict pesticide absorption rates through the skin. The model parameters were fit to absorption data collected in the isolated perfused porcine skin flap (IPPSF) for a mixture of ethyl-parathion in ethanol. The model was investigated both analytically and through simulations using Gillespie's algorithm and was fit to the data using least squares methods. A model with three internal states, two absorbing states plus a delay appears to describe these data adequately. The structure of this model was compared to classical modeling approaches commonly used in dermal absorption studies (e.g. compartmental models and their reduction, PBPK models). Future work will expand the number of pesticide mixtures analyzed as well as search for correlations between absorption parameters and the physical and chemical properties of the pesticides and the mixture components into which they are exposed. These correlations may enable risk assessors to predict absorption profiles after chemical exposures in complex mixtures or formulations based on mixture component physical and chemical properties. (Supported by NIOSH R01 OH 07555).

2098 INCORPORATION OF COMPLEX CHEMICAL MIXTURE EFFECTS INTO A QSAR MODEL OF DERMAL ABSORPTION.

J. E. Riviere[1, 2] and J. D. Brooks[1]. *[1]Center for Chemical Toxicology Research and Pharmacokinetics, North Carolina State University, Raleigh, NC and [2]Biomathematics Program, North Carolina State University, Raleigh, NC.*

Significant progress has been made on predicting dermal absorption/penetration of topically applied compounds by developing quantitative structure activity relationship (QSAR) models based on linear free energy relations (LFER). However, all of these efforts have employed compounds applied to the skin in aqueous or single solvent systems, a dosing scenario that does not mimic occupational, environmental nor pharmaceutical exposure. We have explored using hybrid QSAR equations describing individual compound penetration based on the molecular descriptors for the compound modified by a mixture factor (MF) which accounts for the physiochemical properties of the vehicle/mixture components. The MF is calculated based on percentage composition of the vehicle/mixture components and physical chemical properties selected using principal components analysis. This model has previously been applied to 12 different compounds in 24 mixtures for a total of 288 treatment combinations obtained from flow-through porcine skin diffusion cells (Toxicol. Appl. Pharmacol. 208:99-110, 2005). The data reported here includes using three fundamentally different LFER models (Abraham, Potts and Guy, Hostynek and Magee) on this diffusion cell dataset as well as applying them to a new experimental dataset in the ex vivo isolated perfused porcine skin flap model consisting of 10 of the same compounds in 5 mixtures for a total of 50 treatment combinations. The use of the MF in combination with classic LFERs based on penetrant properties significantly improved the ability to predict dermal absorption of compounds dosed in complex chemical mixtures across three different LFER models and two biological systems. (Supported by NIOSH R01 OH 07555).

2099 CUSTOM MADE PANI FIBER TO ASSESS DERMAL PARTITIONING AND ABSORPTION OF BIOCIDES.

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A custom-made polyaniline (PANI) coated metal alloy fiber was evaluated for its use in assessing dermal partitioning and absorption of certain biocides. This PANI coating provides a unique functionality compared to three commercially available fibers polyacrylate (PA), polydimethylsiloxane (PDMS), and Carbowax/templated resin. The production of this custom-made fiber is a relatively simple process that can be controlled by utilizing cyclic voltammetry (CV). The CV program for coating the metal alloy fiber consisted of one initial scan from –0.2V to +1.1V followed by several sets of scans from –0.2V to +0.8V with a 15 second equilibration time at –0.2V between scan sets and scan rate of 50 mV/sec. The electrolyte solution was 0.1M aniline in 1.0M sulfuric acid. The bare metal alloy fiber SPME assembly, commercially donated, served as the working electrode. In our experiments, cyclic voltammetry appeared to give more consistent results and control in coating the metal alloy fiber with PANI as opposed to using a constant deposition potential. To assess the PANI fiber, solid-phase microextraction (SPME) was performed by direct immersion into water solutions containing either a single component or a mixture of biocides at 37°C and stir rate of 400 R.P.M. The PANI fiber was desorbed directly in the GC-MS injector port for 5 minutes at 200°C following immersion. This PANI coated fiber exhibited good reproducibility and durability. The RSD's averaged 6 to 9% over a period of three days for the first 46 injections of a single component (5ppm 2-phenylphenol) in water with only three outliers. Time profile experiments revealed that both p-chloro-o-cresol and o-phenylphenol reached equilibrium before 10 minutes while the equilibrium time for o-benzyl-p-chlorophenol was greater than 90 minutes. This research was supported by NIH OH003669-06.

2100 PREDICTING SKIN PERMEABILITY OF MOLECULES FROM CHEMICAL MIXTURES USING AN INERT MEMBRANE-COATED FIBER ARRAY.

X. R. Xia, R. E. Baynes, N. A. Monteiro-Riviere and J. E. Riviere. *Center for Chemical Toxicology Research and Pharmacokinetics, North Carolina State University, Raleigh, NC.*

Predicting skin permeability of compounds from chemical mixtures is required for transdermal drug delivery, safety evaluation of cosmetics and risk assessment of chemicals, where most exposure occurs in complicated chemical mixtures, not individual chemicals. We have developed a membrane-coated fiber technique that can be used to measure the partition coefficients of molecules from chemical mixtures with high precision and throughput. This novel approach predicts skin permeability based on its correlation with the partition coefficients from chemical mixtures determined in a fiber array. Each of the membrane-coated fibers represents a pattern of molecular interactions: polydimethylsiloxane (PDMS, lipophilic), polyacrylate (PA, polarizable) and CarboWax (Wax, polar). Molecular interactions occurring during percutaneous absorption can be simulated by the multiple fibers:

log(kp) = c + a $\log K_{MCF1}$ + b $\log K_{MCF2}$ + ··· + $\log K_{MCFn}$. The feasibility of this approach was demonstrated with 25 diverse chemicals; their skin permeability [log(kp)] from chemical mixtures were measured by in vitro flow through diffusion experiments and partition coefficients of the chemicals ($\log K_{MCFn}$) were determined by the membrane-coated fiber technique. Multiple regression analysis was used to define equations linking log(kp) to $\log K_{MCFn}$ for the three MCFs. A significant correlation equation was defined: Log(kp)= -2.73 – 1.31 $\log K_{wax}$ – 0.31 $\log K_{pdms}$ + 2.34 $\log K_{pa}$ with a R^2 of 0.92. The correlation coefficients in the equation reflected the mixture-skin interactions in different vehicles. These data clearly demonstrate that dermal absorption of diverse chemicals can be estimated from data collected in the inert fiber array which reflect the physicochemical diversity of interactions seen when chemicals partition into the stratum corneum. (Supported by NIOSH OH-07555 and USAFOSR FA 9550-04-1-0376).

2101 ENVIRONMENTAL TOBACCO SMOKE (ETS) EXCERBATES ATHEROSCLEROSIS PROGRESSION IN APOE$^{-/-}$ MICE USING NON-INVASIVE REAL-TIME ULTRASOUND BIOMICROSCOPY (UBM) IMAGING.

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Environmental tobacco smoke (ETS) has been listed by American Heart Association as a significant risk factor for cardiovascular diseases. Atherosclerosis is a major underlying cause of angina, heart attacks, strokes, and peripheral vascular disease. In this study, using non-invasive in vivo ultrasound biomicroscopy (UBM), we developed a novel imaging protocol to follow lesion progression in atherogenic mice. We also employed this protocol to assess the effects of long-term, low-concentration ETS exposure on plaque acceleration in atherosclerosis susceptible mice. Tobacco and Health Research Institute's 1R4F cigarettes were used to generate a side-stream cigarette smoke (SS, a surrogate for ETS) atmosphere. ApoE$^{-/-}$ mice (n=24/group) fed with either high-fat chow (HFC), or normal chow (NC), were exposed to a low dose of SS (480 ug/m^3) or filtered air (FA) for 6 hr/d, 5 days/wk, for up to 6 months. Before exposure and at 2, 4, 6 months during exposure, non-invasive UBM (Vevo660, Visualsonics, Canada) was performed on each mouse to assess plaque progression in aorta, brachiocephalic and left carotid arteries. The plaque volume was then measured by ImageJ. In addition, after each UBM assessment, 8 mice per group were sacrificed and histological analysis were performed for comparison with the results obtained using UBM. At 4 and 6 months, using UBM, SS exposure produced the greatest change in plaque volume in the left common carotid artery of HFC mice as compared to FA controls or NC controls, but not in brachiocephalic artery. Furthermore, UBM showed significant increases of plaque volume in the brachiocephalic artery in all four groups every other month. Our results show that this novel UBM imaging protocol is a useful non-invasive tool to follow plaque progression in atherogenic mice. The results also suggest that ETS exposure exacerbates plaque development in atherosclerosis susceptible mice.

2102 ESTROGEN REPLACEMENT THERAPY AND DEVELOPMENT OF VASCULAR LESIONS.

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Estrogen is known to increase vascular endothelial cell growth which may contribute to the increase in risk of coronary heart disease in women exposed to unopposed estrogen replacement therapy (ERT). Although the mechanism is not clear, estrogen may put women at risk by its promotion of abnormal proliferative vascular lesions and subsequent thickening of the vasculature. How estrogen may support or promote vascular lesions is not clear. In this study, we have examined whether estrogen stimulated endothelial tube formation is dependent on cellular redox state. Methods: Vascular lesion formation was determined in a 3-dimensional Matrigel assay. Prior to estrogen treatment, MnSOD and catalase were overexpressed in human umbilical vein endothelial cells (HUVEC) via adenoviral vectors. Endothelial tube formation was measured by AngioQuant software, an automated image analysis tool for quantification of angiogenesis. Results: Physiological concentrations of E2 found in human serum were tested. Estrogen (100pg/ml) treatment for 6 h stimulated a 2-fold increase in endothelial tubes. Endothelial tube formation was significantly inhibited to the level of control by overexpression of both MnSOD and catalase. In addition, co-treatment with the antioxidant ebselen showed a significant reduction in tube formation. Conclusions: We have shown that overexpression of MnSOD and catalase significantly inhibits endothelial tube formation. It appears that early estrogen signaling does not require estrogen receptor genomic signaling because we can inhibit tubule formation by antioxidants. Findings of this study highlight the potential damaging consequences of unopposed ERT in vascular disorders dealing with oxidative stress conditions.

2103 THE DIETARY FLAVONOID QUERCETIN BLOCKS PCB77 INDUCED PRO-INFLAMMATORY RESPONSES IN VASCULAR ENDOTHELIAL CELLS.

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Polychlorinated biphenyls (PCBs) are widespread environmental contaminants that can cause a wide variety of toxic effects in exposed organisms. Co-planar PCBs can induce oxidative stress and activation of pro-inflammatory signaling cascades which are associated with atherosclerosis. Vascular endothelial cells have been shown to be sensitive to chemical insult and cellular dysfunction after co-planar PCB exposure. The majority of the toxicological effects elicited by co-planar PCB exposure are associated to activation of the aryl hydrocarbon receptor (AHR) and subsequent induction of responsive genes. Quercetin, a dietary flavonoid, has been demonstrated to possess antioxidant and anti-inflammatory properties in various in-vivo and in-vitro models. Previous studies from our group have shown that flavonoids can significantly reduce PCB77 induction of oxidative stress and expression of the AHR responsive gene cytochrome P450 1A1 (CYP1A1). To determine if quercetin can block PCB77 induced expression of pro-inflammatory genes associated with atherosclerosis, porcine endothelial cells were exposed to PCB77 in combination with quercetin, and expression of pro-inflammatory proteins was analyzed by western blot. Upon confluence, cells were serum deprived for 8 h, then treated with PCB77 (1 μM), quercetin (10 μM), or PCB77 plus querectin for a period of 16 h. Quercetin co-treatment significantly blocked PCB77 induction of the pro-oxidative and inflammatory proteins: CYP1A1 and vascular cell adhesion molecule 1 (VCAM1). These results suggest that quercetin intervention is protective against PCB77 induced endothelial cell dysfunction. (Supported by grants from NIEHS, NIH (P42ES07380) and the University of Kentucky AES).

2104 HIV ANTIRETROVIRAL DRUG COMBINATIONS INDUCE ENDOTHELIAL MITOCHONDRIAL DYSFUNCTION AND ROS PRODUCTION, BUT NOT APOPTOSIS.

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Numerous studies report that HIV patients administered antiretroviral therapy are at a greater risk for cardiovascular diseases. Endothelial dysfunction is an early event and a sensitive marker for cardiovascular diseases, such as atherosclerosis. We previously reported that HIV antiretroviral therapy induces direct endothelial dysfunction in vivo, and induces only a slight increase in cell death, as indicated by the LDH release assay. We also observed that endothelial mitochondrial function was compromised following antiretroviral treatment. To determine whether antiretroviral-induced endothelial dysfunction is via mitochondrial dysfunction and whether mitochondrial dysfunction culminates in endothelial cell apoptosis, we treated HUVEC with micromolar amounts of AZT, indinavir, or AZT plus indinavir. These treatments induced a decrease in cellular O2 consumption, a collapse in the mitochondrial membrane potential, and an increase in the production of reactive oxygen species (ROS) in endothelial cells. An MnSOD mimetic, MnTBAP, abolished the increased ROS production, suggesting that the ROS were generated by mitochondria. Transfection of the endothelial cells with a mitochondrially-targeted catalase decreased antiretroviral-induced ROS and 8-isoprostane production, confirming the mitochondrial localization of the ROS produced. Finally, to determine whether antiretroviral-mediated mitochondrial dysfunction culminates in endothelial cell apoptosis, we assessed levels of apoptosis using the TUNEL, the DAPI staining, the caspase activation, and the DNA fragmentation assays, but none of these assays indicated a marked increase in apoptotic cells following antiretroviral treatment. Our studies thus suggest that antiretrovirals induce mitochondrial dysfunction and increase mitochondrial ROS in endothelial cells, but the decreased mitochondrial function does not culminate in apoptosis.

2105 PCB 77 ACTIVATES ENOS *VIA* PI3K AND AKT PHOSPHORYLATION IN ENDOTHELIAL CELLS BY A CAVEOLIN-1 DEPENDENT MECHANISM.

E. Lim[2, 3], E. Smart[5], M. Toborek[3, 6] and B. Hennig[1, 2, 3]. *[1]College of Agriculture, University of Kentucky, Lexington, KY, [2]Animal and Food Science, University of Kentucky, Lexington, KY, [3]Graduate Center for Nutrition Science, University of Kentucky, Lexington, KY, [4]Graduate Center for Toxcicology, University of Kentucky, Lexington, KY, [5]Pediatrics, University Kentucky, Lexington, KY and [6]Surgery, University of Kentucky, Lexington, KY.*

Polychlorinated biphenyls (PCBs) are persistent environmental contaminants that can contribute to the pathology of atherosclerosis by activating inflammatory responses in vascular endothelial cells. We hypothesize that plasma membrane mi-

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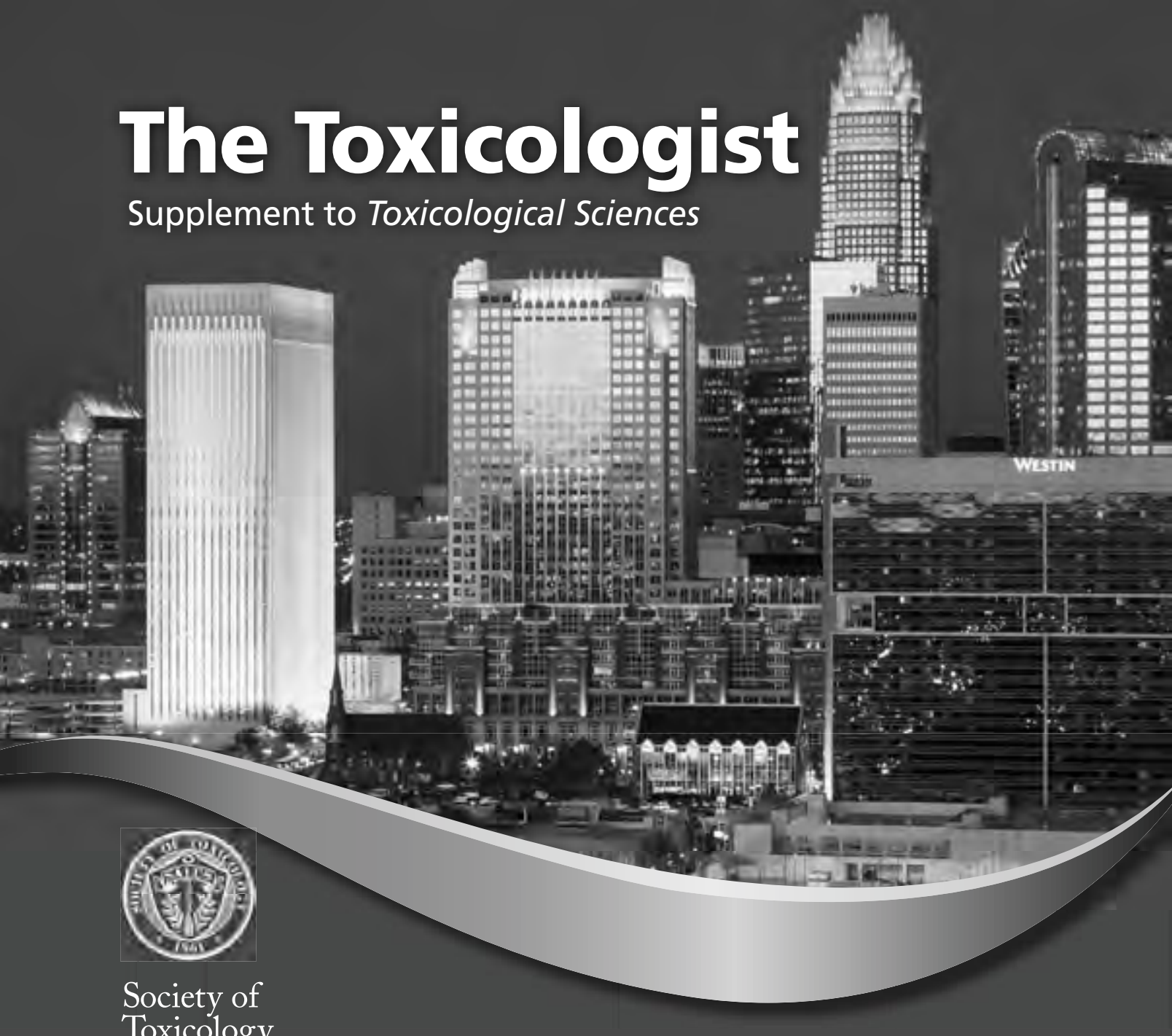

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, and poster sessions of the 46th Annual Meeting of the Society of Toxicology, held at the Charlotte Convention Center, Charlotte, March 25–29, 2007.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 449.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 480.

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