characterizes the *in vitro* toxicity the BDE-153, assessed in different hepatic cell lines using monolayer (2D) and tridimensional cell culture by hang drop (3D cell culture) for more predictive data, in an attempt to elucidate the mechanism of toxicity in different cell lines. HepG2 cells were maintained in DMEM medium and plated in 12-well plate for adhesion or in 96-well hanging drop plate for 3D cell culture. Hepatocytes were isolated from healthy Wistar rats; after cannulating the portal vein, the liver was perfused with Krebs-Henseleit buffer. All cell were exposed to BDE-100 (0.1-25μM). After 24 and 48 hours of exposure to BDE-153 cell viability was assessed using 0.5% MTT. In addition, the determination of mitochondrial membrane potential (Dψ) was performed using the TMRM, and also the total protein/cell mass was evaluated using the SRB assay. Finally, we assessed the damage caused by BDE-153 in HepG2 3D-cultures using the fluorescent dyes Hoechst and Ethidium. BDE-153 has been shown to cause cellular dysfunctions by dissipating Dψ and decreasing cell viability and all cultures in monolayers. Additionally, it was observed an increase in the number of cells labeled with ethidium in HepG2 3D-culture, also indicating cell death. We concluded that the exposure to BDE-153 induces significant damage in both, immortalized and in primary cells, and demonstrated to induce cell death in 3D culture too, a new cell culture model that has been growing in recent years. This damage corroborate with the induction of mitochondrial damage data previously submitted. Supported by: Capes - Proc. PVE A018/2013; FAPESP - Proc. 2012/13123-0.

1128 Liver Transcriptomic and Metabolic Reprogramming After Exposure to Diesel Exhaust

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Background: Exposure to air pollution has been shown to associate with cardiovascular morbi-mortality, insulin resistance and type 2 diabetes. We investigated the mechanisms how air pollution induces metabolic abnormalities in the liver using a combination of ohmics approaches. Methods: Apolipoprotein E (ApoE) null mice were exposed to either diesel exhaust (DE) or filtered air (FA) for 2 weeks. For transcriptomics, RNA was extracted from livers, n=8 per group, and used for Illumina microarrays. Metabolomics analysis of the livers, n=5 per group, was performed by Metabolon Inc. Illumina data was analyzed using the Genomestudio software. *In vitro* experiments used HepG2 cells treated with a methanol extract of diesel exhaust particles (DEP) vs. media. mRNA expression levels were quantified by qPCR. Glucose and glycogen content were determined by biochemical and histological determinations. Results: Liver cholesterol and triglyceride content were significantly increased following DE exposure. Microarray analysis showed differential expression of 477 genes in the DE group compared to FA ($p< 0.05$). Pathways significantly dysregulated by DE included lipid and lipoprotein metabolism, lysosome, oxidative phosphorylation and the citric acid cycle. Metabolomics identified 118 biochemicals with significant differences in their levels between the DE and FA groups. Important pathways enriched with these metabolites included glutathione metabolism, citric acid cycle, glycogen metabolism and glycerolipid metabolism. We identified several key driver genes from the transcriptomic analysis, including PEPCK for biological validation by *in vitro* experiments. HepG2 cells treated with 100ug/ml DEP extract for 8 hours showed a marked increase in PEPCK expression suggesting enhanced gluconeogenesis. DEP treatment also resulted in depletion of glycogen content in HepG2 cells. Conclusion: Integrated analysis of liver transcriptomic and metabolomic data from mice exposed to diesel exhaust for 2 weeks indicated several alterations in metabolic pathways involved in lipid and carbohydrate metabolism, resulting in increased synthesis of triglycerides, increased gluconeogenesis and glycogenolysis.

1129 Extrapolating Salivary Acinar Cell *In Vitro* Pesticide Transport to Whole Animals Using Computational Modeling

C. Timchalk, Z. A. Carver, T. J. Weber and J. N. Smith. *Pacific Northwest National Laboratory (PNNL), Richland, WA.*

Non-invasive biomonitoring with saliva has potential to significantly advance quantitative dosimetry as an integral component of epidemiology. However, predictions of which chemical and/or metabolites are excreted into saliva at detectable concentrations remain a challenge. In order to predict salivary clearance, a combination experimental and computational approach has been developed with 3,5,6-trichloro-2-pyridinol (TCPy) (the major chemical-specific metabolite of chlorpyrifos) to predict potential salivary levels. A Transwell *in vitro* rat salivary acinar cell system was utilized, where protein levels in the basolateral (27.2 mg/mL) and apical (1.3 mg/mL) culture chambers, which represent blood and saliva compartments respectively, were altered using bovine serum albumin to more closely mimic physiological levels. TCPy was dosed to the basolateral chamber at two concentrations (250 and 2500 μM), and both chambers were sampled over time up to 24 hr. The rat salivary cell system maintained the protein gradient and tight junctions over the duration of the experiment as evidenced by consistent transepithelial electrical resistance levels. Levels of TCPy were quantified using gas chromatography-mass spectrometry, and at 24 hr, the predicted median saliva/blood concentration ratio was similar to published values measured *in vivo* (0.021 vs. 0.049). TCPy concentrations were modeled using a mechanistic computational cellular transport model. The resulting model simulations fit the data reasonably well, and fit parameters suggest that TCPy is transported across basolateral and apical cell membranes by passive diffusion. Model parameters were integrated into a physiologically based pharmacokinetic model, and reasonably predicted TCPy concentrations in rat saliva after intravenous administration of TCPy. This poster demonstrates the utility of this combination experimental and computational approach to predict chemical transport in saliva. Supported by CDC/NIOSH grant R01 OH008173.

1130 Non-Invasive Saliva Human Biomonitoring: Development of a Transwell Assay to Support Exposure Science Assessment and Health Impacts

T. J. Weber, J. N. Smith, Z. A. Carver and C. Timchalk. *Health Impacts & Exposure Science, Pacific Northwest National Laboratory, Richland, WA.*

The use of saliva as a biomonitoring matrix can significantly advance quantitative dosimetry as an integral component of epidemiology. A major limitation has been an inability to identify which chemicals are readily cleared in saliva, at levels that can be quantified. To address this limitation, we have developed a primary salivary gland serous-acinar cell model that can be used for chemical transport studies *in vitro*. Serous-acinar biomarkers detected by Western blot include alpha amylase and aquaporin 5 which are uniformly expressed in confluent cultures. Serous-acinar cells express the tight junction marker zona occludens-1 and measurements of transepithelial electrical resistance (TEER) demonstrate exceptional tight junction formation (routinely >2000 Ω/cm2) in a relatively short period of time (6-8 days) in Transwell inserts. When TEER values are > 2000 Ω/cm2, lucifer yellow transport from apical to basolateral chambers is ~ 0.1%/hr. The insecticide chlorpyrifos (CPF) and its primary metabolite trichlorpyridinol (TCPy) can be quantified in saliva at concentrations that are less than, but parallel to blood levels. Results from the Transwell assay indicate that chlorpyrifos transports by diffusion with transport rates that are linear among doses tested. Lucifer yellow passage across the epithelial barrier was clearly disproportional to chlorpyrifos transport. Primary serous-acinar cells showed a low level of CPF metabolism to TCPy, which subsequently localized to both apical and basolateral chambers, consistent with a diffusional process and lack of TCPy concentration gradient. These experiments establish the feasibility of utilizing an *in vitro* cell based uptake/clearance assay coupled with pharmacokinetic modeling as a novel chemical screening strategy to identify ideal chemical candidates for saliva biomonitoring. Future studies will begin linking the transwell assay to higher content chemical screening capabilities to increase throughput. Supported by CDC/NIOSH grant R01 OH008173.

1131 2, 4 - Dichlorophenoxyacetic Acid (2, 4-D) Transport Across an *In Vitro* Salivary Acinar Cell System: A Novel Approach to Biomonitoring

Z. A. Carver, C. Timchalk, J. N. Smith and T. J. Weber. *Health Impacts & Exposure Sci, Pacific Northwest National Laboratory, Richland, WA.*

The non-invasive use of saliva for biomonitoring has the potential to significantly advance quantitative dosimetry as an integral component of public health. A major limitation for this approach has been an inability to identify which chemicals are readily cleared in saliva, at levels that can be quantified at relevant exposure levels. 2, 4-D is a widely used herbicide and its renal clearance mechanism involves both glomerular filtration and active organic ion transport. 2, 4-D was dosed in the basolateral chamber at 2 different concentrations (10 or 100 μg/mL), and both chambers were sampled longitudinally up to 24 hr post dosing. At these doses and time-points cells were viable and maintained tight junction function based upon: transepithelial electrical resistance (TEER) and lucifer yellow permeability (LY) testing. 2, 4-D concentrations in the apical chambers increased over time, and 2, 4-D concentrations in both

chambers were equivalent within 24 hours post dosing with the high dose; however with the low dose, basolateral 2, 4-D concentrations remained higher than apical 2, 4-D concentrations (p=0.04) at 24 hr. To evaluate the potential role of active transport, a competitive substrate experiment with the OAT substrate para-aminohippuric acid (PAH), was conducted (0, 0.515, 5.15, or 51.5 µg/ml PAH + 10 µg/ml 2, 4-D) at 4 hr post-dose. Preliminary evaluations suggest that PAH did not significantly alter the concentration of 2, 4-D transported across the SGEC monolayer at 4 hours, suggesting that passive processes may predominate under these conditions. Once the salivary transport mechanism and kinetic parameters of 2, 4-D have been fully characterized, results will be incorporated into a mechanistic computational cellular transport model and used to further inform a PBPK for 2,4-D. This approach, once established, can be exploited for human biomonitoring without the need to conduct more challenging *in vivo* saliva clearance studies. Supported by CDC/NIOSH grant R01 OH008173.

1132 Navajo Birth Cohort Study: Metal Biomonitoring and Source Attribution

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The Navajo Birth Cohort Study (NBCS) investigates the relationships among exposure to atomic bomb and Cold War Era legacy mixed metal wastes from >1100 uranium mine waste sites on Navajo Nation (NN), birth outcomes, and child development. Although the last mine were closed in 1986, communities are chronically exposed to the unremediated wastes. The study is being conducted as a cooperative agreement among CDC/ATSDR, Navajo Area IHS, Navajo Department of Health, Southwest Research and Information Center, and University of New Mexico's Community Environmental Health Program. Of the target of 1500 families, 568 mothers, 406 babies, and ~30% of fathers are currently enrolled in the study. Blood and urine samples collected at multiple time points from enrollment until baby is one year of age are analyzed for 36 metals at CDC/ATSDR/DLS/IRAT labs. Measured body burden of metals is likely due to contributions from multiple exposure pathways. Thus, to obtain a complete exposure profile, in-home dust swipes are analyzed for 24 metals, and surveys querying land-use activities, occupational and health history, and nutritional information are administered. Concentrations of uranium, manganese, mercury, antimony, tin and tungsten in NBCS participants exceed those expected relative to the US population (NHANES, 2015). To date, no predictor by itself explains these elevated levels, though correlations between blood mercury (p=0.36) and lead (p=0.05) concentrations are significantly correlated with home dust levels. Modeling of urine uranium concentrations including limited land-use predictors (local food consumption, family mining history, home heating) indicates wood and/or coal burning as a significant (p=0.04) predictor. Source attribution modeling incorporating additional exposure profile information from surveys, particularly nutritional information, is in progress for the metals for which NBCS participants exhibit unexpectedly high concentrations. Source attribution is a vital aspect of NBCS in order to identify exposure mitigation strategies and environmental clean-up prioritization.

1133 Increased Oxidative Stress Status, Cadmium, Lead and Selenium of Roadside Dispensers of Gasoline in Nigeria

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Gasoline, a very volatile petrochemical used for fueling automobiles and some power generating machines contains organic and inorganic constituents which when activated leads to continuous production of reactive oxygen species (ROS) and consumption of antioxidants. Work place exposure to toxic chemicals is a major public health concern worldwide and exposure to gasoline vapors has been associated with a great deal of hematological alteration, increased risk of malignancies and other chronic diseases among humans and rats. This risk is greatest in the developing countries, including Nigeria, where limited facilities to reduce over exposure to the toxic effects of the chemicals are rampant. Knowledge on the safe handling and transportation of chemicals is also very limited. This study aimed at assessing the oxidative stress status of road side gasoline dispensers in Nigeria by assaying their plasma total antioxidant status, cadmium, lead and selenium as paradigm. Materials and Methods: Markers of oxidative stress including plasma levels of total anti oxidant status (TAS), antioxidant trace metal, selenium and known free radical generating heavy metals (lead and cadmium) were compared between 90 road side dispensers of gasoline and 90 age and sex matched controls. Plasma selenium, lead and cadmium were analyzed using Atomic Absorption Spectrophotometer (AAS) and total anti oxidant status, was determined using standard colorimetric methods. Results: study shows statistically significantly higher levels of oxidative stress and heavy metals, (Pb & Cd) in road side dispensers of gasoline compared to the controls. This is an indication that road side gasoline dispensers are probably at greater risk of developing chronic diseases associated with increase oxidative stress and heavy metal toxicity. Antioxidant supplementation may be of benefit to the road side gasoline dispensers and legislation on road side gasoline dispensing should be enforced to reduce incidence of long term complications from exposure.

1134 Validation of Dried Blood Spot Method for Detection of Aflatoxin B1-Lysine Adduct in Animals and Humans

K. Xue, L. Tang and J.-S. Wang. *Environmental Health Sciences, University of Georgia, Athens, GA.*

Aflatoxin B1 (AFB1), a potent mycotoxin and group 1 human carcinogen, is a ubiquitous contaminant among groundnuts- and corn-based foods. Public health concerns has been raised for AFB1-induced growth stunting and impediments in growth and development among infant and children in many low-income developing countries. Dried blood spots (DBS), popularly used in new-born congenital disease screening, were proposed as a potential means for screening biomarkers of exposure for various environmental toxicants, due to its less invasiveness and ease of storage and shipment. We previous developed a HPLC-based experimental protocol to detect AFB1-Lysine adduct in DBS samples. This study aimed to validate the analytical protocol and examine the correlation between AFB1 exposure and levels of AFB1-Lysine adduct in DBS samples in animals and human samples. F344 rats were treated with single or repeated-dose AFB1 and DBS cards were prepared from the whole blood. Serum was also prepared from the whole blood to serve as comparison purpose between two methods in detection of AFB1-Lysine adduct. DBS cards prepared from human whole blood were spiked with known levels of AFB1-Lysine adduct and human serum samples from Kenya and Uganda were used for validation study. A significant dose and time effects of adduct levels were found in DBS cards treated with single- and repeated-dose AFB1. Pearson correlations comparing AFB1-Lysine adduct levels in DBS and serum samples were 0.997 for the single-dose study, 0.998 for the repeated-dose study, and 0.843 for spiked human samples. Using Bland-Altman plot, the log difference between the results of two sample types were found to be within limit of agreement approximately 95% of the time for both human and animal samples. Our results showed that AFB1-Lysine adduct levels in DBS cards and serum samples from animals and from spiked human samples are comparable, and the DBS technique and analytical protocol is ready to move to field study aimed to assess AFB1 exposure in infant and children populations.

1135 Prenatal Exposure to Pyrethroid Insecticides Metabolites Measured in Umbilical Cord Blood Serum

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Greater use of pyrethroid insecticides in residential and agricultural pest control has increased the potential for exposure to the general population. The fetus may be at greater risk of developing exposure-related neurological dysfunction due to immature metabolic capabilities and sensitivity to chemical insult during critical developmental windows, although little research has been conducted in the area. Pyrethroids in umbilical cord blood best represent the biologically effective dose received by the fetus during an exposure event in the late third trimester of pregnancy. Previous methods had minimal success in measuring pyrethroid parent compounds and metabolites in serum. Pyrethroid metabolites may be better biomarkers in serum, as parent compounds are rapidly metabolized. A GC-MS/MS method was developed to quantify low concentrations of six pyrethroid insecticide metabolites, cis- and trans-3-(2,2-dichlorovinyl)-2,2-dimethyl-cyclopropane carboxylic acid (cis/trans-DCCA), cis- and trans-chrysanthemum dicarboxylic acid (cis/trans-CDCA), cis-3-(2,2-dibromovinyl)-2,2-dimethyl-cyclopropane carboxylic acid (cis-DBCA), 4-fluoro-3-phenoxybenzoic acid (4-F-PBA), and

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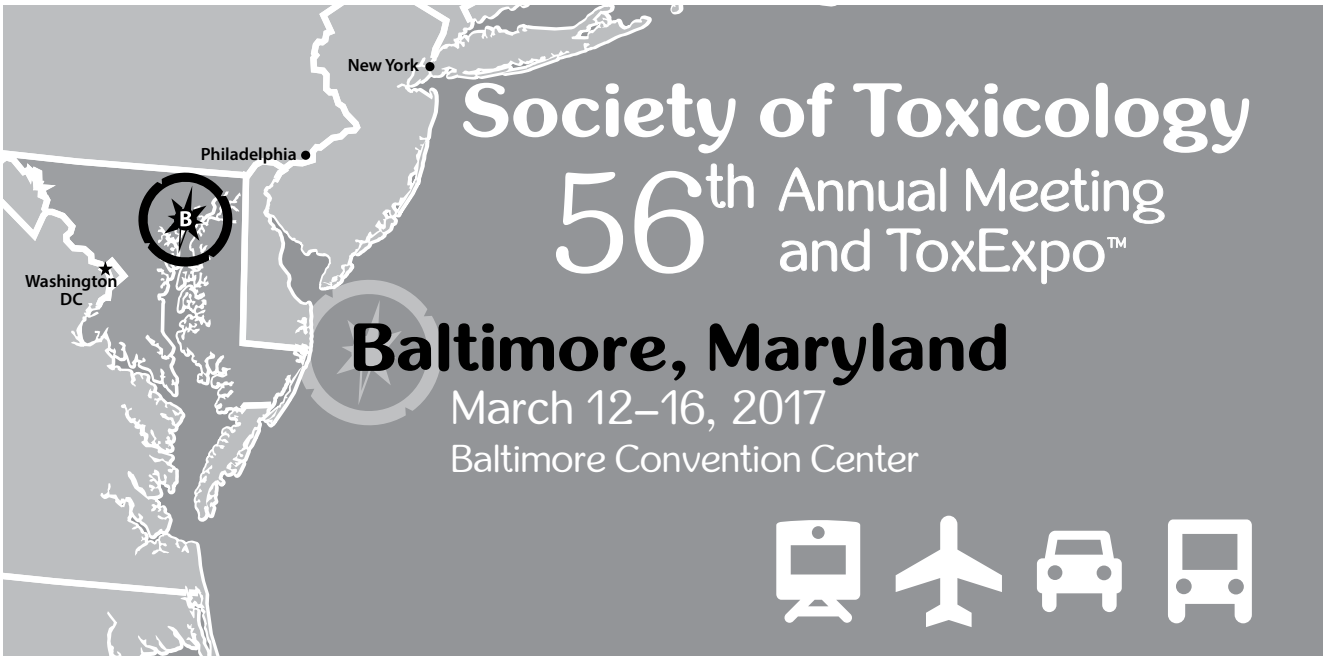

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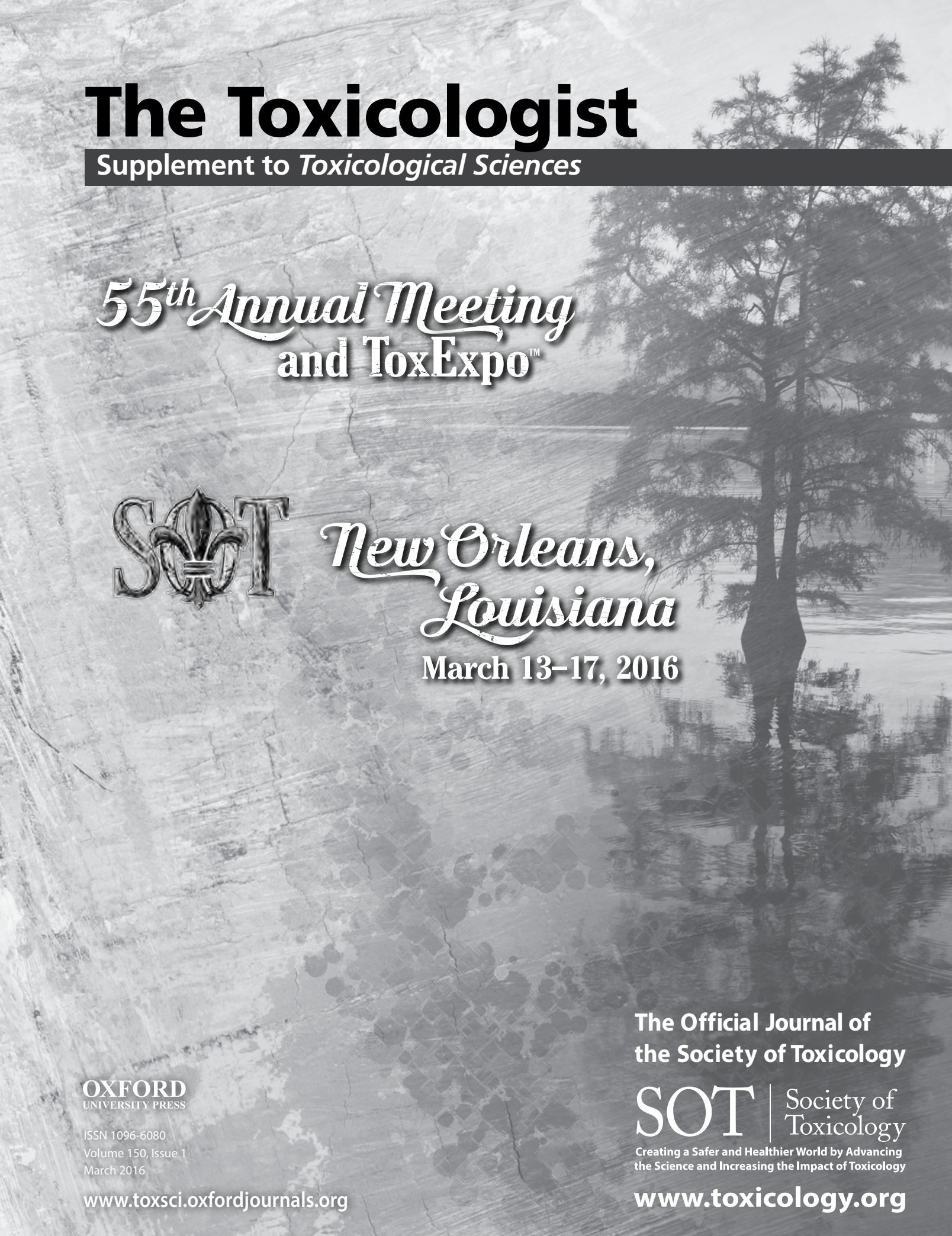

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Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 55th Annual Meeting of the Society of Toxicology, held at the New Orleans Ernest N. Morial Convention Center, March 13–17, 2016.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 603.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 629.

The abstracts are reproduced as accepted by the Scientific Program Committee of the Society of Toxicology and appear in numerical sequence. Author names which are underlined in the author block indicate the author is a member of the Society of Toxicology. For example, J. Smith.

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- CE Continuing Education Courses
- EC Education-Career Development Sessions
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- HH Historical Highlights Sessions
- IS Informational Sessions
- PL Platform Sessions
- PS Poster Sessions
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