3314 Overview of the Biomarker Initiative to Identify Biological Fluid-Based Indicators of Neurotoxicity

W. Slikker. *US FDA/NCTR, Jefferson, AR.*

In order to identify biomarkers associated with the development and expression of neurotoxicity, the Health and Environmental Sciences Institute (HESI) Technical Committee on Translational Biomarkers of Neurotoxicity conducted a pilot study in which potential biomarkers were assessed in concert with confirmation of TMT-induced neuropathology by traditional histopathological assessments and behavioral changes. Tissue samples, behavioral observations, and MRI scans were obtained simultaneously at 2, 6, 10, or 14 days post-TMT treatment. Samples collected included plasma, serum, CSF, and urine with a goal towards identifying in bodily fluids key biomolecules associated with the expression of frank neurotoxicity. Behavioral and neuropathology data confirmed the effectiveness of TMT to induce functional and morphological derangements and will be key anchors in attempts to identify biomarkers that portend the onset, or confirm the presence of, neurotoxicity.

3315 Glial Fibrillary Acidic Protein (GFAP) and Related Astroglial Proteins as Biomarkers of Neurotoxicity

J. O'Callaghan. *NIOSH, Morgantown, WV.*

The glial reaction to nervous system damage, often termed gliosis, represents a hallmark of all types of nervous system injury. As such, development and implementation of gliosis biomarkers represents a broadly applicable approach for neurotoxicity safety assessment. Using a panel of known neurotoxic agents, we have previously shown that the astroglial protein, GFAP, can serve as one such biomarker of neurotoxicity. Qualitative and quantitative analyses of GFAP have shown this biomarker to be a sensitive and specific indicator of the neurotoxic condition. Decades ago, assays and immunohistochemistry of GFAP were used to detect and quantify TMT-induced damage to its known target, hippocampus, and to identify novel CNS targets damaged by this compound. These studies revealed the sensitivity and target specificity of the GFAP/glial biomarker-based approach to neurotoxicity assessment. In the current study, time-dependent and significant increases in GFAP reactivity was observed in hippocampus and increased protein levels were detected in plasma and serum. The GFAP data from the HESI pilot study using TMT was used as a metric to which other potential markers of neurotoxicity can be compared for relative sensitivity and specificity. GFAP and related glial biomarkers may serve as the basis for further development of molecular signatures predictive of adverse effects on the nervous system.

3316 Changes in the Metabolome May Serve as Peripheral Biomarkers of CNS Toxicity

D. Herr. *US EPA, Research Triangle Park, NC.*

Since our observation that an acute exposure to different classes of pesticides resulted in different changes in plasma metabolomics markers, a study of the metabolome has become of high interest for identifying markers of neurotoxicity. A Biocrates AbsoluteIDQTM p180 platform was used for targeted identification of metabolite changes in rat CSF, plasma, and urine. Metabolite classes included acylcarnitines, amino acids, biogenic amines, hexoses, phosphatidylcholines, lysophosphatidylcholines, and sphingomyelins. From among 186 metabolites, 31 were detected in all CSF samples, and 135 were detected in all plasma samples. A principal component analysis indicated that certain metabolites were differentially altered in trimethyl tin (TMT)-treated groups when compared to controls. This was especially true in the CSF. Analysis of metabolite fold changes in the CSF indicated increases in acylcarnitines and phosphatidylcholines at 2 and 6 days, with increases in amino acids observed as long as 14 days after treatment. These changes suggest alterations in energy metabolism and mitochondrial and membrane damage in the central nervous system. In the plasma, there were increased levels of acylcarnitines, phosphatidyl- and lyso-phosphatidylcholines, amino acids, and sphingomyelins at 2 and 6 days. Additionally, the increased levels of acylcarnitines in urine at 2 and 6 days were most similar to the changes in metabolites noted in CSF and plasma. Our data provide evidence of significant changes in energy metabolism and mitochondrial and membrane damage in CNS, which were reflected in a peripheral fluid. Should it be demonstrated that plasma and urine markers mirror CSF markers and track aspects of CNS damage as evidenced by frank neuropathology (cell death), they may serve as useful, readily accessible surrogates of neurotoxicity. *This is an abstract of a proposed presentation, and does not represent US EPA policy.*

3317 Neurotoxicant Effects on Non-Brain Tissues: Understanding Biomarker Specificity

I. D. Pardo. *Pfizer, Inc., Groton, CT.*

Animal testing of a potential new drug often reveals multiple target organs, some of which may limit further drug development, and others that are manageable. A biomarker used to understand translation of target organ toxicity to human risk will need to have both high sensitivity and specificity for the target organ of concern. Thus, a peripheral biomarker of neurotoxicity must be very sensitive to nervous system injury while not being influenced by effects in non-nervous tissues. In the present study, the phenotypic anchor of frank CNS toxicity was quantified using Fluoro-jade stain of hippocampal cells. Histopathological evaluation of kidney, liver, thymus, adrenal glands, sciatic nerve, and lumbar cord was then performed. TMT-related microscopic findings consisted of minimal to mild degeneration of renal tubules within the distal nephron. These findings were accompanied by renal tubular epithelial necrosis and/or tubular dilation at 6 (at least n=3/10), 10 (3/6) and 14 (3/5) days. Minimal hepatocellular hypertrophy and minimal vacuolation (lipid) of portal hepatocytes were observed in one animal of one post-TMT group. Similarly, diffuse decreased cellularity (lymphoid cells) was observed in the thymus cortex in single animal on post dosing days 6, 10, and 14. There were no TMT-related microscopic findings in the lumbar spinal cord, sciatic nerve, or adrenal glands. Thus, putative biomarkers described in other presentations in this session are likely reflective of TMT-induced brain toxicity and not derived from other organ systems. However, because urinary TGF-beta may be altered by renal toxicity this marker requires further study to determine its brain specificity.

3318 Biochemical and Molecular End-Points as Biomarkers of Neurotoxicity and Their Correlation with Neuropathological Damage

S. Z. Imam. *US FDA, Jefferson, AR.*

An effort to perform a comprehensive identification of biomarkers that circulate in bodily fluids and tissue that are associated with the expression of neurotoxicity was undertaken using a young adult male rat model. Here, preliminary observations are presented on biomolecules that have some promise for identification of neurotoxicity that was induced by a single intraperitoneal injection of the known neurotoxic agent, trimethyltin (TMT). A single dose of TMT led to significant alterations in total oxidative stress markers, changes in lipid homeostasis, circulating interleukins and related factors, and markers of neuroinflammation, thus, providing opportunities to explore their correlation with the traditional pathology that defines neurotoxicity. Finally, a comprehensive correlation of TMT-induced neuropathology with several observed biomarkers suggest specific pathways that can be assessed using peripheral fluids.

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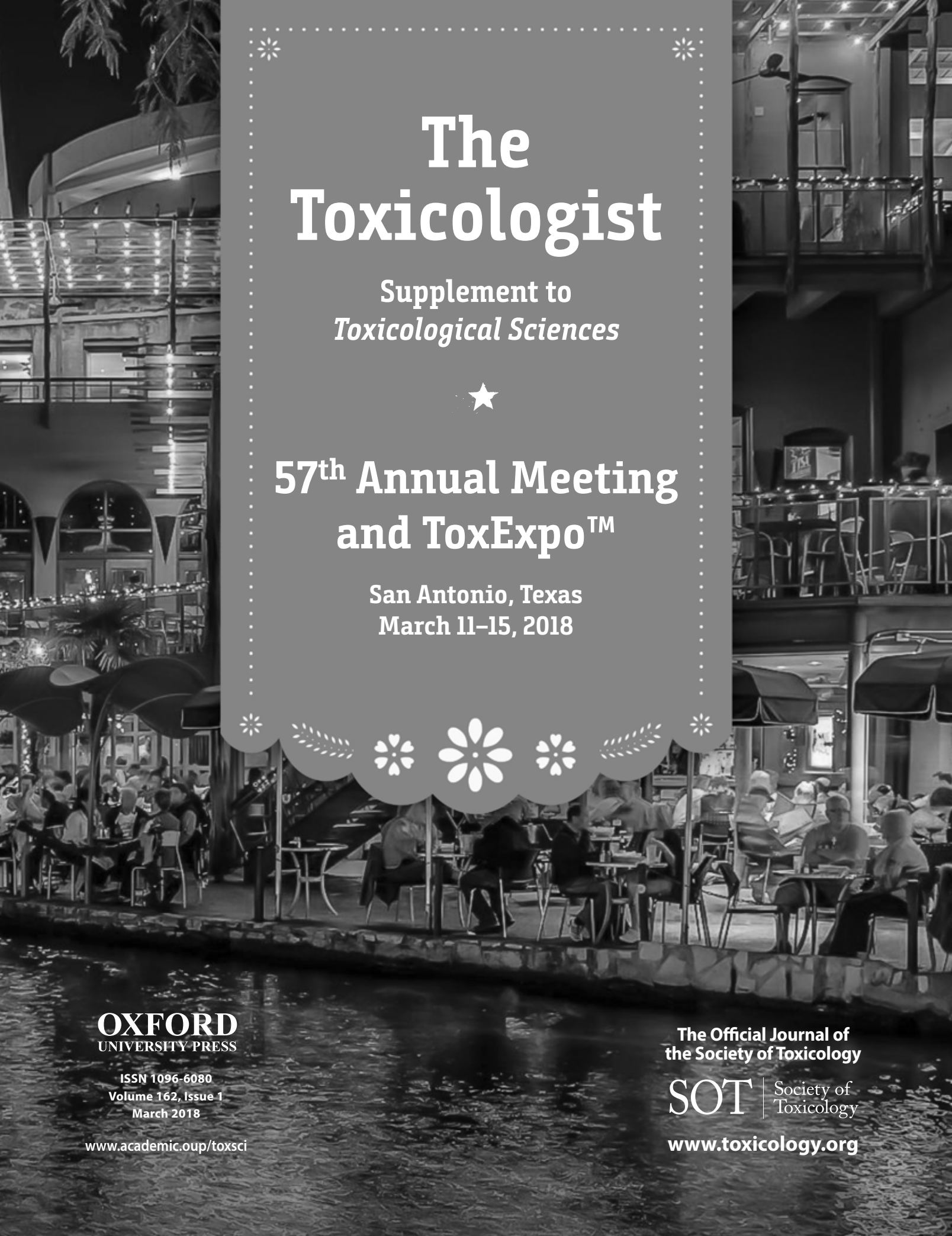

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