due to low solubility of Pb acetate in our medium which could not be resolved by sonication, acidification, or the presence of serum. Use of medium without phosphate solved the problem, resulting in efficient uptake of Pb into the cells. Our data so far also show that co-exposure to PCBs and Pb lowers the concentration threshold where cytotoxicity is seen and results in elevated ROS levels at lower concentrations and earlier time points. Dopamine and gene expression analysis is in progress to elucidate the mechanisms of this this increased toxicity. These results show that occupational co-exposure to PCBs and Pb from old buildings may be hazardous to workers at concentrations that individually are considered as safe. (Supported by NIEHS Iowa Superfund Program P42 ES013661)

1593 Adult-Only Lead Exposure Impairs Adult Hippocampal Neurogenesis and Cognitive Behavior in Knock-In Mice Expressing the Human Apolipoprotein E4 Allele

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Through a process called adult neurogenesis, adult neural precursor cells (aNPCs) in the dentate gyrus (DG) of the hippocampus generate adult-born neurons. These neurons functionally integrate into existing neuronal circuits and may contribute to hippocampus-dependent learning and memory. A variety of physiological and pathological stimuli have been shown to modulate adult hippocampal neurogenesis, and the disruption of this process may impair learning and memory, accelerate cognitive decline, and contribute to neurodegenerative disease. However, little is known about how gene-environment interactions (GxE) between toxicants and genetic risk factors may perturb adult hippocampal neurogenesis and accelerate cognitive decline. We previously found that the heavy metal lead inhibits adult neurogenesis *in vitro*. Based on our *in vitro* findings, we chose to determine whether there is a GxE between the heavy metal lead and the ε4 allele of the apolipoprotein E gene (APOE-ε4) - the strongest genetic risk factor for late-onset, sporadic AD. Humanized knock-in mice expressing either the human APOE-ε4 or APOE-ε3 alleles were exposed to 0.2% lead acetate via drinking water for 3 months starting at 8 weeks of age. Lead treatment significantly impaired adult hippocampal neurogenesis in APOE-ε4 mice compared to control (APOE-ε3) animals. In addition, compared to APOE-ε3 animals, lead-treated APOE-ε4 mice had significant and persistent deficits in hippocampus-dependent learning and memory, including impaired spatial memory in the novel object location test and decreased contextual fear memory. Our preliminary results suggest that a GxE between lead and APOE-ε4 may perturb adult hippocampal neurogenesis.

1594 The Toxic Effects of Cadmium on Adult Neurogenesis

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Adult neurogenesis is a process that occurs throughout life in the subgranular zone (SGZ) of the dentate gyrus in the hippocampus and in the subventricular zone (SVZ) along the lateral ventricles in mammalian brains. It plays an important role for the formation of hippocampus-dependent memory and olfaction. The effect of neurotoxicants on adult neurogenesis is just beginning to be elucidated. Cadmium (Cd) is a heavy metal with a long biological half-life in humans (from ten to thirty years) and has been recognized as one of the most toxic environmental and industrial pollutants. Cd is a neurotoxicant and can cause cognitive and olfactory impairment. However, molecular and cellular mechanisms underlying Cd neurotoxicity are not fully understood. The goal of our study is to investigate the effects of cadmium on adult neurogenesis and the potential underlying molecular mechanisms. To accomplish this goal, we prepared adult neural stem/progenitor cells (aNPSCs) isolated from the SGZ or SVZ of adult mice. We found that exposure of low concentrations of Cd decreased cell number and cell proliferation while induced apoptosis in cultured aNPSCs. Cd also inhibited the spontaneous neuronal differentiation of SVZ-derived aNPSCs. Furthermore, Cd exposure significantly increased phosphorylation of c-Jun NH2-terminal kinase (JNK), and p38 MAP kinase in SVZ cells, indicative of their activation. By using pharmacological inhibitors and SVZ-derived aNPSCs prepared from JNK3 knock-out mice, we found that the JNK and p-38 MAPK signaling pathways are critical for Cd neurotoxicity in aNPSCs. Moreover, *in vivo* Cd exposure significantly decreased the survival of adult born neurons in the SGZ of adult mice. Our data suggests that Cd exposure can impair adult neurogenesis, and that activation of the JNK and p38 MAP kinases play important roles in the neurotoxicity of Cd in aNPSCs. These results are, to our knowledge, the first demonstration that Cd impairs adult neurogenesis, providing new insights concerning molecular and cellular mechanisms of Cd neurotoxicity.

1595 A Gene-Environment Interaction Study to Understand the Role of Native Alpha-Synuclein in Cadmium-Induced Neurotoxicity

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Alpha-synuclein (α-syn) is a ubiquitous protein whose native function is unknown. α-syn comprises 60% of Lewy bodies that are aggregates present in the brains of postmortem Parkinson's disease (PD) patients and implicated in the pathogenesis of dopaminergic neurons. 5-10% of PD cases are familial with the remaining being idiopathic. Long-term exposure to pesticides or metals such as cadmium (Cd) has been proposed to represent a risk factor for PD. Cd is an industrial and environmental pollutant that causes severe damage to a variety of organs, including the brain, and impairs cellular mechanisms implicated in PD. Here we investigated the role of native α-syn in Cd-induced neurotoxicity in an established α-syn dopaminergic cell model of PD that overexpresses human native α-syn (N27-syn) or empty vector (N27-vec). We demonstrate that N27-syn expressing cells exhibit a significant dose-dependent susceptibility to Cd neurotoxicity compared to N27-vec following a 24h exposure. Furthermore, we show that N27-syn cells exhibit lower levels of the antioxidant glutathione and increased production of reactive species compared to N27-vec, suggesting oxidative stress mediated cell death. As α-syn may be a protein localized to the cell membrane, we hypothesized that the protein may play an important role in modulating metal transporters. Consequently, we quantified intracellular Cd levels in N27 cells following a 6h and 24h Cd exposure with inductively-coupled plasma mass spectrometry (ICP-MS) and report that N27-syn cells accumulate significantly more Cd in a time-dependent manner compared to N27-vec cells. Together these findings suggest that α-syn enhances Cd-induced neurotoxicity resulting in oxidative stress mediated cell death by playing a role in Cd homeostasis. In conclusion, we have identified a novel gene-environment interaction between α-syn and Cd that may contribute to the understanding of the function of native α-syn and its response to heavy metals, potentially modifying PD neuropathology.

1596 Exposure to Metal Mixtures in Welding Fume: Effects on Neuropsychological Functions

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Welding fume is a mixture of metals and gases to which millions of welders worldwide are exposed to everyday. Contrary to most previous studies, who focused on single metal exposures, we investigated the neurological effects of exposure to Mn as well as other prevalent welding fume metals, such as, Copper (Cu), Zinc (Zn), Iron (Fe), Aluminum (Al), and Lead (Pb). Exposure of 28 welders and 18 controls was assessed using two methods. Firstly, air exposure to each metal was calculated for individuals based on their personal work history and current departmental airborne concentration levels. Secondly, human toenail metal concentrations were used, which has recently been validated as good biomarker of Mn exposure in welders, including in our own studies. On average, the welders' respirable airborne concentrations were Mn (0.12mg/m3), Zn (0.01 mg/m3), Cu (0.02 mg/m3), and Fe (1.19 mg /m3). In testing neuropsychological performance three cognitive and three motor tests were chosen. Psychomotor function was assessed with the Finger Tapping test (FTT), Grooved Pegboard test, and Parallel Lines test. Results indicate that decreases of cognitive flexibility (Rey-O Immediate recall) and executive function (Trail making Tests B), are associated with higher toenail Cu ($P < 0.01$); higher Pb ($P < 0.02$ and $P < 0.04$); and higher Al ($P < 0.05$). Verbal category fluency scores (Animal and Fruit Naming Tests) were found to decrease in individuals with increased toenail Mn ($P < 0.01$), Cu ($P < 0.001$ and $P < 0.02$), Pb ($P < 0.01$). Psychomotor speed (assessed by the Finger Tapping Test), and fine tactile dexterity (Grooved-Pegboard Test) were associated with increased toenail Mn ($P < 0.01$ and $P < 0.05$). Lastly, increased toenail Fe was associated with greater graphomotor tremor on the Parallel Lines Test ($P < 0.01$). These current results indicate that chronic exposure to any of the metals Cu, Pb, Al, Fe and Mn in welding fume metals have an effect on neurological performance. (Supported by NIEHS R01 ES020529 and CDC/NIOSH T03 OH008615)

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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
- RI Regional Interest Sessions
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