PS 222 COMPARATIVE NEUROTOXICITY AND INTRACELLULAR ACCUMULATION OF FIVE POLYBROMINATED DIPHENYL ETHER (PBDE) CONGENERS IN MOUSE CEREBELLAR GRANULE NEURONS.

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Polybrominated diphenyl ethers (PBDEs), a group of flame retardants comprising 209 congeners, have become widespread environmental pollutants. High levels of PBDEs have been detected in human tissues, particularly in North America, and body burden is especially high in infants and toddlers, because of exposure through breast milk and house dust. Increasing evidence, provided by animal studies, suggests that PBDEs are developmental neurotoxicants, though the underlying mechanisms are still unknown. Various PBDEs have been reported to cause oxidative stress and to induce apoptotic cell death in several cell types. In the present study, we investigated the comparative neurotoxicity in mouse cerebellar granule neurons, of five BDE congeners, chosen among the most commonly found at the highest levels in human tissues. All BDE congener tested (BDE-47, -99, -100, -153, and -209) decreased cell viability and induced apoptotic cell death. They also caused oxidative stress, as indicated by an increase in reactive oxygen species and in lipid peroxidation. For all end-points measured, the potency ranking of the congeners was BDE-100>BDE-47>BDE-99>BDE-153>>BDE-209. Measurement of BDE congener levels in neurons after exposure to different concentrations showed a significant accumulation in cells, which followed the same relative ranking. The findings suggest that all BDE congeners tested exhibit the same general mode of action (induction of oxidative stress-mediated apoptosis), and that the ability of each isomer to elicit such effects is dependent upon their accumulation in neurons, particularly in mitochondria.

PS 223 INVOLVEMENT OF CALCIUM-RELATED PROCESSES IN THE INHIBITION OF DEPOLARIZATION-EVOKED CALCIUM INCREASE BY HYDROXYLATED PBDES IN PC12 CELLS.

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Hydroxylated polybrominated diphenyl ethers (OH-PBDEs) increase basal intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) by inducing release of Ca^{2+} from endoplasmic and mitochondrial Ca^{2+} stores. Considering the strong association of these intracellular Ca^{2+} stores with voltage-gated Ca^{2+} channels (VGCCs) for regulating Ca^{2+} homeostasis, effects on depolarization-evoked increase in $[Ca^{2+}]_i$ were investigated in neuroendocrine pheochromocytoma (PC12) cells exposed to PBDEs (BDE-47, BDE-49, BDE-99, BDE-100, BDE-153) and metabolites of BDE-47 (3-OH-BDE-47, 4'-OH-BDE-49, 5-OH-BDE-47, 6'-OH-BDE-49 and 6-OH-BDE-47 and its methoxylated analogue 6-MeO-BDE-47) using the Ca^{2+}-responsive dye Fura-2. PBDEs and 6-MeO-BDE-47 neither affect basal nor depolarization-evoked $[Ca^{2+}]_i$, with the exception of BDE-47, which increased fluctuations in basal $[Ca^{2+}]_i$ and moderately increased depolarization-evoked $[Ca^{2+}]_i$. After 20-min pre-exposure, OH-PBDEs dose-dependently inhibit depolarization-evoked $[Ca^{2+}]_i$. This inhibition is potentiated by a preceding increase in basal $[Ca^{2+}]_i$. Especially at high concentrations of OH-PBDEs, high increases in basal $[Ca^{2+}]_i$ strongly inhibit depolarization-evoked $[Ca^{2+}]_i$. A moderate inhibition of depolarization-evoked $[Ca^{2+}]_i$ was also observed for some OH-PBDEs when applied during depolarization. The present findings demonstrate that OH-PBDEs inhibit the increase in depolarization-evoked $[Ca^{2+}]_i$, which is potentiated by preceding increases in basal $[Ca^{2+}]_i$. Interestingly, inhibition of the increase in depolarization-evoked $[Ca^{2+}]_i$ appeared more sensitive to preceding increases in basal $[Ca^{2+}]_i$ by OH-PBDEs inducing mainly release of Ca^{2+} from intracellular stores compared to OH-PBDEs that induced also influx of extracellular Ca^{2+}. This apparent difference in $[Ca^{2+}]_i$ close to the membrane suggests involvement of Ca^{2+}-dependent regulatory mechanism in close proximity to the VGCCs.

PS 224 ELUCIDATING THE MECHANISMS OF TOXICITY OF TRICHLOROETHYLENE METABOLITES.

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The EPA, Department of Defense and other regulatory agencies list trichloroethylene (TCE) and its metabolites as "emerging contaminants" or chemicals of concern. TCE is well known a by-product of the chlorination of municipal water and is mainly used in industry as a solvent or degreaser. The mechanisms by which TCE exhibits its toxicity are vaguely understood. When TCE is oxidized via the cytochrome P450 pathway, metabolites such as dichloroacetic acid (DCA), trichloroacetic acid (TCA) and trichloroethanol (TCEtOH) are formed. These metabolites are thought to be responsible for the toxic effects observed in past studies. There is overwhelming concern for the possible cancer and reproductive effects, particularly leukemia that TCE can induce. Investigating the mechanisms of toxicity will benefit the areas of toxicology, public health and occupational health and safety. Using the model system S. *cerevisiae* and parallel deletion analysis can provide a better understanding of the pathways involved in TCE toxicity in yeast as well as higher organisms, such as humans. Previous studies with benzene and d-block metals have proven this as a successful tool in elucidating modes of action involved in toxicity and cancer. The goal of this project is to identify yeast genes essential for the response to three TCE metabolites (DCA, TCA, TCEtOH), elucidate their possible mechanisms of action and identify homologs for these genes in higher organisms. IC_{20} values will be determined and will be subsequently utilized in the parallel deletion analyses to identify genes involved in response to the three metabolites. Preliminary results consisting of essential genes identified and possible modes of action will be reported. Future investigations will be conducted to both identify homologous genes in humans and investigate different TCE metabolites produced by the glutathione conjugation pathway. The results of this experiment will be used to gain an overall understanding of the mode of action(s) of trichloroethylene and to identify homologs and gene susceptibility in humans.

PS 225 PFOA AND PFOS-INDUCED OXIDATIVE STRESS RESPONSE IN HUMAN MICROVASCULAR ENDOTHELIAL CELLS.

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Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are the two most widely known perfluorinated chemicals (PFCs), which contain an eight-carbon backbone. They are man-made fluorocarbon-based acids that have been used in various industrial processes. They are non-biodegradable and persistent in the human body and environment. They are released directly from production processes, as well as from their use in manufacturing of new products. Human occupational and environmental exposure to PFOA and PFOS occurs globally. Accumulating surveillance data suggest associations between PFOA and PFOS exposures and adverse effects on human health, including lipid metabolism, uric acid metabolism, and reproductive risks. Whether these biomonitoring associations are etiologic remains a question. In this study, we demonstrated that exposure of human microvascular endothelial cells (HMVECs) to PFOA and PFOS induces the production of reactive oxygen species (ROS) at both high and low concentrations in a time-dependent manner. We have also found that PFOA exposure induces the production of ROS in a dose-dependent manner. Morphologically, we have found that exposure to PFOA and PFOS induces actin filament remodeling, endothelial permeability changes, and endothelial migration and in vitro enhancement of angiogenesis in HMVECs. Furthermore, we have demonstrated that the production of ROS plays a regulatory role in PFOA- and PFOS-induced actin filament remodeling and endothelial migration and permeability increase. Taken together, our results indicate that PFOA- and PFOS-induced ROS production may play a role in the aberrations of endothelial permeability barrier integrity. The results from this study may contribute to dissecting the molecular mechanisms involved in PFOA and PFOS toxicity.

PS 226 THE ROLES OF ORGANIC ANION TRANSPORTERS IN RENAL ELIMINATION OF BRANCHED AND LINEAR PERFLUOROBUTYRATE IN RATS.

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Perfluorobutyrate (PFBA) is widely detected in the environment as a result of industrial uses. It has a much shorter serum half life compared to perfluorooctanoate (PFOA). In addition to the linear form (L-PFBA), there is only one branched form (B-PFBA) for this four carbon perfluorocarboxylate. Previous studies have shown that in the rat both L-PFBA and B-PFBA are mainly eliminated renally. Furthermore, B-PFBA was eliminated much faster than L-PFBA. Given the fact that both linear and branched PFBAs are organic anions, we tested the hypothesis that organic anion transporters in the kidney may mediate the transport of L-PFBA and/or B-PFBA and contribute to the differences in their elimination patterns. We

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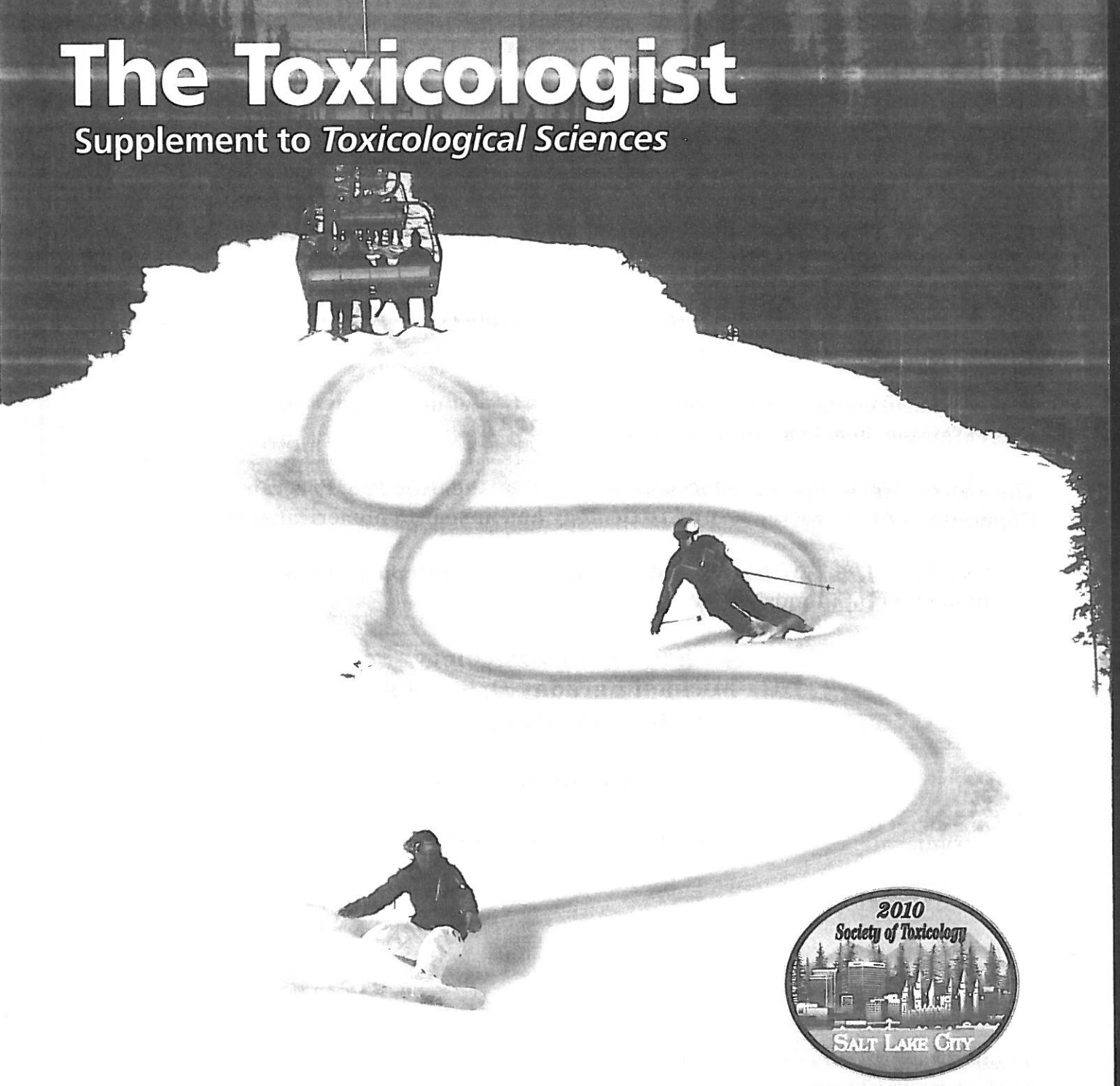

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Preface

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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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