analytical responses of binary (AChE/BChE) and ternary (AChE/BChE/CaE) mixtures using esters of choline and phenol as the esterase substrates. Procedures for input data preparation (analytical responses of the test mixtures) along with different algorithms for calculation of the component concentrations in a mixture were developed. The algorithms for the calculation of the concentrations of separate components in the mixture (concentrations of AChE/BChE/CaE) were developed based on methods of formal kinetics and neural networks. The mean error of the calculation of the component concentrations in the mixture was about 8% for binary mixtures and 15-20% for ternary mixtures of esterases. Preliminary experiments were performed on the quantitative determination of the content of AChE/BChE/CaE in samples of plasma and whole blood of rats and humans. The results were validated using standard biochemical methods for the respective esterase assays. Supported by ISTC project # 3130.

PS 2119 KINETIC DIFFERENCES IN THE INTERACTIONS OF CHLORPYRIFOS OXON WITH BUTYRYLCHOLINESTERASE AND ACETYLCHOLINESTERASE.

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The organophosphorus insecticides are commonly utilized throughout the world, and account for about half of all insecticide use in the United States. The acute toxicity observed following exposure to toxic levels of these chemicals is the accumulation of excess acetylcholine resulting from inhibition of acetylcholinesterase (EC 3.1.1.7) and probably butyrylcholinesterase (EC 3.1.1.8). Previous studies from this laboratory have shown that the interactions of some organosphates with acetylcholinesterase are far more complex than originally thought, with the inhibitory rate constant k_i changing as a function of inhibitor concentration (concentration-dependent inhibition kinetics). In the present study, chlorpryifos oxon (*O,O*-diethyl *O*-(3,5,6-trichloro-2-pyridyl) phosphate) displayed concentration-dependent inhibition kinetics towards human recombinant acetylcholinesterase. For example, 2 nM chlorpyrifos oxon yielded a k_i of 9.32 $nM^{-1}h^{-1}$, whereas 10 nM inhibitor gave a k_i of 1.36 $nM^{-1}h^{-1}$. In sharp contrast, no evidence of concentration-dependent inhibition kinetics was observed with the inhibition of butyrylcholinesterase with chlorpyrifos oxon. With a range of chlorpyrifos oxon concentrations from 0.3-10 nM, estimates of the k_i ranged from 30 $nM^{-1}h^{-1}$ – 70 $nM^{-1}h^{-1}$, with no pattern of concentration-dependent inhibition. Stopped-flow studies determined the K_d for chlorpyrifos oxon binding to butyrylcholinesterase to be 2.52 nM. These data suggest that active site gorge differences between these two enzymes have important mechanistic implications for concentration-dependent inhibition kinetics. (Supported by Grant ES012648 from NIEHS).

PS 2120 DOSE-RESPONSE EVALUATION OF C57BL/6 MICE FOR MOTOR ABNORMALITIES AND PARKINSON-PATTERNED NEUROPATHOLOGY AFTER PARAQUAT AND MANEB EXPOSURE.

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The combination of paraquat and maneb (PQ/MB) has been proposed to be a risk factor for Parkinson's Disease. C57Bl/6 mice were dosed daily from PND 5-19 (0.3/1.0 mg/kg PQ/MB) and/or twice weekly from week 28-31 of age (10/30 mg/kg PQ/MB), the levels reported in the literature to cause loss of substantia nigra cells. This high dose was reduced to 5/15 mg/kg PQ/MB following lethality in naïve males after the fourth of seven injections as adults. Additionally, two other doses were derived from human PQ exposure models and were administered as a middle dose (0.06/0.18 mg/kg PQ/MB juvenile, 0.6/1.8 mg/kg PQ/MB adult) and a low dose (0.0007/0.002 mg/kg PQ/MB juvenile and adult) to represent exposure levels more relevant to humans. Animals dosed as juveniles only, as adults only, or both, were tested for motor activity and arena behavior at 32 weeks, and then perfusion fixed for evaluation of neuropathology at 33 weeks. One additional group dosed as juveniles and adults was tested again at 62 weeks and sacrificed at 70 weeks of age. At 32 weeks of age, there were no effects of treatment on behavioral endpoints. At 62 weeks of age, treated animals were similar to controls in the arena and activity cage, except in high dose females where ambulatory and rearing activity was increased. Staining with anti-GFAP and deOlmos' amino cupric silver method did not detect any degenerative response related to treatment across the entire brain at either 33 or 70 weeks of age in either gender. Stereological analysis and quantification of dopaminergic neurons in the substantia nigra is ongoing.

PS 2121 PRENATAL EXPOSURE TO PERMETHRIN CAUSES VASCULAR MALFORMATIONS IN THE FETAL BRAIN AND DECREASES MOTILITY OF ADULT MICE.

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Recently, permethrin, a pyrethroid insecticide, was shown to cause abnormalities in the central nervous system (CNS). Previously, we demonstrated that permethrin decreased both endothelial differentiation from mouse embryonic stem cells and angiogenesis of human brain microvascular endothelial cells in vitro. Abnormalities in the CNS may result from defects in formation of the brain vasculature. In the present study, we investigated the effect of prenatal exposure to permethrin on brain vascular formation in the mouse fetus and on the behavior of mice after maturation. Mice at embryonic day (ED) 10 were administered permethrin at the dose of 0, 2, 10, 50 or 75 mg/kg dissolved in corn oil. Fetal brains were obtained at ED17. The length of the anterior-posterior axis was shorter in the groups treated with permethrin at the dose of 10, 50 or 75 mg/kg than those treated with corn oil alone. Vascular malformation were observed in all of the permethrin treated groups, and included shortened lengths of vessels, an increased number of small branches and, in some cases, insufficient fusion of the anterior communicating arteries. For the behavioral test, mice at ED10 were administrated permethrin at the dose of 0, 2, or 50 mg/kg dissolved in corn oil. Motility was examined at 8 weeks and 12 weeks using the Modified-SHIRPA test. At 8 weeks, although no change was observed in spontaneous behavior, motility of male mice in an open field was significantly decreased in both permethrin treated groups. At 12 weeks, no change was detected in female mice, while a significant decrease of spontaneous behavior and open field motility was detected in male mice. However, no significant change was detected in brain weight, body weight or brain morphology. Our results suggest that morphologic abnormalities in the fetal brain caused by prenatal exposure to permethrin recover in the postnatal period, but functional abnormalities in the male brain worsen.

PS 2122 DELAYED EFFECTS OF ACUTE EXPOSURE TO CHLORPYRIFOS IN AN ANIMAL MODEL (TG2576) OF ALZHEIMER`S DISEASE.

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In mammals, exposure to organophosphates (OP) has been related to long lasting cognitive effects. Although the OP insecticide chlorpyrifos (CPF) is widely used in agricultural activities and household, it acts as a cholinesterase (ChE) inhibitor. In the present study, we evaluated the delayed effects produced by administration of a single s.c. dose of CPF (0.50 mg/kg) to male adult transgenic mice carrying the Swedish mutation for the familiar Alzheimer disease (Tg2576) and their corresponding wild-type mice. Body weight changes were recorded during the experiment. ChE activity was measured in brain 72 hr after CPF treatment in order to determine the inhibition percent achieved. A functional observation battery (FOB) was applied at 72 hr and at 8 weeks after CPF exposure. Effects on spatial learning and memory were evaluated 17 weeks after treatment in a Morris water maze test. Motor coordination and balance were tested using a rotarod 19 weeks after CPF administration. A 52.7% ChE inhibition, and a decrease in body weight 72 hr after treatment were observed. No differences between Tg2576 and wild-type were noted in spatial task acquisition. However, CPF-treated transgenic mice showed an improvement in the retention task. On the other hand, motor learning and coordination were impaired in treated transgenic mice. The current results suggest that a moderately low CPF exposure improves long term memory in Tg2576 mice in the classic version of the water maze task, but it impairs motor function.

PS 2123 COMPARATIVE SENSITIVITY OF EEG AND THE PHOTIC AFTERDISCHARGE (PHAD) TO BRAIN CHOLINESTERASE (CHE) INHIBITION BY CARBARYL.

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We have reported that inhibition of brain ChE by treatment with carbaryl decreased the duration of the flash-evoked PhAD (Mwanza *et al.*, 2008) and may increase Theta activity in the EEG (Graff *et al.*, 2007). We examined if changes in the non-stimulus evoked EEG were more sensitive to brain ChE inhibition than the PhAD. Long Evans rats were implanted with epidural screw electrodes. After recovery, restrained animals were tested for 2 days using similar conditions (no flash stimulus) as PhAD studies for acclimation. On day 3, the rats' pupils were dilated,

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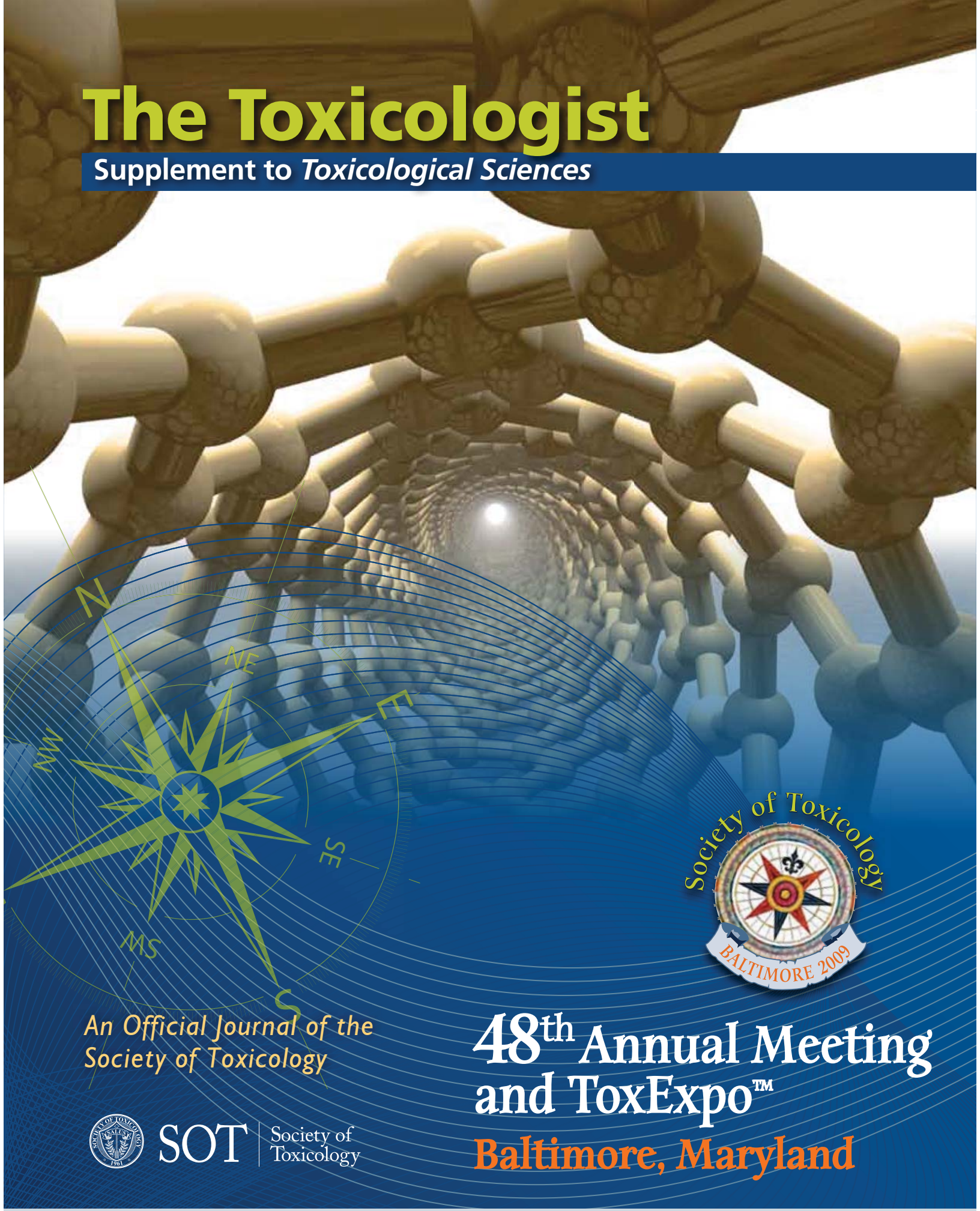

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