hippocampal slices were monitored by electrophysiological measurements. Field excitatory postsynaptic potential (fEPSP) was evoked by single pulse stimulation of Schaffer Collateral/commissural fibers at striatum radiatum of the CA1 region in the hippocampus. Following exposure to 100 nM PCB 170, time-dependent changes in the slope and amplitude of fEPSP were seen, with phases of enhancement and depression. To investigate the contribution of inhibitory neurons in the actions of PCB 170, hippocampal slices were pre-treated with the GABAa receptor antagonist, picrotoxin (PTX, 100 μM). Pre-treatment with PTX resulted in negligible change in fEPSP slope elicited by single pulse stimuli. Importantly PCB170 introduced in the presence of GABAa blockade produced a threshold response at 1nM and enhanced fEPSP slope of 250% at 100nM, revealing a significant facilitation of synaptic transmission. Non-coplanar PCBs therefore influence both excitatory and inhibitory pathways in CA1 that can mask their potent effects. These results demonstrate that blockade of inhibitory inputs with PTX can unmask the potent actions of ortho-substituted PCB 170 toward facilitating excitatory transmission. Studies of perinatal exposure to PCB 95 (6mg/kg/day) from GD5 to PND 21 were also performed to examine influences on hippocampal excitability in the offspring. PTX (100 μM) application to hippocampal slices from PCB-treatment groups displayed a much higher sensitivity to synaptic facilitation in comparison slices isolated from corn oil control groups. These results show that ortho-substituted PCBs are especially potent excitatory neurotoxicants in the presence of GABAergic insufficiency. Highly synergistic xenobiotic mechanisms can dramatically enhance susceptibility of the hippocampus to non-coplanar PCBs.

47 OVEREXPRESSION OF NQO1 PROTECTS HUMAN DOPAMINERGIC SK-N-MC NEUROBLASTOMA CELLS AGAINST DOPAMINE INDUCED CELL DEATH.

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Dopaminergic neurons are selectively vulnerable to dopamine-quinones and reactive oxygen species generated by dopamine oxidation and destruction of dopaminergic neurons has been implicated in the pathogenesis of Parkinson's disease. NAD(P)H: quinone oxidoreductase (NQO1) can metabolize dopamine derived quinones (DAQ) and a lack of NQO1 due to NQO1*2 polymorphism has been suggested to be a risk factor for PD. We have recently shown high NQO1 immunoreactivity in the substantia nigra of human Parkinson's brains. In order to confirm the role of NQO1 in the metabolism of dopamine, we have examined the potential role of NQO1 in human neuroblastoma cell line (SK-N-MC), which was transfected with NQO1. The NQO1 activity of stably transfected cells was 350nmole /mg/ min while vector control and parental cells had NQO1 activities of less than 40nmole/ mg/ min using standard activity assays. Incubation of 500μM dopamine for 24 hrs in both parental and vector control SK-N-MC cells resulted in 88% and 72% cell death as assessed by annexin-V/Propidium iodide analysis using flow cytometry. In agreement, 88% and 84% of parental and vector control cells respectively underwent loss of mitochondrial membrane potential (MMP) assessed by tetramethylrhodamine ethyl ester. In contrast, NQO1 transfected cells were resistant to dopamine toxicity and both cell death and loss of MMP were abrogated in NQO1-transfected SK-N-MC cells. Dopamine resistance in NQO1 over-expressed cells may be attributed to the role of NQO1 in the detoxification of DAQ and/or direct scavenging of reactive oxygen species (Siegel et al (2004), Mol Pharmacology 65; 1238-47) and may play an important role in the pathogenesis of Parkinson's disease. (This work is supported by NIH RO1 NS44613)

48 FORCED EXERCISE ATTENUATES KAINIC ACID-INDUCED NEUROTOXICITY IN THE HIPPOCAMPUS OF C57BL/6J MICE.

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Exercise is considered beneficial to overall health and may enhance the resiliency of the body to insult. Here, we investigated the ability of exercise to modulate neurotoxicity caused by kainic acid in male C57Bl/6J mice. Forced walking was achieved in a motorized exercise wheel (10 s/rev., 30 min., 4:00 P.M.). Mice were trained for three days, then exercised for 14 days prior to kainate treatment. On day 14 of exercise, mice received an injection of saline or kainic acid (20 mg/kg, intraperitoneal, at 12:00 P.M.). Additional non-exercised mice received similar injections for a total of four groups: saline, kainate, wheel saline, wheel kainate. Seizure severity was scored according to the Racine scale. At 24 hours post-injection, mice were decapitated, the brain was removed and bisected; the left hippocampus was dissected for analysis of GFAP by ELISA while the right hemisphere was immersion fixed for histological analysis of neurodegeneration by Fluoro-Jade B staining. Body, thymus, and spleen weights were recorded, and plasma was prepared for analysis of corticosterone levels. The 24 hour time point for sacrifice was selected based on previous experimentation evaluating kainate-induced neurodegeneration, but preceded the peak of induction of GFAP. Kainic acid treatment caused minimal seizures (mouth and facial movements). Fluoro-Jade B staining revealed fluorescent pyramidal cells in kainate-treated animals indicating neuronal damage; no fluorescent neurons were observed in any exercised mice. GFAP levels were not significantly different between groups, but protein levels were slightly elevated in kainate treated mice, and attenuated in exercised animals. Additional time points will be examined which correlate with the peak of reactive gliosis. No differences in body or organ weights were observed; however, there was a trend of decreasing thymus weight in exercised animals. These data suggest exercise may be protective against kainate-induced excitotoxicity. The generality of these findings for other types of brain insults will be the topic of future investigations.

49 EVALUATING THE NMDA-GLUTAMATE RECEPTOR AS A SITE OF ACTION FOR TOLUENE, *IN VIVO*.

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In vitro studies have demonstrated that toluene disrupts the function of several ion channels localized in the brain, including the NMDA-glutamate receptor. This has led to the hypothesis that effects on ion channel function may contribute to toluene neurotoxicity, CNS depressive behavior, and altered visual evoked potentials observed in animals and humans. However, this hypothesis has not been tested *in vivo*. The present experiment examines potential toluene targets in whole animals by measuring visual evoked potentials (VEPs) during toluene exposure and challenging with a drug that antagonizes toluene's action at the NMDA-glutamate receptor. Therefore the goal of this study was to verify changes in VEPs during toluene exposure and demonstrate that toluene inhibits NMDA-glutamate receptor mediated functions in visual evoked potentials elicited from rats. One week prior to testing, recording electrodes were implanted in the rat skull above left visual cortex. Awake, restrained rats were presented with an onset/offset pattern containing a spatial frequency of 0.16 cpd, temporal frequency of 4.55 Hz, with a 60 percent contrast between bars. Baseline VEPs were recorded and rats were injected with either saline or NMDA (10 mg/kg, i.p.). Ten minutes after injection animals were exposed to air or toluene (2000 ppm). VEP amplitudes were calculated for 2X stimulus frequency (F2) for each rat. Thirty minutes after injection of NMDA or saline, NMDA/air (n=5) treatments decreased F2 by 15 percent, saline/toluene (n=6) decreased F2 by 42 percent and toluene/NMDA (n=6) decreased F2 amplitude by 63 percent, contrary to expectations. These results indicate an unanticipated, additive effect of toluene and NMDA on decreasing F2 amplitude. Thus, there appears to be an interaction between NMDA and toluene in the visual system. (This abstract does not reflect EPA policy)

50 INVOLVEMENT OF OXIDATIVE STRESS IN POTENTIATION OF NOISE INDUCED HEARING LOSS (NIHL) BY CHEMICAL CONTAMINANTS.

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Permissible workplace exposure limits for noise and for chemical contaminants generally rely upon laboratory and epidemiological investigations that entail exposure to the single agent of interest. However, a growing body of research shows that a variety of chemical contaminants, including those that have no effect upon auditory function, can potentiate noise induced hearing loss. Such potentiation is particularly noteworthy when it occurs for low intensity noise exposures that approach the permissible human noise exposure standards.We predict that chemicals able to impair intrinsic antioxidant mechanisms potentiate NIHL since reactive oxygen species may be generated even at low noise levels. Combined exposure of rats to hydrogen cyanide and mild noise yields significant auditory impairment while at neither agent given alone resulted in hearing loss. Using antioxidant drug treatments to protect auditory function and pro-oxidant drugs to promote oxidative stress we find support for our hypothesis that oxidative stress does play a role in potentiation of noise induced hearing loss by hydrogen cyanide. supported in part by NIOSH OH03481.

51 MODULATION OF CHOLINERGIC TOXICITY BY CANNABINOIDS.

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Endogenous (e.g., anandamide) and exogenous (e.g., tetrahydrocannabinol) cannabinoids have been reported to decrease or increase acetylcholine release in different brain regions. Both the cholinergic agonist carbachol and the cholinesterase

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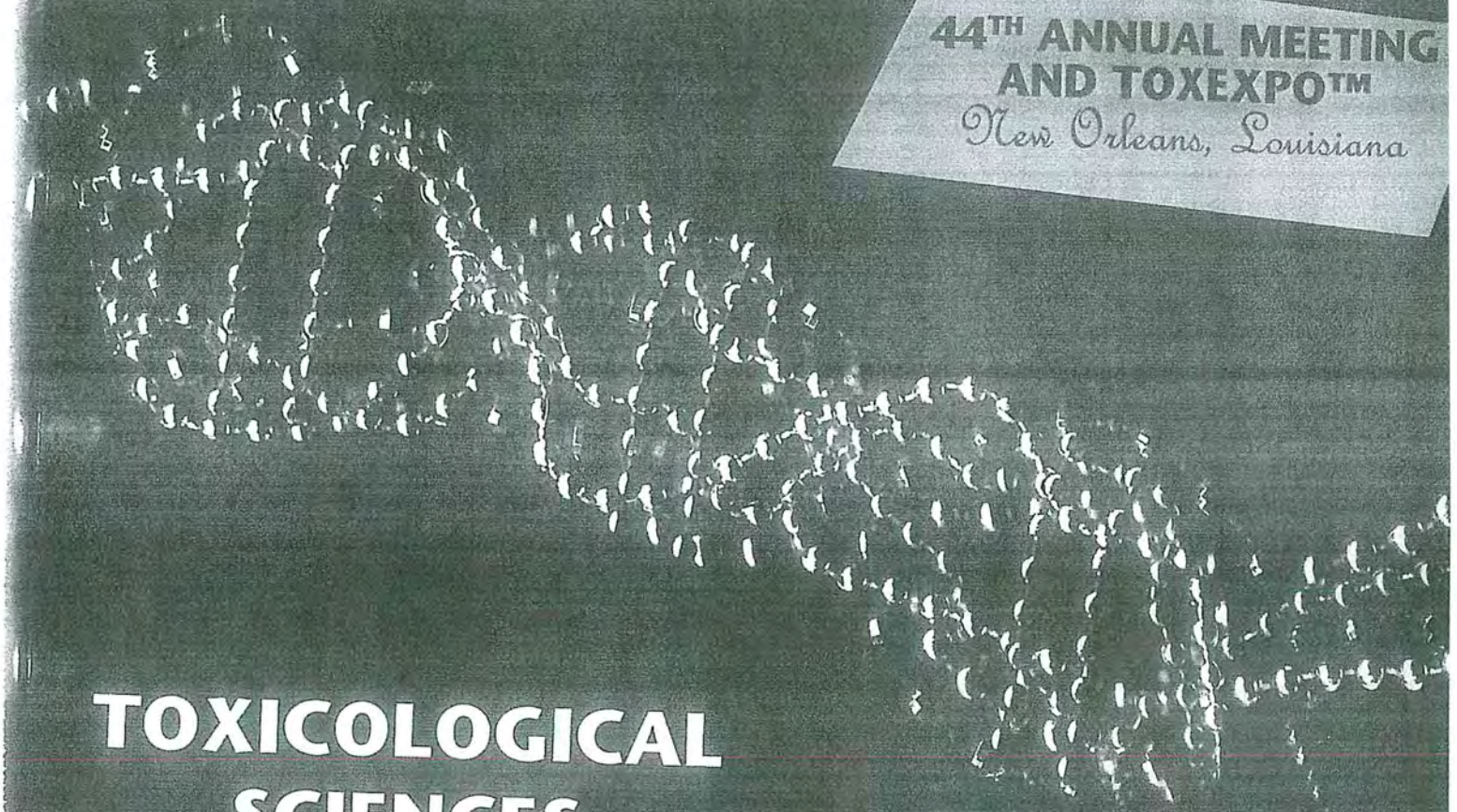

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