1480 BRAIN ESTERASE ACTIVITIES IN RATS GIVEN MULTIPLE DOSES OF ORGANOPHOSPHORUS (OP) COMPOUNDS OVER 63 DAYS WITH 30 DAYS RECOVERY.

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Acetylcholinesterase (AChE) and neurotoxic esterase (NTE) activities in the hippocampus (H), cerebral cortex (CC), basal forebrain (BP) and caudate putamen (CP) were examined in adult male Long-Evans rats given OP compounds during a 63-day dosing period with 30 days recovery. Corticosterone 400 mcg/ml in drinking water was given throughout the 90-day test period. The insecticide chlorpyrifos (60 mg/kg sc) was given on Days 7 and 42. Tri-ortho-tolyl phosphate (TOTP), 300 mg/kg PO, was given 7 times between Days 14 & 28 and again between Days 49 & 63. At 63 days, AChE activities in H, CC, BP and CP of rats given only chlorpyrifos were 40%+/-7 (mean+/-SEM, n=6), 32%+/-4, 35%+/-6, and 30%+/-3 of control, respectively. AChE activities after chlorpyrifos + TOTP were <15% of control. Rats drinking corticosterone-treated water and given chlorpyrifos + TOTP also had AChE activities <15% of control. On Day 91, AChE activities were 62%+/-3, 74%+/-2, 61%+/-9 and 62%+/-9, respectively, in the H, CC, BF and CP of rats given only chlorpyrifos. The activities of AChE in rats given TOTP only or given chlorpyrifos + TOTP ranged from 41-75% of control. Corticosterone treatment did not appear to affect AChE activities alone or in OP-treated rats. NTE activities in the H, CC, BF and CP were only affected by TOTP, with activities at 43%+/-5, 40%+/-5, 33%+/-4, and 45%+/-8 of control in these brain regions, respectively, at 63 days. NTE activities in all brain regions were at control values on Day 91. These results demonstrate that the OP treatments had great effects on AChE activity in all brain regions examined, and that recovery was not complete even 30 days after cessation of treatment with TOTP or 47 days after treatment with chlorpyrifos. The 30-day time period was, however, sufficient for recovery of NTE activity in rats given TOTP in multiple doses. (Supported by DAMD 17-99-1-9489. This abstract does not necessarily reflect the position or policy of the US Government.)

1481 NEUROPATHOLOGICAL STUDY OF THE INTERACTIONS OF STRESS AND TWO NEUROTOXIC ORGANOPHOSPHATES IN RATS.

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Interest exists concerning toxic actions of chemical mixtures and the role of stress in modulating such events. We previously reported data from a study designed to assess effects of stress and the concurrent exposure to two organophosphorus compounds in rats (Society for Neuroscience Abstracts, 2002). The present work updates the neuropathologic findings. The toxicants used were the insecticide chlorpyrifos (as a single 60 mg/kg subcutaneous dose) and the classical delayed neurotoxicant tri-ortho-tolyl phosphate (TOTP, given seven times over a two-week period as 75, 150 or 300 mg/kg gavage doses). Stress was mimicked by administration of corticosterone in the drinking water (400 ug/ml) over a 63-day period. The toxicants were given in two courses between days 7-27 and days 42-62, with sacrifice on day 63 (experimental groups n=12). Neurochemical findings are reported in an abstract by M. Ehrich et al. at this meeting. Neuropathologic studies demonstrated an axonopathy in the distal (medullary and cervical) levels of the gracile fasciculus, which progressed to overt myelinated fiber degeneration. Lesions included swollen or collapsed axons and myelinated fiber breakdown. These were primarily related to the TOTP dosage, with the 300 mg/kg group having a higher incidence and more extensive changes (including enhanced proximal extent of the nerve fiber lesions) than those animals given 150 mg/kg. Stress did not appear to affect the expression of the neuropathic process. Preliminary studies suggest that chlorpyrifos enhanced the severity of the lesions. The nature and distribution of this nerve fiber degeneration are consistent with this being a rat model of organophosphorus ester-induced delayed neuropathy (OPIDN). (Supported by: US Army Medical Research and Materiel Command DAMD17-99-1-9489. This abstract does not necessarily reflect the position or policy of the US Government.)

1482 THE TOXICOKINETICS OF PERIPHERAL CHOLINESTERASE INHIBITION FROM ORALLY ADMINISTERED CARBOFURAN IN RATS.

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This study was performed with the carbamate pesticide carbofuran to determine the time course of inhibition and recovery of cholinesterase activity (CA) after oral administration. A single dose of carbofuran in corn oil vehicle was administered *via* oral gavage to cannulated adult male and female CD rats at one of three dose levels: 0, 0.5, or 1.0 mg/kg. Blood samples were collected at -15 (predose baseline), 15, 30, 45, 60, 75, 90, 120, 150, 180, 240, 360 and 480 minutes after dosing for determination of plasma and erythrocyte (RBC) CA. Carbofuran did not inhibit plasma CA at either dose level when compared to controls. Following a single oral administration of 0, 0.5, or 1.0 mg/kg, RBC CA was inhibited at the low and high dose levels in both the males and females. To account for inherent variability as seen in the control values, the percent of baseline RBC CA was calculated at each time point (for each animal in each dose group). For the 0.5 mg/kg dose group, the percent of baseline activity was not statistically different from controls from 150 through 480 minutes for males and from 75 through 480 minutes for females (with the exception of the 240 min time point in males and the 360 min time point in females). For the 1.0 mg/kg dose group, percent of baseline RBC CA was not significantly different from controls at the 180 and 360 minute time points for males and the 240 and 480 minute time points for females. When normal variability is taken into account by evaluating the data as percent of baseline value, a return to normal RBC CA occurred by 150 minutes (males) and 75 minutes (females) in the low dose group.

1483 DEVELOPMENT OF A NEONATAL RAT PHYSIOLOGICALLY BASED PHARMACOKINETIC/PHARMACODYNAMIC (PBPK/PD) MODEL FOR CHLORPYRIFOS.

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Juvenile rats are more susceptible than adults to the high dose effects of organophosphate (OP) insecticides, like chlorpyrifos (CPF); therefore, it is assumed that infants and children are likewise more susceptible. Age-dependent differences are primarily a function of metabolic capacity for several important enzyme systems. This includes CYP450 activation to CPF-oxon, and detoxification to trichloropyridinol (TCP), as well as B-esterase (B-EST) and A-esterase (A-EST) detoxification of CPF-oxon to TCP. A PBPK/PD model describing the time-course of CPF, CPF-oxon, and the inhibition of acetylcholinesterase (AChE) in adult rats and humans was modified to allometrically scale (based on body weight) the age-dependent development of CYP450 and A-EST enzyme activity. The model provided a good simulation of brain and RBC AChE inhibition in post-natal day (PND) 17 rats orally administered 15 mg/kg CPF. The model was used to simulate concentrations of CPF-oxon in the brain of neonatal rats (PND4) following single acute oral exposure to a range of CPF doses (0.5-50 mg/kg). Doses greater than 5 mg/kg resulted in theoretical concentrations of CPF-oxon in the brain of PND4 rats that was greater than in adults, this difference increased with dose. Doses less than 1 mg/kg resulted in brain CPF-oxon concentrations in PND4 rats that were similar to theoretical adult AUCs. The model simulation suggests that neonatal rats are more sensitive than adults to the effects of acute high dose exposures. However, the model also indicates that even though neonatal rats have lower metabolic capacity, it is adequate to detoxify CPF at relevant environmental exposure levels. These simulations are consistent with differences in the acute toxicity response noted between neonatal and adult rats following exposure to CPF. This model represents an important starting point in the development of a PBPK/PD model to better define the potential of CPF to cause neurotoxicity in sensitive populations, such as infants and children. (Supported by EPA grant R828608)

1484 POTENTIAL UTILITY OF SALIVA BIOMONITORING FOR ORGANOPHOSPHATE INSECTICIDE DOSIMETRY AND ESTERASE INHIBITION.

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Chlorpyrifos is a phosphothioate, which is a commonly used organophosphate (OP) insecticide. Its active metabolite CPF-oxon is a potential inhibitor of cholinesterase enzymes (ChE), such as acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Whereas the inhibition of AChE is associated with neurotoxicity, BuChE inhibition represents a detoxification mechanism and a potential biomarker of exposure/response. In the current study CPF, dissolved in corn oil, was administered orally as a single dose (0, 1, 10, and 50 mg/kg) to male Sprague-Dawley rats followed by saliva and blood collection at 0, 3, 6, and 12 hour post-dosing. CPF and its major metabolite trichloropyridinol (TCP) were quantified in blood and saliva using gas chromatography (GC) and a modified Ellman method was used to monitor the resultant ChE inhibition. A preliminary *in vitro* study, using both AChE and BuChE specific inhibitors, indicated that the vast majority (>90%) of rat salivary ChE activity was due to BuChE. Utilizing saliva as a source of BuChE, the bimolecular inhibition rate constant (Ki) and the first-order reactivation rate (Kr) were ~8000 $\mu M^{-1}\ h^{-1}$ and 0.08 h^{-1}, respectively. Oral administration produced a dose-dependent inhibition of ChE in plasma and saliva. At all dose levels the maximum salivary ChE inhibition (3-6 hr post-exposure) was slightly less than that of the plasma, and saliva exhibited a faster ChE recovery. CPF and TCP