tuitary and the testes. Further studies are needed to determine the specific targets responsible for the effects here reported. (Partially supported by CONACyT (Grant No. 28403-M), WHO (Grant No. 96349) and by The Advanced Training Program of The Border XXI Initiative.

## 1522 NEUROBEHAVIORAL EVALUATION OF RESIDUAL EFFECTS OF LOW-LEVEL BYSTANDER ORGANOPHOSPHATE PESTICIDE EXPOSURE.

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Organophosphate pesticides (OP's) may cause neurotoxicity at low-levels of exposure. Subject: A female, 42 years old, high school graduate, farmer, working in a hay field, wearing shorts and a swim suit top, without respiratory protection was exposed to Thimet and possibly Lorsban applied to a downwind neighboring field in 6/98, with re-exposure by working in the adjacent field 6-8 times over the next 3 days. The evening of the exposure, she experienced headache, nausea, vomiting, leg pain, diarrhea, chest tightness, dizziness, blurred vision, and weakness in legs and arms - symptoms of OP poisoning - with continuing vertigo, nausea, pain etc.. Later and persistent symptoms included memory loss, sleep disorder, fatigue, irritability, and impaired executive function. ACHE testing was inconclusive. Assessment: Included comprehensive neurobehavioral toxicity evaluations, 2 years post-exposure, with an extensive interview and testing, and record review (educational, medical, letters of reference). Findings: Prior IQ was at the 80%tile. The Neurotoxicity Screening Survey showed results consistent with those of patients diagnosed with neurotoxicity. Current Full-scale IQ had declined to the 47%tile, with Processing Speed (a factor very sensitive to global neurotoxicity) at the 8%tile. Additional deficits were seen in detecting visual figure-ground relationships - 36%tile; Selective Reminding Test (measures learning) <1%tile; Stroop Color and Word Test (evaluates mental flexibility ) 31%tile; Visual Search and Attention Test 23%tile; logical memory <1%tile; with moderate anxiety and moderate-severe depression. Distortion was below the level of detection. Malingering was ruled out by 5 separate tests. Personality testing using the NEO Personality Inventory found no personality disorders that could contribute to the findings. Record review found no competing explanations of her illness. Conclusion: Relatively low-level organophosphate exposure can cause neurotoxicity, revealed by neurobehavioral evaluation, lasting many years after exposure.

## 1523 AN APPROACH FOR SCREENING CHOLINESTERASE INHIBITORS IN DRINKING WATER.

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Under the 1996 amended Safe Drinking Water Act (SDWA), a Contaminant Candidates List (CCL) has been compiled in 1998 (FR 63:40). Several Cholinesterase (ChE) inhibitors were identified in this list, some are organophosphates and others are carbamates. Prior to 1996, ChE inhibitors in drinking water were regulated individually and monitored by using conventional analytical methods to detect the presence and concentration of individual contaminants. Because of specific advances in analytical chemistry and the need for cumulative risk assessment of chemicals that have a common mechanism of toxicity, we developed an approach for initially screening for the presence of ChE inhibitors in drinking water. This approach is based on the use of a Microwell Plate Assay kit. In this method, Acetyl Cholinesterase (AChE) was stabilized in a gelatin film to determine low levels of pesticide contaminants in drinking water that inhibit ChE activity. The remarkable properties of the dry immobilized ChE preparation include its stability to prolonged storage at room temperature as well as its stability to short term elevated temperatures (60 degrees C). The enzyme could be maintained in dry gel form for 365 days at room temperature without substantial loss of activity. Several procedures were evaluated to oxidize less potent organothionophosphate (P=S ) compounds to their more inhibitory oxon forms. Inhibition profiles were run for six commonly used carbamate insecticides (and some of their metabolites) and eight organophosphate insecticides using this assay. $IC_{50}$ and $IC_{20}$ values were determined for purified water and several drinking water matrices. Results using this assay were also compared to a commercially available test kit. This method may be successfully used for screening drinking water ChE inhibitors individually or in mixture. The opinions expressed are those of the authors and do not necessarily reflect USEPA policy.

## 1524 ACETYLCHOLINESTERASE INHIBITION: PREDICTION USING THREE-DIMENSIONAL QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS.

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Organophosphorus pesticides are known to produce their biological effects through the inhibition of a number of esterases, including acetylcholinesterase (AChE), the enzyme responsible for the degradation of the neurotransmitter acetylcholine. The combined use of conformational analysis and three dimensional (3D), quantitative structure-activity relationship (QSAR) methods were used to rationalize the inhibitory potencies of a series of organosphorus pesticides against AChE. The CATALYST program was used to identify the structural features in the group of eight inhibitors whose $IC_{50}$ values ranged from 0.34 nM to 1.2 μM. The 3-D pharmacophore models were characterized by at least one hydrogen bond acceptor site and 2-3 hydrophobic sites and demonstrated good correlation ($r^2$=0.994) between the predicted and experimental $IC_{50}$ values. This approach can be used to screen databases of organophosphorous and other chemicals for their neurotoxic potential *via* the inhibition of AChE.

## 1525 ASSESSING THE IMPACT OF HUMAN PON1 POLYMORPHISMS: SENSITIVITY AND MONTE CARLO ANALYSES USING A PHYSIOLOGICALLY BASED PHARMACOKINETIC/PHARMACODYNAMIC (PBPK/PD) MODEL FOR CHLORPYRIFOS.

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A PBPK/PD model was developed for chlorpyrifos (CPF) and the active metabolite CPF-oxon. Susceptibility to organophosphate (OP) insecticides is associated with variation in pharmacokinetic/ pharmacodynamic response. A genetic polymorphism in the PON1 (arylesterase) detoxification of OPs results in the expression of a range of PON1 enzyme activities within humans. The objective was to identify sensitive parameters that influence the model output, and to investigate the impact of human PON1 status on CPF-oxon brain concentration over a range (5 μg/kg - 5 mg/kg) of CPF doses. The model was used for parameter sensitivity analysis, and Monte Carlo simulations for PON1 activity utilizing the human PON1 polymorphic distributions. Based on the sensitivity coefficients (SC), the model was sensitive to the following parameters: CPF-oxon plasma protein-binding, liver partitioning, liver PON1 metabolism, plasma butyrylcholinesterase (BuChE) and blood flow to the liver and brain. In addition, the SC for plasma protein binding, PON1, and BuChE demonstrated a clear dose-dependency. The model simulations suggest a dose-dependent non-linear increase in the brain CPF-oxon AUC, at doses >0.5 mg/kg, which is a function of both dose and PON1 activity. In contrast, at low environmentally relevant doses (~5 μg/kg) the model is relatively insensitive to the variability in PON1 activity. The results suggest that other esterase detoxification pathways may adequately compensate for lower PON1 activity; hence an increased sensitivity to low PON1 is not observable until non-target esterases have been appreciably depleted. This response is consistent with simulations that show an increased sensitivity to PON1 status at doses that significantly deplete plasma BuChE activity in humans (>90% inhibited). This study illustrates the utility of PBPK/PD modeling for determining the overall impact of parameter uncertainty and variability on risk assessment predictions for OP insecticides. (Supported by EPA grant R828608)

## 1526 EFFECTS OF DIETARY CHLORPYRIFOS ON PERIPHERAL TISSUE *VERSUS* BRAIN AND RBC ACETYLCHOLINESTERASE ACTIVITY IN DOGS.

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Chlorpyrifos (CPF) is a widely-used broad-spectrum insecticide. At the request of the United Kingdom's Advisory Committee on Pesticides, a 6-week dog study was conducted to examine the effects of dietary exposure to CPF on peripheral tissue (left atrium, nodose ganglia, diaphragm, and quadriceps muscle) acetylcholinesterase (AChE) activity as compared to AChE in brain and red blood cells (RBC). Six-month old Beagle dogs (n = 4/sex/dose) were given 0, 0.5, 1.0, or 2.0 mg/kg/day CPF in their diets. AChE was assayed using acetylthiocholine in the presence of the butyrylcholinesterase inhibitor iso-OMPA (0.1 mM). AChE activities were compared using Dunnett's test (alpha = 0.05). RBC AChE showed a slight (~10%) but statistically significant decrease in the mid- and high-dose groups after 1 day of exposure to CPF. RBC AChE was inhibited at all dose levels after one week, reaching a steady-state of inhibition within three weeks of exposure. After 6 weeks of treatment at 2.0 mg/kg/day, a small difference in brain AChE (~7% inhibition; males and females combined) may represent a true treatment effect but was not statistically significant and was not considered adverse (<20% inhibition). Peripheral tissue AChE activity was corrected for connective tissue content as AChE activity in diaphragm, quadriceps, and nodose ganglia was inversely-correlated with the amount of connective tissue in the sample ($r^2$ < 0.49). No statistically significant differences in peripheral tissue AChE were found. However, the left atrium AChE activity in high-dose males was about 25% lower than controls, and may represent a true treatment effect despite a comparable but opposite effect in females, which indicated random variability. We conclude that RBC AChE is more

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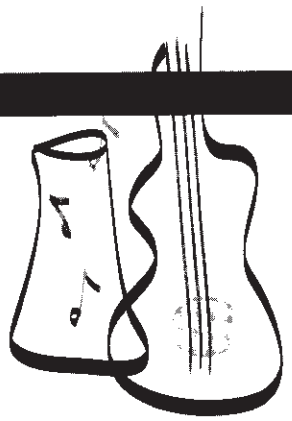

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