Development of a Physiologically Based Pharmacokinetic and Pharmacodynamic Model to Quantitate Biomarkers of Exposure to Organophosphorus Insecticides

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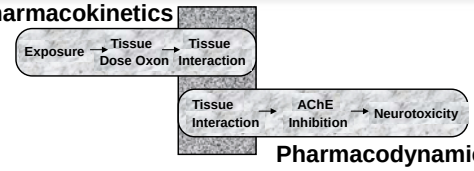
EPA Science Forum 2004
Healthy Communities and Ecosystems

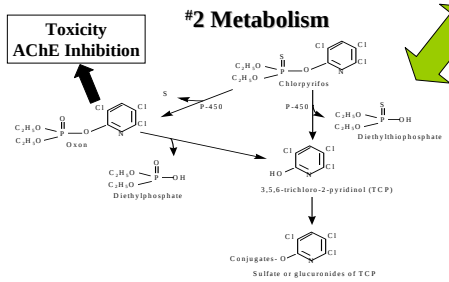
Background:

- This project entails development and validation of a physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model (see #**1**) for the organophosphorus insecticide chlorpyrifos (CPF) to quantitate dosimetry and acetylcholinesterase (AChE) inhibition in young rats and children.
- Chlorpyrifos is metabolized to an active oxon metabolite which is a potent inhibitor of AChE. Toxicity is due to the inhibition of AChE resulting in a broad range of neurotoxic effects (see #**2**).
- It is hypothesized that an age-dependent decrement in chlorpyrifos metabolism correlates with increased sensitivity of young animals and potentially children. A balance between the contribution of various parameters like metabolism can increase or decrease the potential toxicity (see #**3**).
- PBPK/PD models (see #**4**) allow for the integration of all the key parameters associated with toxicity and can be used to quantitate both the dosimetry and biological response (AChE inhibition), over a range of doses, exposure conditions (single vs. repeated), and exposure routes (oral, dermal or inhalation). This tool can be used by risk assessors to make a more biologically based assessment for risk associated with exposure to organophosphorus insecticides.

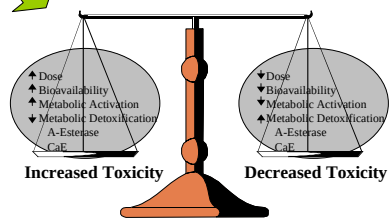
#1 Pharmacokinetics



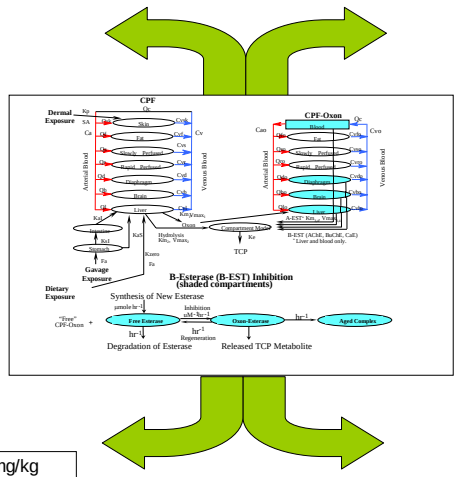
#2 Metabolism



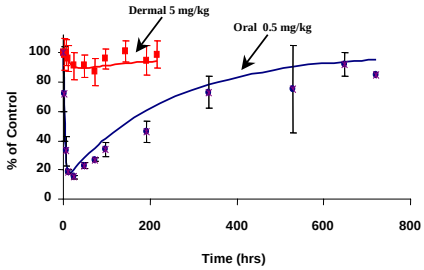
#3 OP Pharmacokinetic Balance



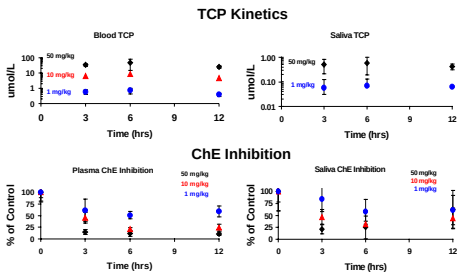
#4 PBPK/PD Model



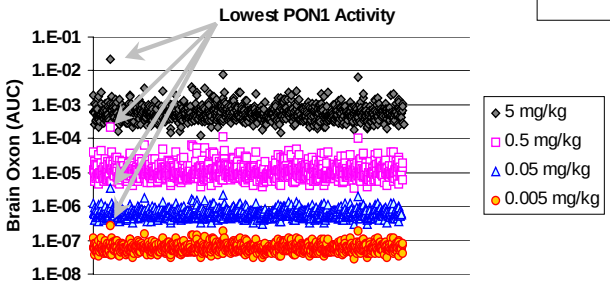
#5 Rat & Human Validation Studies



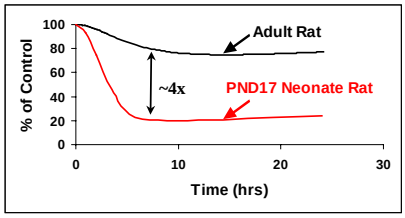
#6 Saliva Biomonitoring



#7 Variability



#8 Age-Dependent Response



#9 Dose Comparison Adult vs. Neonatal Rat

Groups	Brain CPF-Oxon AUC (μmoles L^{-1} hr^{-1})				
	0.5 mg/kg	1.0 mg/kg	5 mg/kg	10 mg/kg	50 mg/kg
Adult Rat	0.02	0.03	0.13	0.31	1.64
Neonatal Rat (PND4)	0.02 (1.0)	0.06 (2.0)	0.36 (2.8)	0.77 (2.5)	6.51** (4.0)

Values in parenthesis are the ratio of brain CPF-oxon AUC for neonatal: adult rats.
**Lethal dose level.

Results:

- The PBPK/PD model has been validated using dosimetry and dynamic response (cholinesterase (ChE) inhibition) data obtained from animal and human studies. Figure #**5** illustrates the plasma ChE response (data points) and PBPK/PD model fit (lines) for human volunteers exposed to chlorpyrifos both dermally and orally. The model does an excellent job of fitting a range of experimental data.
- To evaluate the potential utility of saliva for biomonitoring, studies were undertaken to measure the amount of metabolite (TCP) present in saliva and the degree of salivary ChE inhibition following a oral exposure to chlorpyrifos (see Figure #**6**). These results suggest that saliva may be useful for biomonitoring for organophosphorus insecticides.
- To assess the impact of variability associated with detoxification by human metabolism in adults a Monte Carlo analysis was conducted over a broad ranges of doses (see Figure #**7**). A metabolic polymorphism has the greatest impact on dosimetry (brain oxon AUC) at doses that overwhelm other detoxification pathways.
- The PBPK/PD model was modified to allometrically scale (based on body weight) the age-dependent development of metabolizing enzymes and ChE enzyme activity, and simulations were compared against experimental data. These simulations (see Figures #**8** and #**9**) are consistent with differences in the acute toxicity response between neonatal and adult rats (4-fold difference in sensitivity). However, the model also suggest that metabolism in neonates my be adequate at environmentally relevant exposure concentrations.

Conclusions & Impact:

- This EPA-STAR project has resulted in the development and validation of an integrated PBPK/PD model for organophosphorus insecticides that can be used to quantitate age-dependent dosimetry and dynamic response following exposure to chlorpyrifos. This model can be used to address risk assessment issues specifically dealing with children's susceptibility and cumulative risk.
- The model framework can be readily extended to other important organophosphorus and carbamate insecticides.
- The quantitation of key metabolites and ChE activity in saliva following *in vivo* exposure represents an important opportunity for development of non-invasive biomonitoring technology for the rapid detection of organophosphorus insecticide exposure. This approach can be readily adapted to other important pesticides and potentially used as a tool for the rapid assessment of exposure to chemical warfare nerve agents.