

US EPA ARCHIVE DOCUMENT

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

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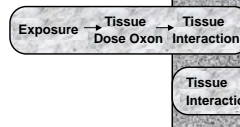
EPA Science Forum

Healthy Communities and Ecosystems

Background:

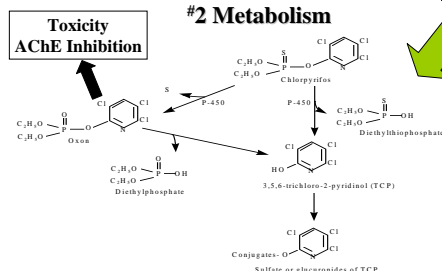
- This project entails development and validation of a physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model (see #1) for the organophosphorus insecticide chlorpyrifos (CPF) to quantitate dosimetry and acetylcholinesterase (AChE) inhibition in young rats and children.
- Chlorpyrifos 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

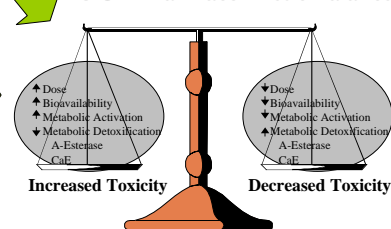


Pharmacodynamics

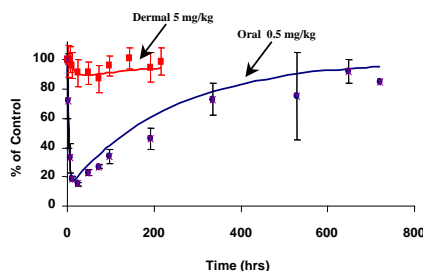
#2 Metabolism



#3 OP Pharmacokinetic Balance



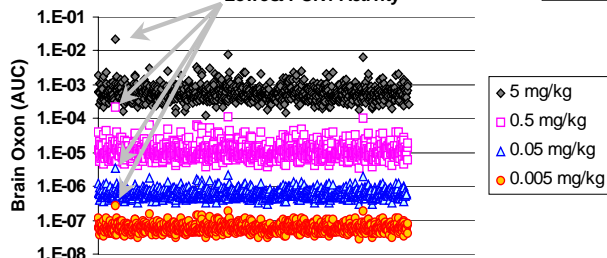
#5 Rat & Human Validation Studies



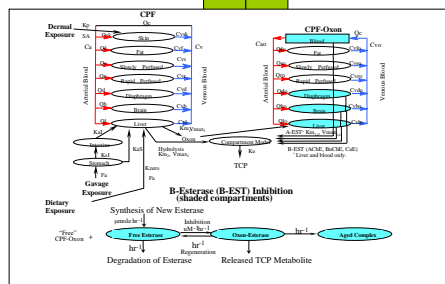
#7 Variability

QQ PON1 Polymorphism

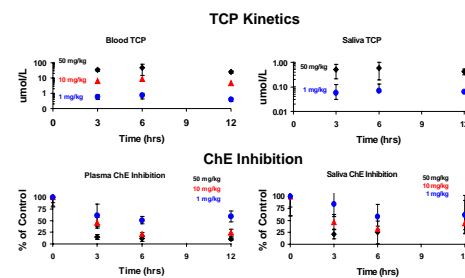
Lowest PON1 Activity



#4 PBPK/PD Model

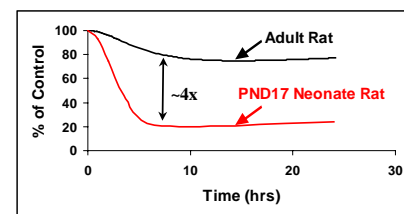


#6 Saliva Biomonitoring



#8 Age-Dependent Response

Brain AChE Inhibition, Oral 15 mg/kg



#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 an 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 range 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 may 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.