Informing the Cumulative Risk Assessment of Pyrethroid Insecticides through Linked Human Exposure and Dose Models

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Contributing Organizations: ORD: NHEERL NERL; NCCT; Office of Pesticides and Toxic Substances

LTG 2 Poster 05

Science Questions

The research addresses the following key science questions:

- How can linked population exposure-pharmacokinetic models help inform probabilistic risk assessment?
- What is the risk contribution of different exposure pathways?
- What is the relationship between exposure, brain tissue dose, and urinary biomarkers?
- Can this science and tools be used to inform cumulative neurological risks to pyrethroid pesticides?

Research Goals

Previous assessments involving the organophosphate and N-methyl carbamate pesticides (see Posters LTG 2-1 and 2-4) combined exposure and hazard data without explicit consideration of intervening ADME processes that modulate the availability of toxicant at the target site. The overall goal of this task is to develop and link state-of-the-art exposure (Stochastic Human Exposure and Dose Simulation [SHEDS]) and dose (Exposure-Related Dose Estimating Model [ERDEM]) modeling tools to:

(1) estimate longitudinal dietary and residential exposure to pyrethroids;

(2) estimate brain tissue burden and urinary concentrations of pyrethroids; and,

(3) relate cumulative exposure to risk by application of PBPK models and tissue-based relative potency factors (RPFs) (see Poster LTG 2-6).

Findings and Conclusions

Model-to-model comparisons of SHEDS with other probabilistic exposure models indicates consistency between models (eg., EPA SOPs., SHEDS, CARES, Calendex). The evaluation was performed for an indoor fogger application.

A common PBPK model structure has been developed for the pyrethroid class of pesticide. This approach leverages structure-property relationships within the chemical class to decrease the burden of *in vivo* kinetic data needed to model additional members of its class. It has been applied to deltamethrin and permethrin.

The main focus of FQPA is to protect the public from pesticide residues in dietary and non-dietary sources. Application of SHEDS-PBPK modeling to interpret dietary exposure to pyrethroids and comparison of predicted urinary markers with 2001-2002 NHANES results indicates that non-dietary sources exceed dietary exposure.

New approaches have been developed to consider dietary and residential exposure and population ADME in the risk assessment of residential use pesticides.

Methods/Approach

Application of the Stochastic Human Exposure and Dose Simulation (SHEDS) model to support OPP Residential Exposure SOP Revisions and Cumulative Pyrethroids Assessment

Figure 1 illustrates the SHEDS methodology for estimation of exposures to pyrethroids. SHEDS Multimedia V.3 simulates aggregate exposure to pyrethroids via non-dietary ingestion oral and dermal and inhalation routes. Figure 2 shows application of SHEDS V.3 for an indoor fogger scenario for a generic pyrethroid. Environmental concentration data is employed in SHEDS development. Figures 3 shows environmental co-occurrence data from the First National Environmental Health Survey of Child Care Centers (**HUD-CCC**) a collaboration between U.S. EPA, U.S. Department of Housing and Urban Development, and the U.S. Consumer Product Safety Commission.

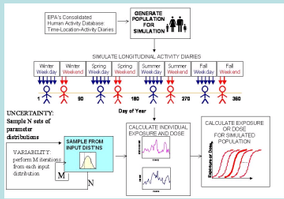


Figure 1. SHEDS Methodology

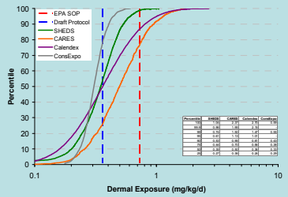
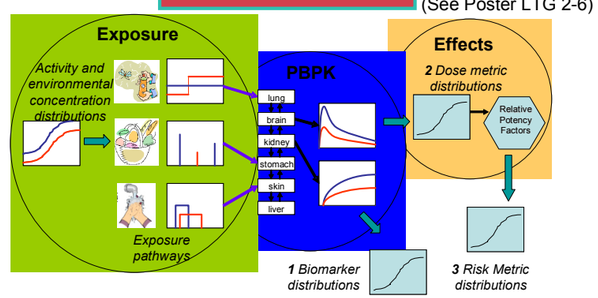


Figure 2. Model-to-Model Exposure Pathway Comparison with SHEDS (Example for Indoor Fogger Scenario)

Figure 3. Environmental Concentration data on Pyrethroids and Other Pesticides from the HUD-CCC Study in Floor Wipe Samples (ng/cm^2; n=167) (Tulve et. al 2006)

compound	% detect	mean	SE	GM
chlorpyrifos	89	0.42	0.21	0.03
trans-permethrin	72	0.30	0.09	0.03
cis-permethrin	72	0.16	0.04	0.03
diazinon	67	0.33	0.24	0.01
cypermethrin	23	0.26	0.09	0.01
piperonyl butoxide	23	0.30	0.16	0.01
malathion	18	0.02	0.003	0.01
diazinon oxon	17	0.01	0.01	0.002
fipronil	8	0.01	0.01	0.005
lambda-cyhalothrin	7	0.02	0.004	0.005
cyfluthrin	7	0.13	0.07	0.01
esfenvalerate	6	0.02	0.01	0.01
bifenthrin	5	0.01	0.002	0.004
trans-mevinphos	5	0.004	<0.001	0.004

(See Poster LTG 2-6)



Development of Physiologically-based pharmacokinetic (PBPK) models of pyrethroids.

The goal of this research is to predict dose metrics of concern for the pyrethroid class of pesticide. In model development, a "family modeling approach" has been applied, recognizing the structural similarities of the pyrethroids in these steps: (1) developing a testable model structure (Figure 4) leading to a generic model structure with chemical specific adjustments as needed; (2) extension of models to other pyrethroids (and humans) via a chemical-class based parallelogram approach (Figure 5); and, (3) decisions on both *in vivo* an *in vitro* experimental design.

Figure 5. Parallelogram Approaches.

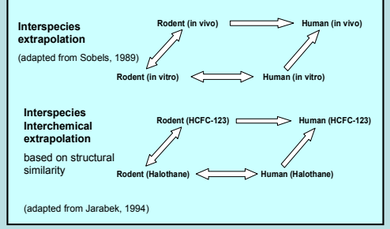
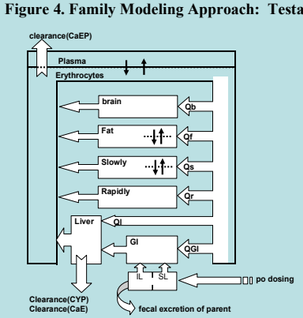
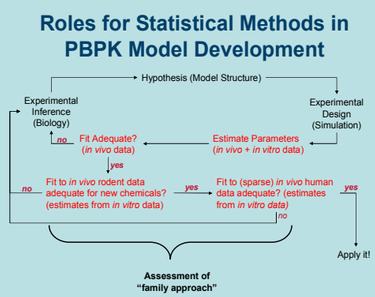


Figure 4. Family Modeling Approach: Testable Model Structure.





Applying Linked Exposure-Dose Models of Pyrethroids

The central figure to the left shows that linked exposure-dose models may be used to predict biomarkers (**1**) such as urinary metabolites. National survey data (e.g., NHANES) and EPA-sponsored studies (e.g., CTEPP) studies provide the necessary data to ground-truth models. Most importantly, linked exposure-dose models may be used to predict tissue-based dose metrics (**2**) and, finally, risk characterization metrics (**3**). Figure 6 shows aggregation of exposure pathways in an annual simulation of permethrin and estimation of brain concentrations (mg/g). Based on the findings of dose-response analyses (LTG 2-6) the appropriate dose-metrics and risk characterization metrics may be computed (e.g., MOE). Bayesian methods are being applied to assess uncertainties in parameter values in the PBPK rodent models. In the linked exposure-dose models, two stage Monte Carlo is ultimately applied to forecast distributions of risk characterization metrics and associated uncertainties (Figure 7).

Figure 6. Annual Aggregation of Oral and Inhalation Routes of Exposure

SHEDS simulation of inhalation and ingestion exposure to permethrin by a 15.6 kg child (**6a**). Exposure events were at 1h intervals, for a total of 8760 exposure events. Figure **6B** shows aggregation of exposure by a PBPK model for permethrin. The y-axis is brain concentration (ug/g), the x-axis is hours. Processing the exposure data took approximately 15 seconds using EPA software R Dynamic on a desktop computer.

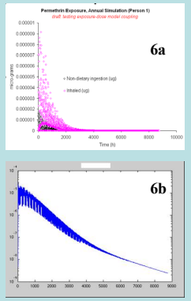
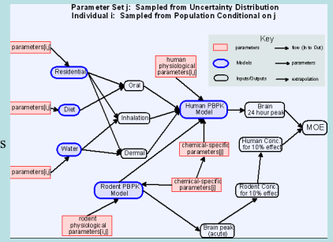


Figure 7. Evaluation of Variability and Uncertainty in Distributions of Risk Metrics

Two-stage Monte Carlo is applied to assess population distributions of risk metrics, where individual (i) has a specific set of parameters (j) which are sampled from the distributions characterizing uncertainty.



Impact and Outcomes

The enhanced science and products of this research will reduce uncertainty in risk assessment/management by providing ORD, OPP, other Agency, academia, and industry exposure and risk assessors with:

- A peer-reviewed probabilistic exposure model for aggregate exposure assessment of pyrethroids
- A peer-reviewed approach for structure-based descriptions of pyrethroid pharmacokinetics
- An established conceptual model for considering cumulative risk assessment for compounds considered in the future.

Future Directions

Much of the pyrethroid-specific work for this project has been completed, and research on this class of chemicals will be declining. The following projects are ongoing or planned for the future:

- Demonstrating the utility of the linked exposure-dose models for permethrin in support of the pyrethroid cumulative risk assessment (2010 FIFRA SAP)
- Demonstrating the robustness of the linked models for assessing cumulative risks for a mixture of three pyrethroids and comparing the predictions against the NHANES biomonitoring data (2011 FIFRA SAP)
- Refining the modeling components
- Improving the model linkage and ease of use
- Improving the fundamental science and demonstrating the predictability of the model outputs
- Improving the statistical and computational power of the models and characterizing the model uncertainty
- Applying the linked models for supporting cumulative risk assessments for other chemicals/classes of compounds

Researchers Involved

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Cumulative Risk