Bayesian Population Analysis of Age-Related Physiologically Based Pharmacokinetic Model of Pyrethroids in Rats

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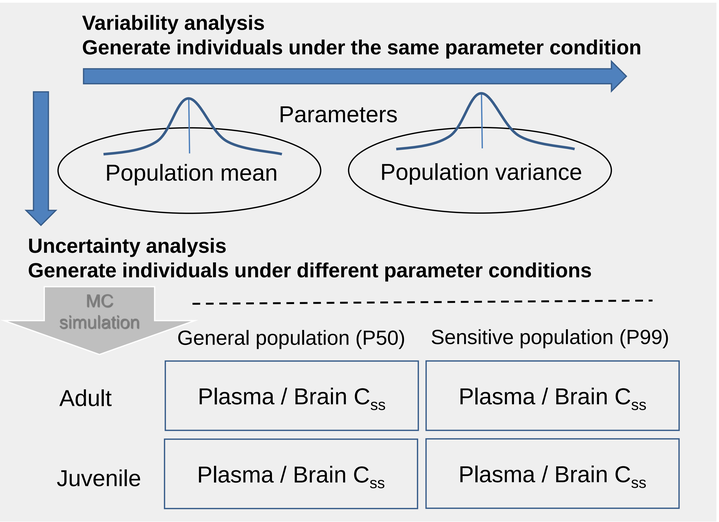
MOTIVATION

- In chemical risk assessment, there is a challenge to quantify **population variability** and understand the exposure risk for potentially **sensitive individuals or populations** [1].
- To address this issue, this study applied **Bayesian** population modeling [2], an advanced statistical approach that can enhance the performance of physiologically based pharmacokinetic (PBPK) models for assessing the exposure risk of pyrethroid insecticides in potentially sensitive populations and compare with general populations.
- Through this approach, we aim to identify the **different exposure levels between and within the age groups**.

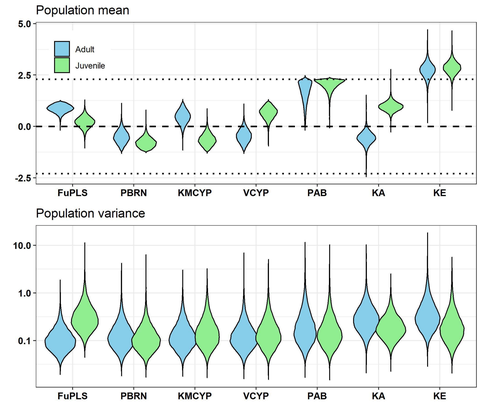
DATA, MODEL, AND WORKFLOW

1. The original data and rat PBPK model were sourced from Gina et al. [3], which includes the time-concentration data (**plasma** & **brain**) for **adult** (PND90) and **juvenile** (PND15) male Sprague Dawley rats under the three **oral** exposure levels of three representative pyrethroids (deltamethrin, cis-permethrin, and trans-permethrin).
2. Identifying the **influential parameters** in the PBPK model through global sensitivity analysis to reduce the computational burden [4].
3. Using the Markov chain Monte Carlo (MCMC) approach yielded estimates of parameter **uncertainty** and **variability** among experimental groups under different given doses in the pyrethroids' toxicokinetics.
4. Predicting the **steady-state plasma and brain peak concentrations** through the joint posterior distributions.



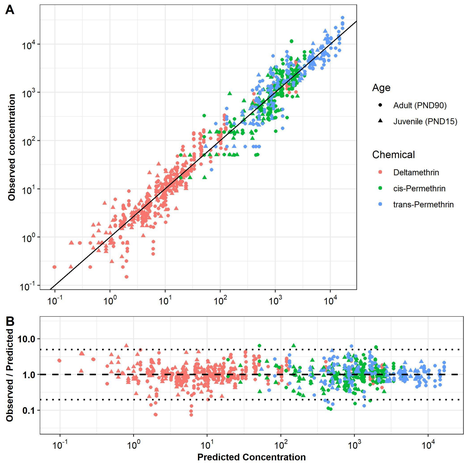
RESULTS

Posterior Distribution

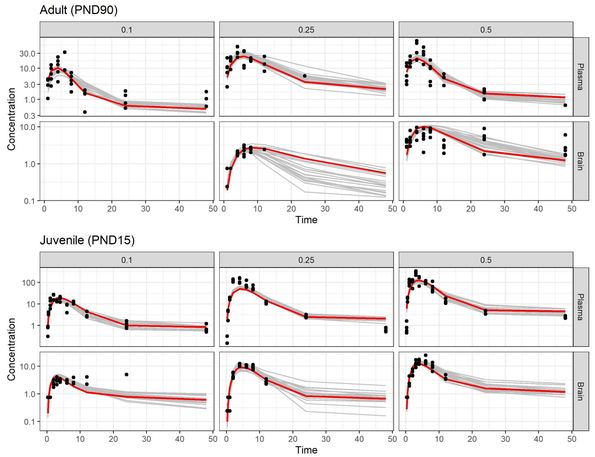


Violin plots of posterior parameter distributions of population means and variances. The dashed line represents the central estimate of the default value. The dotted lines are the boundaries of 10x difference from the default. FuPLS, fraction unbound in plasma; PBRN, brain partition coefficient; KMCYP & VCYP, Michaelis constant and maximum rate for metabolism by liver CYP; PAB, brain permeability; KA, uptake rate; KE, fecal excretion rate. Only show deltamethrin result as an example.

Evaluating the Fit of the PBPK model

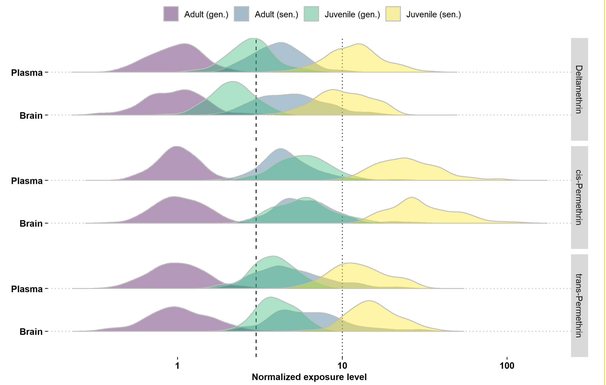


(A) Observed data values vs. maximum posterior model predictions for all experimental data sets.
(B) The relative error estimates show the model goodness-of-fit. Dotted lines represent the 5x difference between observed and predicted values.



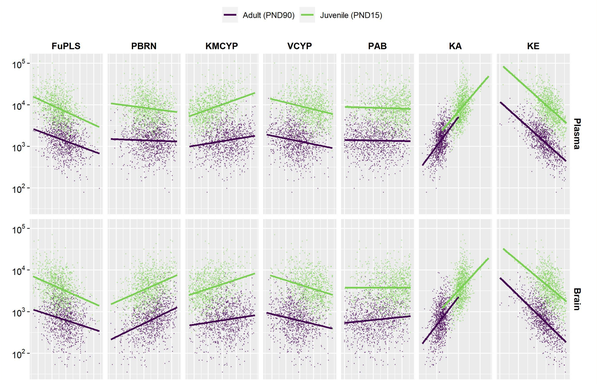
Posterior fitted result of the concentration of plasma (ng/ml) & brain (ng/g) from PND 90 and PND15 rats. The concentrations were simulated over a period of 2 days. Red line represents the maximum posterior predictions. Grey line represents 20 random posterior fits. Only the deltamethrin result are shown as an example. The given doses were 0.1, 0.25, 0.5 mg/kg.

Inference for cumulative exposure level



Estimates of the steady-state plasma and brain peak concentrations (120 days) for four designed subpopulations under the exposure of three representative pyrethroids. The exposure was based on the external point of departure of 1.5 and 44.4 mg/kg/day for deltamethrin and permethrin from Wolansky et al. [5]. All concentrations were normalized based on the medium concentration in the general adult populations. The dashed and dotted lines are the boundaries of 3x and 10x differences from the median of the general adult population, respectively.

Influential factor & Model Sensitivity



Posterior simulation draws the steady-state peak concentration (120 days). The scatter plots show the relationship between model parameters and the steady-state peak concentration for cis-Permethrin, which had a higher exposure difference between the adult and juvenile populations. The correlation slope reflects the impact of each parameter. The result shows that all parameters can make contributions. However, the absorption rate (KA) is the most influential parameter that significantly determines the final cumulative level.

SUMMARY

- The current study demonstrates the application of Bayesian population workflow in age-related PBPK modeling. The difference between general and sensitive populations can also be quantified through this approach.
- Different pyrethroid active ingredients might cause different cumulative exposure levels across age groups. It is necessary to conduct a further risk assessment for the potential exposure to additional pyrethroids.
- The **absorption** was found to be the most influential factor that causes the high cumulative level in the early age group. Generally, the immature age-group had high ability in absorption than the adult.

REFERENCES

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[2] Bois, Frédéric Y., Masoud Jamei, and Harvey J. Clewell. "PBPK modelling of inter-individual variability in the pharmacokinetics of environmental chemicals." *Toxicology* 278.3 (2010): 256-267.
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[4] Hsieh, Nan-Hung, et al. "Applying a global sensitivity analysis workflow to improve the computational efficiencies in physiologically-based pharmacokinetic modeling." *Frontiers in pharmacology* 9 (2018): 588.
[5] Wolansky, M. J., C. Gennings, and K. M. Crofton. "Relative potencies for acute effects of pyrethroids on motor function in rats." *Toxicological Sciences* 89.1 (2006): 271-277.