Applying Uncertainty Analysis to a Risk Assessment for the Pesticide Permethrin

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research&development

Science Question

ORD is engaged in a collaboration across labs (NHEERL, NERL, NCCT) in consultation with the Agency's Office of Pesticide Programs (OPP) to develop *coupled* models for exposure (Stochastic Human Exposure and Dose Simulation – SHEDS – exposure model), dose (PBPK models) and effect (dose-response models based on measured and inferred internal dose) to inform the Agency's pyrethroid cumulative risk assessment. Critical questions for the larger model are initially being answered for the pyrethroid pesticide permethrin:

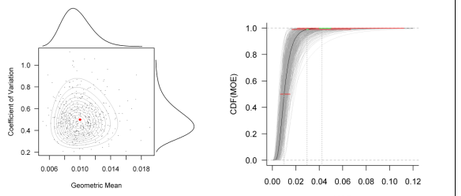
- How to efficiently couple the output of SHEDS to the PBPK model?
- How to evaluate the uncertainty in PBPK model predictions?
- How to efficiently characterize and communicate the uncertainty in the predictions of the coupled model?
- How to identify the important sources of uncertainty?

Research Goals

- Develop software implementation of PBPK model and file formats for transferring exposure simulations from SHEDS, allowing loose coupling of the two sub-models.
- Estimate a baseline for computation times for PBPK uncertainty runs to estimate uncertainty and variability.
- Compute Bayesian posteriors for permethrin model parameters and informative priors for chemical-specific parameters.
- Quantify the uncertainty of animal to human PBPK extrapolation.
- Develop uncertainty analysis for coupled exposure-dose model for an example dose-metric (say, 24-hour peak brain permethrin concentration) for subset of proposed exposure scenarios.
- Develop quantitative sensitivity analysis approaches to quantify relative importance of different sources of uncertainty to overall uncertainty.

Methods/Approach

Motivation

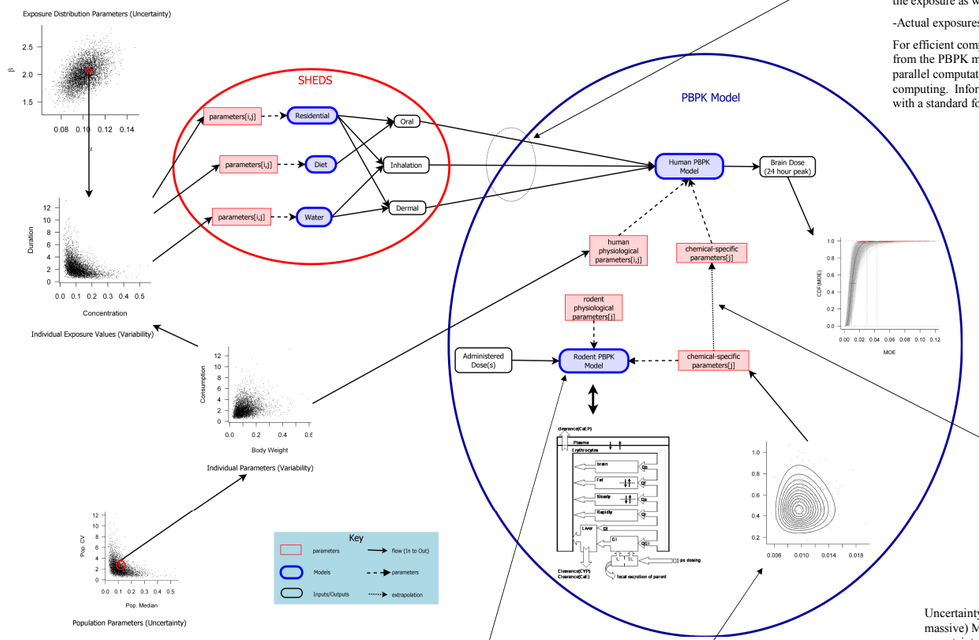


The problem this project addresses is akin to this simple example. We want to estimate the distribution of doses to critical subsegments of the population (say, children), for a given exposure scenario (say, the current pattern of use of a pesticide on food crops and for residential pest treatment). For sake of the example, suppose we can characterize this distribution with a lognormal distribution, depending on its median and coefficient of variation (CV).

Even a modest amount of uncertainty in parameter values can have a large impact on uncertainty of extreme quantiles. The solid curve in the right figure represents the empirical distribution function of 10000 subjects sampled from a log-normal distribution with median 0.1 and CV 0.5 (represented by the larger red point on the left. Horizontal green bars mark 95% confidence intervals for the 50, 99, and 99.9 percentiles in the right figure.

Now, what happens when you are uncertain about the parameters for the lognormal distribution? Suppose the uncertainty is characterized by a CV of 20% for the median and 30% for the CV. The black points in the left figure represent a sample of 500 from such a distribution (centered on the nominal values), and the gray curves in the right figure plot corresponding distribution functions for 10000 samples for each realized parameter value. Horizontal red bars show the extent of the same quantiles as before.

Integrating Models for Risk Assessment



Coupling of SHEDS to PBPK model. The PBPK model needs two sets of information:

-Characteristics of the person being exposed, which may affect the exposure as well as physiology

-Actual exposures and durations for each route of exposure

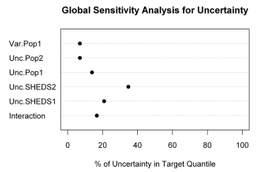
For efficient computation, we separate the SHEDS computations from the PBPK model computations. This allows embarrassingly parallel computations, making full use of EPA's cluster computing. Information is passed from SHEDS to PBPK via files with a standard format.

Uncertainty analysis for coupled model. Depends on uncertainties in exposure parameters, PBPK model parameters, and *rodent to human extrapolation (in the "parallelogram approach" in risk assessment)*. We estimate the uncertainty here by quantitatively evaluating the success of conventional approaches to animal to human extrapolation (e.g., body weight scaling, direct extrapolation of partition coefficients).

Uncertainty analysis involves simple (but massive) Monte Carlo sampling from uncertainty distributions, and projecting the resulting uncertainty in the distribution of the target dose metric. We have developed a core structure for translating a PBPK model into compiled code to be run in the statistical language R, which runs efficiently on multiple platforms (*Milestone: R package 'RDynamic', in part*).

Bayesian computation of posteriors for rodent parameters for PBPK model informs uncertainty in *model* and *rodent-specific parameters*.

Milestone: Parameter estimates and model comparison for permethrin.



Global sensitivity analysis, focusing on the effect of the variances for uncertainty and variability distributions, provides an estimate of the relative importance of different sources of variability and uncertainty and their interactions, on the overall uncertainty of the distribution of the target dose metric.
Milestone: Uncertainty analysis and global sensitivity analysis for permethrin.

Results/Conclusions

Projected – work in progress:
-prediction of the population distribution of the dose-metric, with confidence intervals
-characterization of the contribution to the overall uncertainty (which is quantified by the confidence intervals) which is due to various sources of uncertainty (e.g., uncertainty about exposure parameters, extrapolation, PBPK model parameters)
-Ultimately, use in the Agency's cumulative risk assessment for the pyrethroid pesticides.

Impact and Outcomes

- Incorporation into the Agency's cumulative risk assessment for pyrethroid pesticides, which will be used to inform reregistration decisions.
-Better characterization of uncertainty of the internal dose, allowing more refined risk management decisions (a better sense of what is a 'conservative' choice).
-Characterization of the critical contributors to overall uncertainty, including uncertainty in internal dosimetry, so future studies can efficiently reduce the overall uncertainty.
-Science Advisory Panel (SAP) Review, late July, 2009.
-SAP Review of a mini-cumulative assessment, mid 2010.

Future Directions

-Similar assessment of uncertainty in cumulative model (multiple pyrethroids)
Milestones: Estimation of PBPK parameters for deltamethrin and other pyrethroids; SAP review of cumulative assessment for pyrethroids.
- Add effects model, using rodent PBPK model to infer rodent dose-metric and extrapolating rodent potency to human potency, strict dose-additivity at the level of internal dose.
- Generalize methods for other dynamic models, such as vLiver, vEmbryo.
Milestones: Planning and execution of uncertainty analysis for vLiver and vEmbryo.