Urinary Biomarker Data Analysis and Study Design for Children Along the U.S.- Mexico Border

Start Date: 9/2004 **Completion Date: 9/2007**

Project Purpose:

The purpose of this study is to estimate the absorbed dose of pesticides for children along the U.S.-Mexico border. Urine samples have been previously collected and analyzed for pesticide metabolites. The analysis of the urine data will incorporate mathematical models of pesticide absorption, distribution, metabolism and excretion (ADME) with questionnaire and environmental measurement data. This study will provide 1) estimates of absorbed pesticide doses, 2) identification of probable exposure scenarios and associated activities, 3) computational tools for analysis of urinary metabolite data, and 4) recommendations for the design of future field studies, including those for the population along the U.S.-Mexico border.

Background:

Concentrations of pesticides or their metabolites in urine are evidence of past exposure to pesticides. A challenge in field studies is the quantification of the relationship of the measurement to an absorbed dose – the amount of chemical that passed through the tissue barriers associated with the lung, skin, and digestive tract. Uncertainty exists about the exposure scenarios and the timing relative to urine collection, and these issues are compounded by personal variability in absorption, metabolism, and excretion rates. Analysis of urinary biomarker data with dynamic models enables the estimation of the absorbed dose and reconstruction of possible exposure scenarios. Physiologically-based pharmacokinetic (PBPK) models simulate the urine metabolite concentrations over time based on the magnitude and timing of chemical absorption, and this information can be compared with activity models and environmental measurements to establish probable exposure scenarios. The absorbed dose estimates can be compared to known risk metrics for the pesticides of interest, and the analysis of exposure scenarios can be used to optimize the design of future studies

Project Description:

In this research, techniques will be developed and refined to incorporate questionnaires, environmental measurements, and urinary biomarker data in a unified analysis. Mathematical models of pesticide ADME, such as physiologically-based pharmacokinetic (PBPK) models, are able to include the diverse data that have been collected for children along the U.S.-Mexico border. Comprehensive pesticide PBPK models will be developed in the EPA's Exposure Related Dose Estimation Model (ERDEM) platform (http://www.epa.gov/heasdweb/erdem/erdem.htm), analyzed, and appropriately simplified to obtain the solutions for various exposure scenarios. Plausible exposure scenarios will be constructed based on questionnaire results and environmental measurements, and estimates of the absorbed dose will be made from comparisons to the biomarker data. Uncertainty analysis of the model and scenarios will illustrate the most important measurements to collect, questions to include, and optimal times to collect urine for the design of future studies.

The specific pesticide models will be identified based on the analyzed metabolites in urine and environmental pesticide measurements. The comprehensive PBPK models will be evaluated against existing laboratory and clinical data. Although the laboratory and clinical subjects are not children, the PBPK model framework allows for animal-to-child or adult-to-child extrapolations of the model parameters based on known physiological and biochemical differences. In the absence of such knowledge, default assumptions of body-weight scaling will be applied. The

model assumptions and evaluation data will be documented for review.

A major assumption in estimation of absorbed dose from a urinary biomarker measurement is the exposure scenario: the timing and magnitude of the absorbed dose(s). The questionnaires and environmental measurements will be analyzed to develop probable exposure scenarios for each subject for a particular pesticide. The expected timing of the absorbed dose for each scenario will be used as a constraint for the PBPK model, and the magnitude of the absorbed dose will be established from the urinary biomarker measurements. The plausibility of the simulated scenario will be established on comparing the absorbed dose estimated by the PBPK model to the dose estimated by exposure models and corresponding environmental measurements.

Uncertainty analysis of the models and absorbed dose estimates will focus on the following questions:
1) Are the uncertainties in the PBPK models limited enough to provide a meaningful range of absorbed dose estimates? Note that this is specific to each chemical.
2) What additional questions or measurements would reduce the uncertainty in the absorbed dose estimate?
3) For urinary concentrations without plausible exposure scenarios, what questions or measurements were missing to capture the event(s)?

The PBPK model-based analysis also provides additional metrics on the health status of the population. Included metrics for each subject and exposure scenario are the following: total absorbed dose corresponding to the urinary biomarker measurement, peak concentrations and area-under-the-curve of parent chemical or toxic metabolite in tissues of interest (dependent on mechanism of action), and maximum degree of cholinesterase inhibition associated with the hypothesized exposure.

Expected Outcomes
The interpretation of urinary biomarker measurements is important for the monitoring of the population along the U.S.-Mexico border, as well as in future field studies. The PBPK model-based analyses will identify the activities associated with elevated pesticide exposure, which provides the basis for education and appropriate intervention programs. The methods for urinary biomarker analysis will also be available for future monitoring of the population along the U.S.-Mexico border, as well as for other field studies.

The results and methods will be communicated through the following products:
1) Journal article: Absorbed pesticide dose associated with urine biomarker measurements for children along the U.S.-Mexico border
2) Journal article: PBPK model-based analysis of urinary biomarker data

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