Characterizing Risks of Chemicals Exhibiting Extensive Low Dose Clearance in the Gut, Liver, and Blood: Dietary Chlorpyrifos as a Case Example

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This project uses a case study to demonstrate the potential for coupling physiologically based pharmacokinetic and pharmacodynamic models with human exposure models to characterize risks of noncancer effects. These coupled models create a single "source to effect" model that allows the inclusion of data on the metabolic mode of action determinants in the risk assessment process. This approach eliminates the need for uncertainty factors and will more accurately predict the potential for noncarcinogenic effects than current risk assessment approaches.

This case study is an assessment of effects from dietary exposures of chlorpyrifos. The project builds on recent advances in modeling exposure and interindividual variation in metabolism of the compound in the gut and the liver. The project will quantitatively model 1) uncertainty from extrapolation across species; 2) inter-individual variation in exposure preferences, metabolism, and physiology; and 3) the uncertainty in characterizing effects in children. The result of the study will be a prediction of the occurrence of non-adverse effects in adults and children in the general U.S. population resulting from dietary exposures. Finally, the effort will predict variation in blood levels of chlorpyrifos that can be compared to biomonitoring data.

While the case study is based on a pesticide that has a specific mechanism of action, the major focus of this effort is the modeling of low-dose "first pass" metabolism in the gut, liver, and blood, and the implications of such metabolism on the risk of adverse effects. Such metabolism is relevant to a wide range of compounds.

Implications: This project will demonstrate how to integrate state-of-the-science exposure, physiologically based pharmacokinetic, and pharmacodynamic models. Although many advances have been made in each of these modeling areas, and each type of model has been used in the risk assessment process, no one has linked the three types of models together to make quantitative predictions of the frequency of specific adverse effects in human populations. This project will demonstrate how models can be integrated to predict risk directly and provide an example of how the application of more scientifically advanced risk assessment methods can improve the risk assessment process.

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Presentations:

Hinderliter, P.M, Price, P.S., Schnelle, K.D., Timchalk, C., and Poet, T.S. (2009). Improving risk assessment from dietary exposures by modeling variation and uncertainty in exposure and dose-response using linked exposure and PBPK/PD models. Poster presented at the Annual Meeting of the Society of Toxicology, Baltimore, MD, March 16, 2009.

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