Development of a Physiologically Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) Model To Quantitate Biomarkers of Exposure to Organophosphorus Insecticides
Charles Timchalk, Battelle Memorial Institute

The development of a physiologically based pharmacokinetic and pharmacodynamic (PBPK/PD) model to quantitate biomarkers of exposure to organophosphorus insecticides (chlorpyrifos) will be used to assess exposure and biological response during development. Coupling kinetic models with dynamic models allows the assessment of both target tissue dose and target interaction with a pharmacodynamic response. For this model system, cholinesterase inhibition is used as the marker for biological response, and the parent compound or its metabolites serve as the dosimetry marker. Both children and young animals (neonatal rats) are more sensitive to insecticides than are adults. The increased sensitivity may be related to age-dependent differences in the metabolism of the insecticides. The ontogeny of developing enzyme systems are similar in rats and humans; therefore, neonatal rats were used to develop this model. A model system previously developed for chlorpyrifos will be modified using different types of metabolism scaling and enzyme systems to incorporate age-dependent changes into the dynamics. The modeling strategy focuses on quantitating the chlorpyrifos metabolites oxon and trichloropyridinol (TCP); chlorpyrifos is metabolized by cytochrome P450 to the reactive oxon, which inhibits acetylcholinesterase.

A series of experiments in rats involved exposing neonatal rats to two doses (1 mg/kg or 10 mg/kg) of chlorpyrifos, determining kinetics and dynamics in these rats, and fitting experimental data points to the model. Levels of chlorpyrifos in blood at postnatal days 5, 12, and 17 are proportional; a higher concentration was observed in neonates than in adults, which indicated lower rates of chlorpyrifos metabolism in the neonates. Dynamic data show a clear dose response between 1 and 10 mg/kg of chlorpyrifos, with the 1 mg dose resulting in greater inhibition in neonates than in adults. Greater inhibition of cholinesterase is observed in younger animals. The model reasonably simulates age-dependent responses in the rat, although many questions remain. Sensitivity analysis is needed to determine parameters that estimate age-related sensitivity more accurately.

Another goal of this project is to develop noninvasive biomonitoring strategies to measure levels of cholinesterase in saliva. Using classical pharmacological approaches, cholinesterase activity in the presence of inhibitors was measured in the rat brain, plasma, and saliva. Inhibition was observed in the blood and plasma but not in saliva. Further studies suggest that in rat saliva, cholinesterase is mostly butyrlcholinesterase, consistent with what has been reported in humans. Comparing blood to saliva shows a good parallel response, although the magnitude of cholinesterase levels in saliva is significantly less than in blood. This suggests that saliva could be used to measure dosimetry and cholinesterase response; however, quantitation limits may be an issue.

Discussion

A participant asked about plans to develop a fetal rat PBPK/PD model. Dr. Timchalk plans to pursue this and also is working on developing a monkey model system. A participant asked about plans to scale the PBPK/PD model for human fetal development, particularly correlating the brain development in rats with humans. Dr. Timchalk responded that these plans are underway, that a scaling approach would be needed, and that the monkey model might be more relevant and could help with extrapolation.

Biomarkers of Human Exposure to Pesticides Utilizing a New PBPK/PD Model and Kinetic Data on Pesticide Metabolism in Humans
James Olson, The State University of New York at Buffalo

This project aims to develop age- and gender-specific kinetic parameters for the metabolism of model pesticides (parathion and chlorpyrifos) in the liver of humans in various age groups. These parameters will be used in a PBPK/PD model (the Exposure Related Dose Estimating Model [ERDEM]) to estimate individual susceptibilities using biomarkers of susceptibility (paraoxonase and cytochrome P450 genotypes), exposure (urinary

Proceedings

Human Health Symposium—A STAR Progress Review Workshop

October 28-29, 2004
Philadelphia, PA