1048-92-232 **Nicholas S Luke*** (luke.nicholas@epa.gov), 109 T.W. Alexander Drive, Mail Drop B143-01, RTP, NC 27711, and **Michael J DeVito**, **Imran Shah** and **Hisham A El-Masri**. *Development of a Quantitative Model for Nuclear Receptor-Mediated Induction of Xenobiotic Metabolizing Enzymes.*

The pregnane X receptor plays an integral role in the regulation of hepatic metabolism. It has been shown to regulate CYP3A4, which is the most abundant cytochrome P450 in the human liver. With its large and flexible ligand-binding domain, PXR can be activated by an enormous range of relatively small, hydrophobic, exogenous compounds. Upon activation, PXR partners with the retinoid X receptor (RXR) to form a heterodimer. The newly formed heterodimer binds to an appropriate DNA response element, causing increased transcription. This leads to an induction in the level of CYP3A4. These mechanistic steps are included into a biologically-based mathematical model. The quantitative model predicts fold level inductions of CYP3A4 mRNA and protein in response to PXR activation. Model parameter values have been taken from literature when appropriate. Unknown parameter values are estimated by optimizing the model results to published in vivo and in vitro data sets. A sensitivity analysis is performed to evaluate the model structure and identify future data needs which would be critical to revising the model. (Received February 09, 2009)