TITLE: Parameter Sensitivities in a Multiscale model of Acetaminophen Metabolism: from Whole-body to Subcellular Reaction Kinetics.

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ABSTRACT: Multiscale models of biological response to therapeutic and toxic agents link models across a wide range of spatial and temporal scales. Often the mathematical and computational modalities vary between scales, which present issues in parameterizing models and in understanding how changes in parameters at one scale affect responses at other scales. If one or more of the scales includes stochastic components then purely analytic approaches to sensitivity analysis are not possible. We have performed a broad ranging sensitivity analysis of a multiscale model of Acetaminophen (APAP) toxicity that includes models of the whole-body (PBPK), a tissue level multi-cell model of blood flow and APAP uptake from the blood coupled with subcellular reaction kinetic models of phase I and II metabolism of APAP and subsequent recycling of the metabolites back to the multicell and whole body levels. The quality of the model was judged based on the concordance between the predicted blood concentration versus time for APAP and its metabolites compared to human data. Parameter sensitivities were examined by first scanning the large set of parameters (38 total) one at a time. This initial scan suggested parameters that had the largest individual influence on the accuracy of the predicted blood levels. We then proceeded to a randomly sampling approach in which multiple parameters we changed simultaneously. Analysis of these simulations provided information on interactions between parameters at the three modeling scales. The parameter scan results indicated that the model has highly variable sensitivities to model parameters. This information can be used to prioritize wet-lab measurement of parameters. In addition, the parameter sensitivity results may be used as a "first pass" estimation of interindividual variability in APAP pharmacology and toxicity.