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CYTOCHROME P450 ONTOGENY AND DRUG REACTIONS IN CHILDREN

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Administration of prescription drugs to children raises unique issues. Children and adults have functionally different metabolic compositions, which can lead to unexpected reactions. While clinical testing predicts risk in adults, this risk assessment is not sufficient to predict outcome in children, as researchers cannot perform these clinical tests on subjects with pre-adolescent enzyme composition. It is simple, however, to determine the typical enzymatic makeup of a child and, with this data and a knowledge of the enzymes involved in producing toxic metabolites causing adverse drug reactions (ADRs), to predict which drugs will cause ADRs in children. To construct this predictive model, we used data from the Accelrys reaction database to build metabolite trees for specific drugs with documented effects on children. These trees contain all reaction records with a parent metabolite matching our query, and these reaction records point to data for enzyme, isoenzyme, species, and more. We used an in-house reactivity prediction program to assess the most reactive metabolites in the tree and matched these results to external sources to confirm that the search was turning up valid results. Using this, we correctly identified the most reactive metabolites for the anti-convulsants Valproate, and Phenytoin, the sedative Midazolam, and cough medicine Dexamethorphan. With this information demonstrating our method's effectiveness, we set out to restructure how the user interacts with Accelrys. It is packaged as an unformatted collection of raw reaction files, so we parsed these files for all useful information and imported this information to a neo4j graph database. This database allows us to rapidly query over the entire database and filter for the species and isoenzymes of interest, yielding more robust metabolite trees. With further testing and knowledge of enzymatic makeup, targeted queries of this database will be useful in predicting drug reactions as a function of age.