A Data Repository and Visualization Toolbox for Metabolic Pathways and PBPK Parameter Prediction

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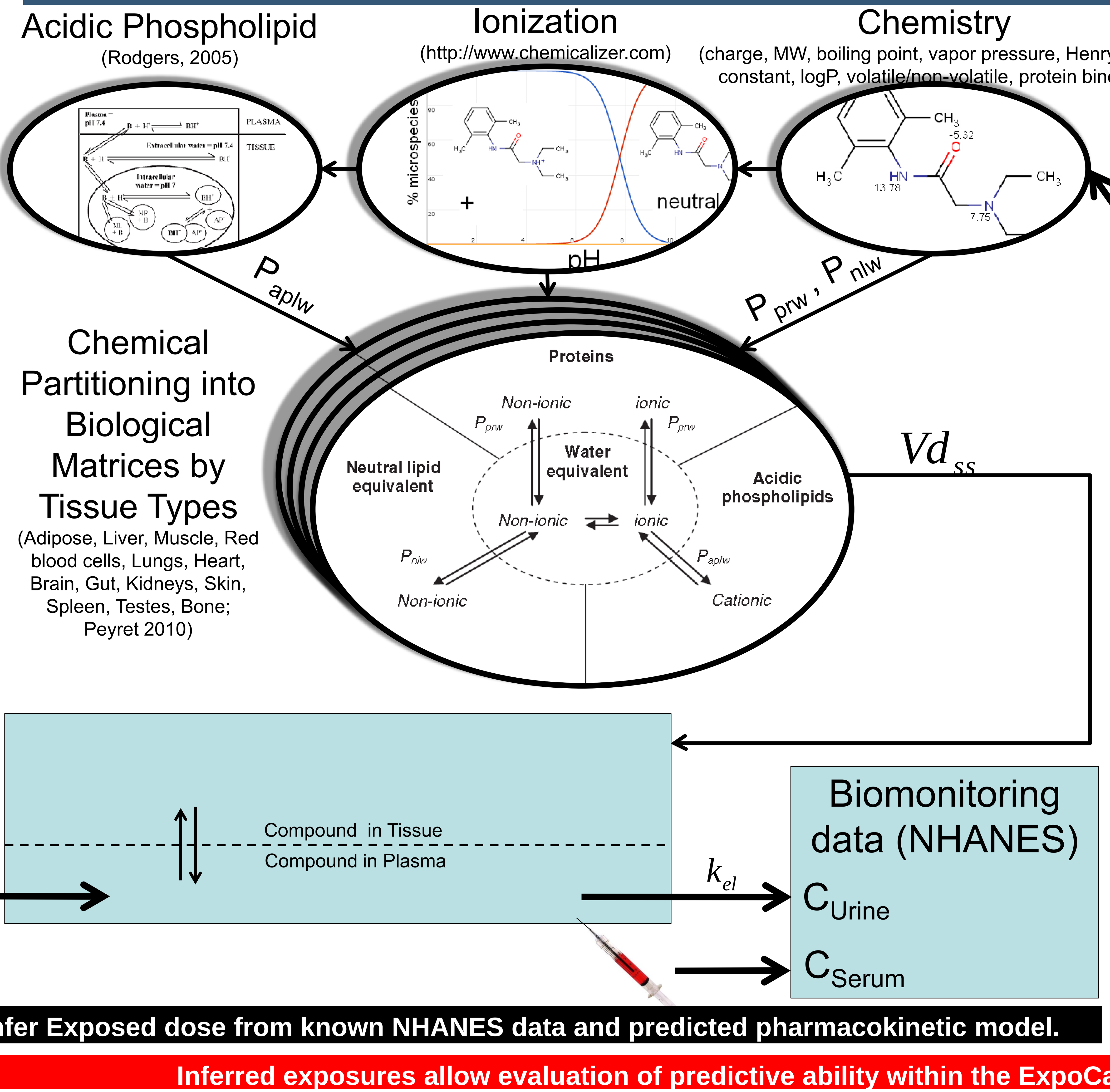
Abstract

NHANES is an extensive, well-structured collection of data about hundreds of chemical products of human metabolism and their concentrations in human biomarkers, which includes parent to product mapping where known. Together, these data can be used to test the efficacy of applications testing chemical exposure/hazard predictions. To help utilize the data in NHANES reports, we have generated a suite of data and tools to act as a companion to the NHANES reports. First, we assembled chemical parent to metabolism product (p2p) mappings, and created a web application for visualizing the p2p. Second, we collected information on all NHANES chemicals and products, including IUPAC name, common name, NHANES name, CAS number(s), SMILES strings, molecular weight, pKa predictions, logP, and pharmacokinetic parameters derived from two general methods for calculating pK tissue partitioning coefficients for a one-compartment pK model (volume of distribution, fraction unbound, and clearance; where possible). Finally, we combined these data into an R package that incorporates the general pK methods and associated algorithms that calculate the fraction of chemical microspecies at each charge state at a particular pH. The collected data is the only publicly available resource for chemical information from the NHANES data, and is a valuable tool for ADME-based chemical exposure inference. The accompanying visualization tool provides further insight into these data, allowing researchers to come up with unique hypotheses for testing. *This abstract does not necessarily reflect EPA policy.*

Model



$$Dose = Vd_{ss} \times C_{matrix}$$

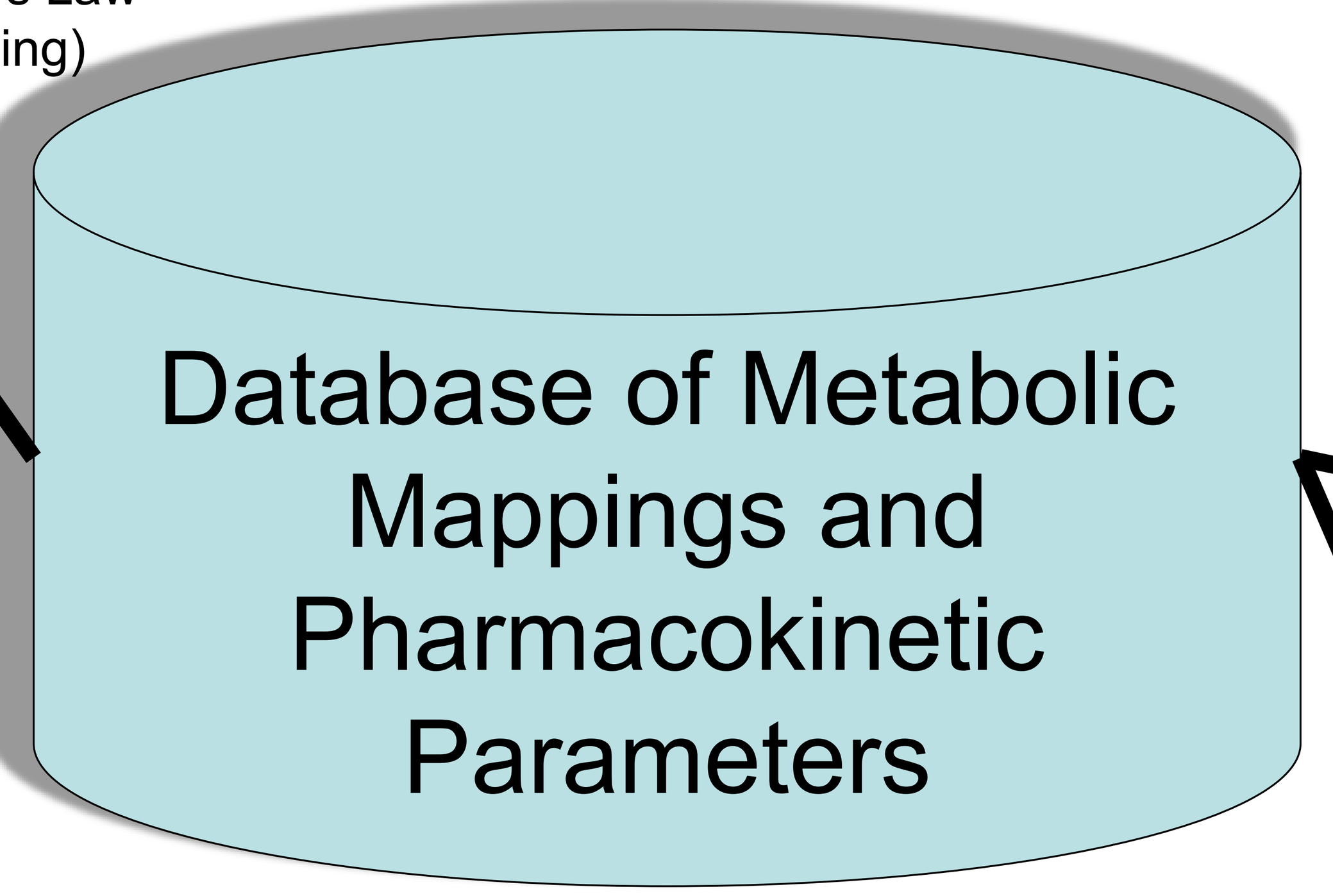
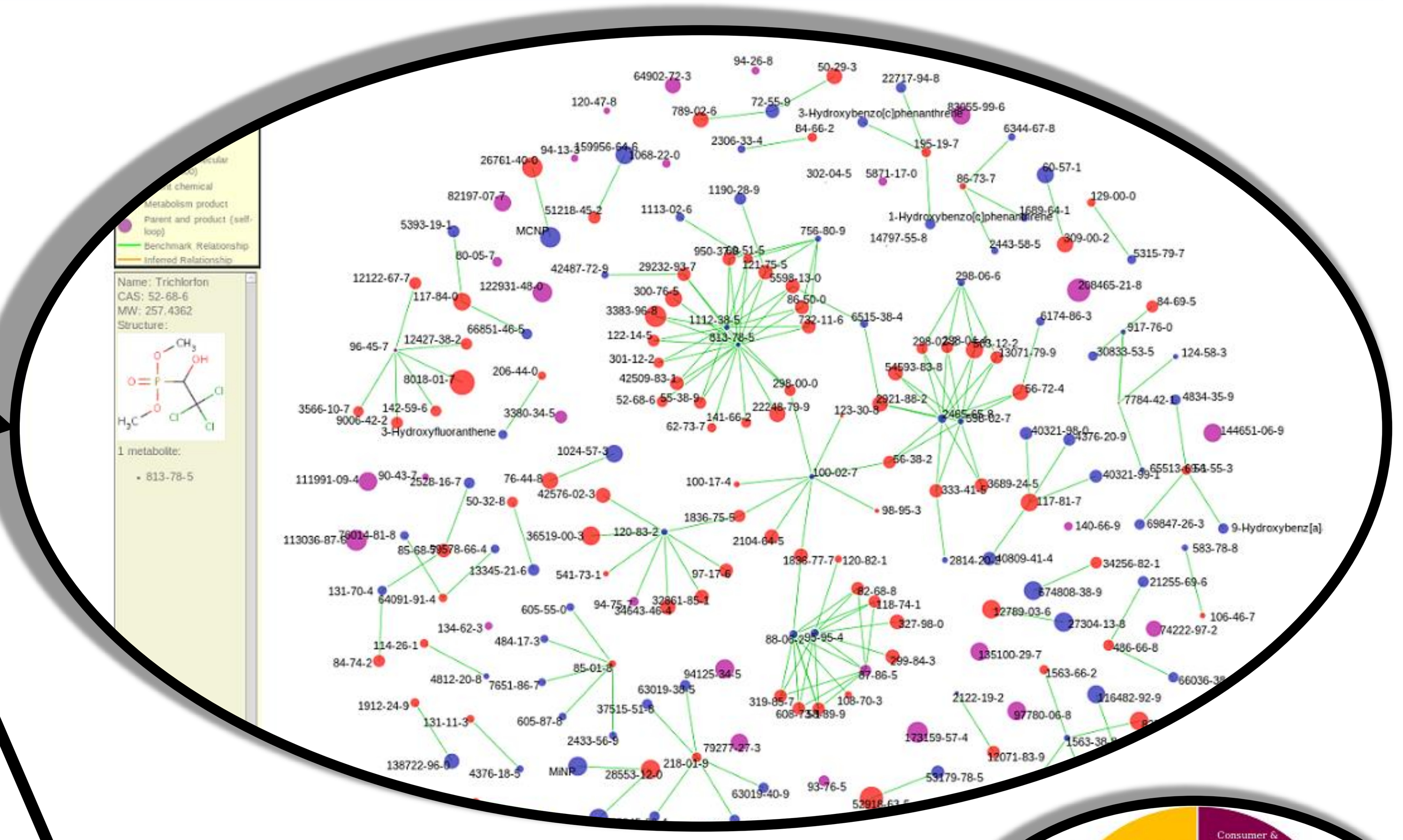


Figure (left): Workflow for inferring exposure from NHANES serum data. *(top)* Parameters for compounds pulled from the database and input into the model for predicting partition coefficients (P). *(bottom)* Ps are input into a one-compartment pK model to predict volume of distribution (Vd_{ss}). Then, given the chemical clearance (k_{el}), infer the exposure to the parent chemical based on the estimated parameters and NHANES metabolite data.



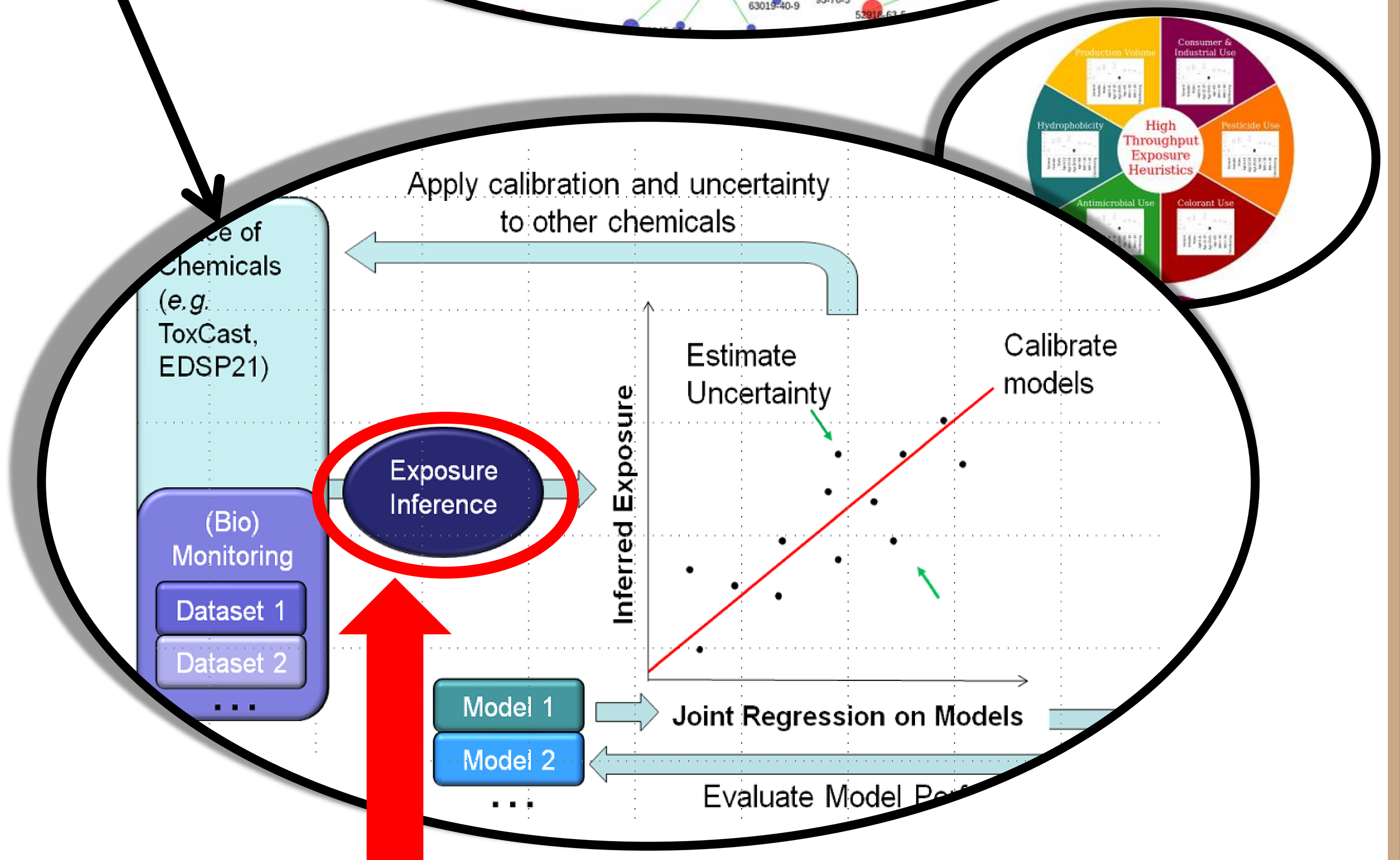


Figure (right): Tools developed that use the information from the database. *(top)* A mapping of the NHANES parent compounds to their associated metabolites. *(bottom)* Workflow of the ExpoCast program for high throughput parent chemical exposure inference. Current direction is being done to incorporate the CPCat use categories of individual chemicals to assist in the parent chemical inference.

Future Work

- Extend model to ToxCast, Tox21, EDSP, and e1K data.
- Use additional metabolism data. Current metabolic data assumes parent chemicals degrade or are metabolized into represented metabolites, causing underpredicted exposure inferences.
- Remove steady state assumption through the incorporation of chemical half-life information dose and clearance.

T Rodgers, D Leahy, and M Rowland. 2005. Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases. *Journal of Pharmaceutical Sciences* **94**:1259-1276.

T Peyret, P Poulin, and K Krishnan. 2010. A unified algorithm for predicting partition coefficients for PBPK modeling of drugs and environmental chemicals. *Toxicology and Applied Pharmacology* **249**:197-207.