Development of a Searchable Metabolite Database and Simulator of Xenobiotic Metabolism

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research&development

Science Question

The Office of Prevention, Pesticides, and Toxic Substances (OPPTS) requires information on the exposure and toxic effects of pesticide metabolites as well as parent chemical. Elucidation of chemical metabolism and formation of reactive intermediates is a major challenge in determining xenobiotic exposure and toxicity for risk assessments. Currently, the Office of Pesticide Programs (OPP) receives metabolic maps with pesticide registrant study data submissions, but there is no efficient method to access previously submitted maps and metabolism data on similar chemicals to aid in the assessment of new chemicals. Information from past studies is used by risk assessors to assess the likelihood that all potentially toxic metabolites have been considered. More efficient use of existing data and development of predictive tools are needed to meet the challenge of resource limitations and aggressive assessment deadlines. Additionally, without efficient access to this data, it is difficult to identify similarities in chemical metabolism and for researchers to formulate and test hypotheses for the types of chemicals that are of highest concern to EPA.

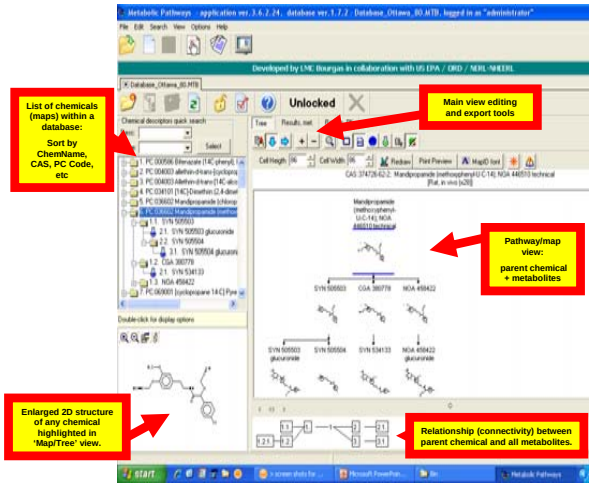
Research Goals

ORD, academic partners, and OPP risk assessors are designing a means to provide structure/text-searchable access to metabolic map information and associated metadata that exists in OPP files and the open literature. Existing data management software (MetaPath) will be enhanced for: the rapid/efficient depiction of metabolic maps; viewing hierarchical connection sequences of parent chemical and metabolites; tracking radiolabel; and searching maps for a specific metabolite or substructure of toxicological concern. Associated bioassay and analytical data are also provided. Software with coded metabolic maps and metadata for pesticides is being tested to identify features and develop evaluation tools needed by OPP risk assessors for efficient recall and analysis of data while providing ORD researchers the tools needed to identify data gaps and target research to reduce uncertainties in risk assessor evaluations of pesticide metabolites. An additional goal is to develop a software template for efficient data entry and to populate the system with newly submitted and archived OPP metabolism study data.
The metabolism database also serves as the foundation of an expert system under development to predict metabolite formation for use by risk assessors and researchers to identify chemicals of concern.

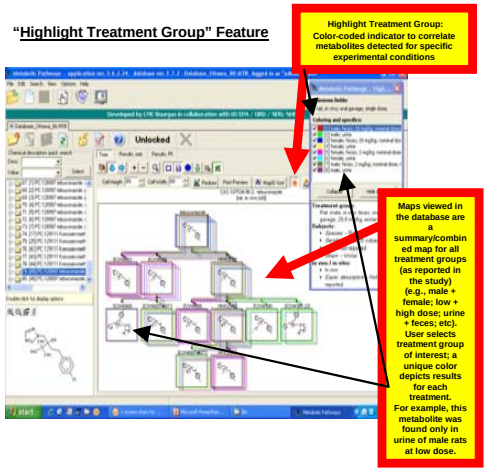
Methods/Approach

Metabolism Database Manager - MetaPath

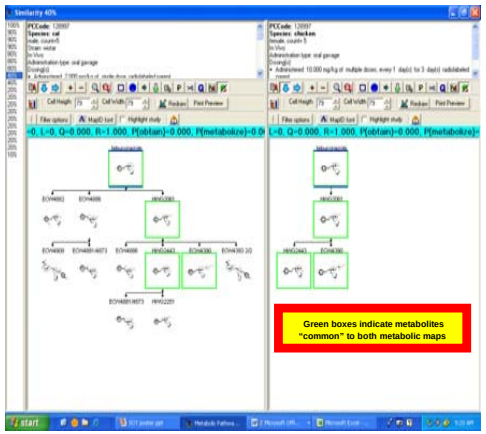
Main display of database software (METAPATH)



"Highlight Treatment Group" Feature



Evaluating metabolism data using "Map Comparison" feature: one map is compared to another



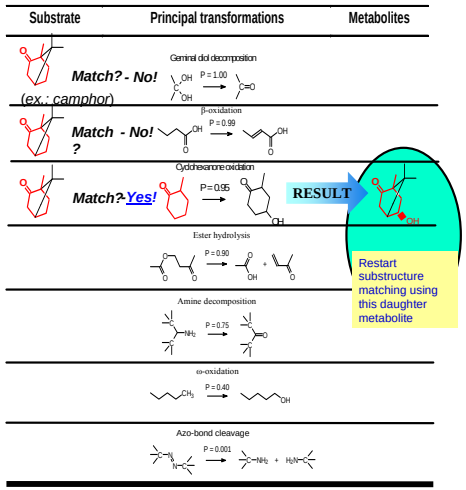
Metabolism Simulator

Metabolic Simulator General Approach

Probabilistic Knowledge-Based Expert System for Forecasting Metabolism of Organic Chemicals

- **Utilizes a library of functional-group transformations targeting a specific system (environment, tissue, etc).**
- **Literature-derived, experimentally determined metabolic maps for diverse chemicals are used for the model training data.**
- **Each functional-group transformation is assigned a "probability" of the reaction occurring. These probabilities are derived based upon how well measured data is simulated.**
- **Most probable transformations are then applied to determine the dominant daughter, granddaughter, great-granddaughter products from a parent compound with an unknown metabolic pathway.**

Substructure matching engine applying a hierarchically ordered list of metabolic transformations (mammalian liver)



*****The current simulator contains a library of > 350 transformation reactions, representing major transformation types including aromatic C-hydroxylation, aliphatic oxidation, arene epoxide formation, oxidative N-dealkylation, dehalogenation, ester and amide hydrolysis, and oxidative dealkylations, to name a few. The training set of data for development of the metabolic simulator consists of >340 metabolic maps of xenobiotic compounds.***

Results/Conclusions

Utility of MetaPath database manager

- Provides a systematic compilation of experimental information on observed metabolites and reaction types in a structure/text-searchable database.
- Provides structure-based accessibility for identifying metabolites and transformations observed under specific testing conditions.
- Identifies differences in metabolic maps traceable to gender, exposure dose, species, etc.
- Identifies similar metabolites/common toxicophores arising from different parent chemicals.
- Identifies metabolites/toxicophores appearing as plant residues helping in the assessment of total toxic residues for risk assessment.
- Assists in the preparation of assessment documents and reports.
- Provides databases of experimentally-determined metabolic maps/pathways for development and improvement of Metabolism Simulators

Impact and Outcomes

This research activity reduces uncertainty in risk assessment by:

- providing access to previously assessed metabolism data in a structure/text-searchable format
- allowing rapid comparisons of metabolic maps from rat metabolism studies with those submitted in food animal residue studies, degradates in soil and water studies, etc
- allowing identification of metabolites common across systems or ones that only occur in certain animals or systems, or under certain experimental conditions.

Future Directions

- Finalize development of the search and data input functions of the metabolism database manager (MetaPath).
- Develop additional XML coding templates for the purpose of simultaneous database population and Data Evaluation Record (DER) production for newly submitted chemicals.
- Systematically populate MetaPath with archived DER metabolism data using XML coding templates to facilitate data transfer and QA.
- Continue development, testing, and validation of metabolic simulators to assess chemical impact on humans and the environment.

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