Development of a Searchable Metabolite Database and Simulator of Xenobiotic Metabolism

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Summary:
A computational tool (MetaPath) has been developed for storage and analysis of metabolic pathways and associated metadata. The system is capable of sophisticated text and chemical structure/substructure searching as well as rapid comparison of metabolites formed across chemicals, species, and/or experimental condition. Using this tool, a metabolism database (metabolic pathways and associated metadata) has been constructed primarily from rat metabolism *in vivo* studies of pesticide chemicals to allow critical analysis and interpretation of data by risk assessors, and to assist researchers in formulating and investigating hypotheses critical to the understanding of metabolic activation. The 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 and tools are needed by the EPA's Office of Prevention, Pesticides, and Toxic Substances (OPPTS) to evaluate and prioritize chemicals for toxicity testing and hazard assessment, and to enhance the interpretation of registrant data that is submitted as part of the regulatory process to improve human health and ecological risk assessments. An often overlooked process, the metabolic activation of chemicals (production of potentially hazardous transformation products from parent chemicals of concern), is considered to be an important factor for assessing risk to the environment and human health. The primary goals of this project are to enhance the ability to interpret metabolism data via development of a metabolism database (mammalian liver) that is searchable by text and chemical structure and additionally to develop an *in silico* capability for reliably forecasting the metabolism of xenobiotic chemicals of EPA concern.

Metabolism data, collected from the peer-reviewed literature and from registrant-submitted data (required for chemical registration/re-registration), has been coded for risk assessor evaluation/use and for development, training and improvement of a metabolic simulator. Metabolic pathway information is electronically stored in MetaPath, a software system allowing sophisticated chemical structure/substructure search queries to identify commonalities and differences in metabolites among chemicals, species, dosing regimes, etc. The system depicts metabolic pathways and provides rapid retrieval of metabolism study information and associated metadata including metabolite quantities where available. The database will be used by OPPTS scientists to increase efficiency of metabolism data access and analysis for performance of risk assessments.

An initial version of a metabolic simulator is under development. The simulator utilizes a library of more than 340 "functional-group" transformations targeting both *in vitro* and *in vivo* mammalian liver metabolism. Literature-derived, experimentally determined metabolic maps for diverse chemicals were used for initial simulator training, with performance of the simulator enhanced by expanding the chemical domain focus on collection of additional metabolism maps for transformations underrepresented in the initial training set. Future research will include linking metabolism predictions with exposure and toxic effects models to enhance prioritization tools for toxicity testing and chemical assessments for large chemical lists of concern. The potential impact of this work is significant as it provides much needed tools to EPA Offices such as OPPTS and the scientific community for evaluating the potential role of metabolism in enhancing or diminishing toxicity. Linkage of these tools with exposure and toxic effects models will assist Agency scientists in prioritizing large chemical lists for further toxicity evaluations, especially for data poor chemicals. These tools will also allow risk assessors to more systematically and efficiently assess the hazard of both parent chemicals and their potentially bioactive metabolites.