Abstract

Development of an *In Silico* Metabolic Simulator and Searchable Metabolism Database for Chemical Risk Assessments

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The US EPA is faced with long lists of chemicals that need to be assessed for hazard, and a gap in evaluating chemical risk is accounting for metabolic activation resulting in increased toxicity. The goals of this project are to develop a capability to predict metabolic maps of xenobiotic chemicals and the most likely formed metabolites. Results will identify metabolites of equal or greater toxicity than the parent chemical. An existing metabolism simulator is being refined by focusing on reactions leading to increased toxicity.

To achieve the goals, metabolism data collected from the peer-reviewed literature as well as from registrant-submitted data required for chemical registration/re-registration will be collected for risk assessor evaluation/use and for training and improvement of the metabolic simulator. Data will be electronically stored, accessed, and visualized using a database manager software under development. The database software is capable of text and chemical structure search functions, depiction of metabolic maps, and provides access via structures to coded metabolism information and associated metadata. The database will be used by US EPA scientists to increase efficiency of metabolism data access and performance of risk assessments. In its simplest mode, the database will furnish curated structures of chemicals/pesticides and their metabolites suitable for searches in other databases and provide metabolic maps plus tabulations of amounts of metabolites and associated metadata. In a more advanced mode, the database will allow the risk assessor to perform searches for specific compounds and toxicophores and identify metabolism commonalities and differences across pesticides and species.

Metabolic simulator performance will be enhanced by collecting chemical metabolism maps from the published literature and EPA Program Office files and determined from *in vitro and in vivo* rat hepatic experiments. Newly acquired maps (and transformations) will be used to re-train the metabolic simulator and improve reliability estimates. Data from these studies are used to improve the metabolic simulator and prioritize chemicals for testing that have the potential to be bioactivated to more toxic species.

Finally, prioritized chemical lists (based upon predicted toxic effects of parent chemical and metabolites) with transformation reliability estimates will be provided to scientists and EPA Program Offices for chemical evaluations (risk assessments) and ranking for toxicity testing. This research will expand the knowledge-base of metabolic pathways and transformation products for important groups of toxic chemicals and demonstrate an approach that integrates metabolism simulation with toxic exposure and effects modeling.