

## Assessing the Exposure-Dose-Toxicity Relationship Within the EPA's ToxCast Program

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The EPA's National Center for Computational Toxicology has initiated a research program called ToxCast, with the intent of improving EPA's chemical toxicity evaluations. This program would develop methods to evaluate a large number of chemicals for potential toxicity and use the information to help prioritize testing of those chemicals that pose the greatest risk. As an adjunct to the ToxCast program, this project was initiated to provide refined exposure-dose-toxicity evaluations that will aid in interpretation of the high-throughput *in vitro* testing results. Such context will be essential for identifying appropriate priorities for follow-up testing and risk evaluation exercises. The project has two parts: (1) assess whether complex, tissue-like *in vitro* systems can predict organ specific toxicity; and (2) develop computational modeling methods that will better estimate the relationship of doses used in the *in vitro* systems to real world exposures.

In the first part of the project, organ slice cultures are being established for rat liver, lung, and kidney. The cultures will be exposed to ToxCast Phase I chemicals in a 5-point dose response, with cytotoxicity measured as the endpoint. The data from these studies will be used to calculate EC<sub>20</sub> (20% effects concentration) values and provide an estimate of organ-specific toxicity in the rat. The second part of the project will be pursued concurrently with the first and will consist of developing the methods and computational infrastructure for the semi-automated physiologically based pharmacokinetic (PBPK) modeling of ToxCast Phase I chemicals. The chemical-specific rate constants and partition coefficients will either be derived from pharmacokinetic data in the literature, or estimated using quantitative structure property relationships (QSPRs). The model structure and associated parameters will be stored in a relational database and computational tools will be developed to interact with the models and perform simulations in a semi-automated workflow. For each chemical, the PBPK model will be used to predict what exposure conditions (i.e., route and dose) would be needed to produce target tissue doses equivalent to the EC<sub>20</sub> values measured in the *in vitro* cytotoxicity experiments. This integration of the two parts of the project will provide estimates of organ-specific toxicity and dosimetry for the ToxCast Phase I chemicals, and serve as a model for evaluating *in vitro* screening data relative to *in vivo* exposures.

**Implications:** Due to reliance on *in vitro* assays without dosimetry and exposure information, the ToxCast program is likely to rapidly identify many hazardous, but possibly irrelevant, properties of chemicals. The primary goal of our research project is to provide refined exposure-dose-toxicity evaluations that will aid in interpretation of the high-throughput *in vitro* testing results in the ToxCast program. Such context will be essential for identifying appropriate priorities for follow-up testing and for risk evaluation exercises. Without these studies, ToxCast could become simply a way to find new hazards and would lack tools for assessing likely risks, if any, expected from these compounds.

**Start and end date:** October 2007 – January 2009

**Presentation(s):** None to date.

**Peer-reviewed publication(s):** None to date.

**Sponsors in addition to the LRI:** None.

**Abstract revision date:** March 2009