The EPA Virtual Liver Project

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The objective of the Virtual Liver (v-Liver) is to provide information for tiered toxicity testing. The project is developing *in silico* decision support tools for analyzing the potential risk of toxic effects from environmental chemicals including, identification of mode of action and characterization of human relevance. These tools leverage available *in vitro* High-Throughput Screening (HTS) and High-Content Screening (HCS) data such as -*omics* data, and public domain sources of biological information to develop computational systems models for predicting toxicity and prioritizing chemicals for further testing. Systems models complement traditional and HTS-based approaches to hazard identification through data-driven mechanistic models of toxicity pathways to enable rapid development of quantitative predictive models that can be used to prioritize chemicals based on the potential for liver toxicity.

The v-Liver is part of a broader EPA effort on Virtual Tissues (VT) aimed at reducing the magnitude and spectrum of animal testing by integrative *in silico* and *in vitro* models, which recapitulate the properties of intact organs. The other VT projects include the Virtual Embryo (v-Embryo) for investigating developmental toxicity and the Virtual Cardio-Pulmonary project. The modular framework of these innovative computational tools can be broadly applied to mining information about signalling and metabolic pathways from literature and databases, a knowledgebase for organizing evidence about 'toxicity pathways', statistical tools to analyze HTS-HCS data, and systems modelling tools to estimate quantitative dose-response.

This talk will present an initial application of the v-Liver tools for step-wise evaluation of 100 environmental chemicals for liver cancer. First, we use public domain biological information to analyze potential toxicity pathways in liver cancer. Second, we include HTS assays from ToxCastTM to analyze how chemicals perturb these pathways based on potency and dosimetry and compare these findings with rodent toxicology data from ToxRefDB. Third, we describe efforts to simulate the dose- and time-dependent perturbations of 22 chemicals on these pathways using a novel systems modelling framework. Fourth, we discuss targeted testing strategies including the development of relevant in vitro models that can be used for HTS, mode of action characterization and determination of human relevance to reduce uncertainties in our predictions. The v-Liver framework aims to integrate these tools into an interactive collaborative workflow that synthesizes expert knowledge, public domain data, HTS and rodent toxicology to address risk assessment goals.