Virtual Liver: Estimating Proliferation and Apoptosis of Hepatocytes Exposed to Environmental Chemicals Using ToxCast™ Data

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The U.S. EPA's ToxCast™ program has screened over a thousand chemicals for potential toxicity using hundreds of high-throughput, *in vitro* assays. The U.S. EPA's Virtual Liver (v-Liver™) is a cellular systems model of hepatic tissues that enables the estimation of *in vivo* effects using *in vitro* data by bridging multiple levels of biological organization. A physiologically-based pharmacokinetic model links environmental exposures to liver dosimetry, while a microdosimetry model simulates the chemical transport through the sinusoids of the hepatic lobule to estimate cell-level concentrations of chemicals and other soluble factors. Finally, an agent-based model of hepatic cells is used to quantitatively estimate cellular decisions – e.g., apoptosis and proliferation – based on the perturbation of an intracellular signaling network by inputs from the microenvironment. Using the literature we reconstructed a putative crosstalk network to mechanistically relate hepatocyte G_1/S progression and apoptosis involving growth factors (e.g., EGF and HGF) and cytokines (e.g., TNFα). Next we related key proteins in this network to a subset of assays in ToxCast including phosphorylation of H2A.X, H3, and c-Jun. We have developed a novel approach for modeling the dynamic response of individual cell-based agents, called Boolean network Ensembles with Asynchronous Threshold Logic (BEATL), to quantitatively estimate the response of hepatocyte populations using *in vitro* data. We used this framework to simulate the concentration dependent perturbations of key signaling molecules in cell proliferation and apoptosis based on ToxCast *in vitro* data for environmental chemicals (e.g., PFOA, Imazalil, Bisphenol A, Triclosan) as well as reference hepatotoxicants (e.g., acetaminophen). The model results were used to evaluate potential changes in hepatocyte fate based on chemical-induced concentration-dependent molecular perturbations. *This abstract does not necessarily reflect U.S. EPA policy.*