**Quantitative simulation of intracellular signaling cascades in a Virtual Liver: estimating dose dependent changes in hepatocellular proliferation and apoptosis**

J Jack[1], M Mennecozzi[2], C Haugh[1], J Wambaugh[1], and I Shah[1]

[1]National Center for Computational Toxicology, US EPA, RTP, NC, United States.

[2]Joint Research Centre, European Commission, Ispra, Italy.

The US EPA Virtual Liver (v-Liver™) is developing an approach to predict dose-dependent hepatotoxicity as an in vivo tissue level response using in vitro data. The v-Liver accomplishes this using an in silico agent-based systems model that dynamically integrates environmental exposure, microdosimetry, and individual cellular responses to simulate the in vivo hepatic lobule. One requirement for the v-Liver models is inclusion of nuclear receptor (NR) pathways critical to nongenotoxic hepatocarcinogenesis. Progress to date has focused on signal transduction networks controlling cell proliferation and apoptosis, which are key events in hepatocarcinogenesis. First, a literature derived knowledgebase was used to reconstruct a biochemical signaling network of cell cycle initiation and caspase-mediated apoptotic signaling events. The network contains 46 proteins and 77 interactions, encompassing pathways relevant to hepatocytes including the epidermal growth factor (EGF) and tumor necrosis factor alpha (TNFα). Second, static analysis of the topology of the crosstalk network revealed key signaling proteins, reducing the overall complexity of the model. Third, the mechanistic model was translated into an asynchronous Boolean network ensemble to simulate the quantitative dose-response of hepatocyte populations to various ligands: growth factors, cytokines, and mitogenic inhibitors. The model predictions are consistent with the synergistic effects of EGF and TNFα on early cell proliferation reported in the literature. Finally, the model was calibrated with ToxCast™ data on environmental compounds, revealing the potential impact of chemical perturbations on normal hepatocyte behavior. This approach of static and dynamic pathway analysis and evaluation using in vitro data provides a foundation for estimating tissue level effects of chemical exposures from the simulation of individual cellular responses. *This abstract does not necessarily reflect US EPA policy*.