VIRTUAL LIVER: AN IN SILICO FRAMEWORK FOR ANALYZING CHEMICAL-INDUCED HEPATOTOXICITY

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The US EPA Virtual Liver (v-LiverTM) is an in silico framework for the dose-dependent perturbation of normal hepatic functions by chemicals using in vitro data. The framework consists of a computable knowledge-base (KB) to infer putative pathways in hepatotoxicity and a cellular systems model to predict the dose-dependent effects of chemicals. We have synthesized diverse evidence about thousands of effects for 650 chemicals in the KB from ToxRefDB, DSSTox, -omics data and the literature using public terminologies (e.g. GeneOntology, Foundational Model of Anatomy, Mouse Pathology Ontology, etc.). Using the KB we related ToxCastTM in vitro bioactivity assay data on 68 rodent hepatotoxicants (e.g. PFOA, Imazalil, Bisphenol A, Triclosan, Acetaminophen, Phenobarbital, WY-14643) to a putative network of events resulting in hepatocyte necrosis, apoptosis and proliferation, which were mediated by constitutive androstane receptor, aryl hydrocarbon receptor, pregnane X receptor, and peroxisome proliferatoractivated receptors. In order to estimate the in vivo effects of these chemicals we encoded this network in a dynamic cell-agent based model that integrates micro-dosimetry, intracellular signaling and cell-cell interactions across the spatial extent of the hepatic lobule to predict histopathologic outcomes. We used experimental data on DNA synthesis following exposure to normal levels of growth factors and cytokines (e.g. Insulin, EGF and TNF-α) to calibrate the dynamics of cell cycle progression through S-phase. Next we used in vitro data (e.g. nuclear receptor activation, oxidative stress and c-Jun activation) to estimate key parameters required for simulating the dose- and time-dependent effects of 20 chemicals on hepatocyte proliferation, apoptosis and necrosis. We are using the v-Liver framework to analyze alternative mitogenic and cytotoxic pathways involved in non-genotoxic cancer.

Abstract does not represent EPA policy.