Simulation of Chronic Liver Injury Due to Environmental Chemicals

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US EPA Virtual Liver (v-Liver™) is a cellular systems model of hepatic tissues to predict the effects of chronic exposure to chemicals. Tens of thousands of chemicals are currently in commerce and hundreds more are introduced every year. Few of these chemicals have been adequately assessed for risk to human health. We use both *in vitro* and *in vivo* datasets coupled with *in silico* modeling to: (i) relate the environmental exposures of an individual to cell-scale concentrations in the liver, and (ii) model the key molecular, cellular and tissue-level consequences pertaining to injury. As a proof of concept we examine long-term consequences of human exposure to nongenotoxic rodent carcinogens.

We couple a virtual hepatic lobule – a spatially extended agent-based model coupled to a graphical model of sinusoidal blood flow – to a model of whole body circulation. These models allow investigation of human hepatic effects following exposure (*e.g.*, oral, inhalation) by simulating cell-level dosimetry and individual agent (cellular) responses, as well as the cumulative effects of thousands of interacting agents as they adapt to perturbations. We find that spatial heterogeneity within the liver (*e.g.* centrilobular necrosis) depends on cellular function and is not strictly a consequence of geometry.

To model injury we have curated evidence about basal liver functions and chemical-induced changes from the literature into a machine-readable knowledgebase (KB). We use the KB and *in vitro* data to design, calibrate and evaluate simulations of key pathways involved in cellular response to chemical stimulation. We have developed discrete models for putative molecular interaction networks involving growth factors and nuclear receptors..

v-Liver provides a platform for integrating multiple types of data and is designed as a predictive tool for examining the link between chemical perturbations and human liver toxicity.

EPA reviewed this work but it does not necessarily reflect official Agency policy.