

## **The Virtual Liver Project: Simulating Tissue Injury through Molecular and Cellular Processes.**

Efficiently and humanely testing the safety of thousands of environmental chemicals is a challenge. The US EPA Virtual Liver Project (v-Liver™) is aimed at simulating the effects of environmental chemicals computationally in order to estimate the risk of toxic outcomes in humans. Adverse tissue level responses are simulated through a biologically-based model of the interplay between dynamic molecular and cellular processes perturbed by environmental chemicals. To capture these multilevel processes a 2D representation of the complex liver acinus (~1 mm diameter) is developed at a cellular resolution. Parenchymal and non-parenchymal cells are represented as autonomous “agents” that are spatially organized according to the acinar morphology in a nutrient and xenobiotic gradient established by blood flow. The project is initially focusing on nuclear receptor-mediated carcinogenesis to investigate the relevance of neoplastic liver lesions in rodents to humans. Background knowledge and experimental data are used to model agent behaviour under stress including, cell injury, repair, death and proliferation. We are investigating the impact of xenobiotic stress on agent-level decisions that give rise to emergent tissue-level responses most related to histologic lesions. Generating relevant data for calibrating and evaluating models is a challenge as measurements are required at multiple biological levels including, global molecular assays, High Content Screening (HCS) / cellular function assays and tissue lesions. To address this issue we are exploring the utility of *in vitro* data generated by the US EPA ToxCast™ project to model cellular responses and their relevance to *in vivo* toxicity. If successful, the Virtual Liver will aid in extrapolating *in vitro* cellular responses quantitatively to *in vivo* clinical outcomes. These predictions can be used to select targeted confirmatory studies in a tiered toxicity testing paradigm for new environmental chemicals.

*This work has been reviewed by EPA and approved for presentation but does not necessarily reflect Agency views.*