Simulating Microdosimetry of Environmental Chemicals for EPA's Virtual Liver

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US EPA Virtual Liver (v-Liver™) is a cellular systems model of hepatic tissues aimed at predicting chemical-induced adverse effects through agent-based modeling. A primary objective of the project is to extrapolate *in vitro* data to *in vivo* outcomes. Agent-based approaches to tissue modeling assume that each constituent cell is an independent system reacting to the microenvironment. For this reason, quantitatively estimating the local nutrient and xenobiotic levels for cells is a prerequisite for modeling the dynamics of cellular responses across microanatomic structures. We model a spatially-extended hepatic lobule connected to a physiologically-based pharmacokinetic (PBPK) model in order to link whole-body exposure through diet or inhalation with cell-scale chemical exposure. We demonstrate that this approach is both efficient for simulating long-term exposure, and flexible, allowing development of detailed models of cellular dynamics. We find that for a simulated compound with minimal metabolism that the average concentration across the simulated lobule is very similar to the predictions for a homogenous, or well-mixed, liver compartment. As the rate of metabolism is increased, however, fluctuations in local concentration arise indicating that cellular function, but not geometry alone, can generate spatial inhomogeniety. When evaluated with a simple threshold model for hepatotoxicity we observe that results can potentially be different in a spatially-extended lobule than would be predicted for a homogenous lobule. By relating environmental exposure to cell-driven fluctuations across a hepatic lobule we have produced a useful tool for virtual tissues in general. *EPA reviewed this work but it does not necessarily reflect official Agency policy.*