Chemical Selection Via *In Vitro-In Vivo* Correlation of ToxCast and ToxRefDB Data to Evaluate the Virtual Liver

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The Virtual Liver Project (v-Liver^{TM}) is a US EPA effort to simulate the function of the human liver with sufficient accuracy to predict how environmental exposure to xenobiotic compounds will perturb homeostasis. The better we understand the liver, the better we will understand the toxicity of many chemicals. Most metabolism occurs in the liver, including the first-pass of most everything that enters through the digestive tract before it moves on to the rest of the body. Our aim is to use an agent-based approach in which each liver cell is represented by an independent realization of a dynamic model of cellular function, *i.e.* agents, that change state in response to chemical and inter-cellular signals. Chemical-specific *in vitro* assay results can be used to determine the inputs to the intra-cellular and chemical distribution models. These simulated cells are arranged in either *in vitro* or *in vivo* configurations, supporting inference of *in vivo* consequences from cell-based assay results. In order to characterize the range of chemical attributes that must be captured and evaluate the usefulness of predictions made by the model, we are selecting chemicals with a range of permutations of known mouse or rat *in vivo* tumorigenicity for model development. We have identified chemicals in four broad categories for specific evaluation: chemicals that caused tumors in rats and mice which were active for ToxCast assays related to RAR, PPAR, LXR, FXR, ER, CAR, AR, PXR, and AhR; mouse-specific tumor-causing compounds that showed activity in all but RXR and LXR assays; rat-specific tumor-causing compounds that showed activity in PXR, CAR, and PPAR assays; and non-tumor-causing compounds with little activity across the assays examined. In the proof of concept we would like to predict non-genotoxic lesion progression for mouse and rat for chemicals from each of these classes.