## Application of an *in silico* liver model to determine nuclear receptor mediated pathways in liver cancer

I Shah[1] , DC Wolf[2], K Houck[1], R Judson[1], J Jack[1], J Wambaugh[1], M Martin[1] and C Corton[2]
[1]National Center for Computational Toxicology (NCCT), US EPA, RTP, NC, USA.
[2]National Health and Environmental Effects Lab (NHEERL), US EPA, RTP, NC, USA.

Nuclear receptors (NRs) are ligand-activated transcription factors that control diverse cellular processes. Chronic stimulation of some NRs in rodents can result in increased incidence of liver tumors. These are generally thought to develop through a non-genotoxic mechanism with unclear relevance to humans. Human CAR, PXR, PPARα, LXR, ER, AR and AhR activity assays were performed on 309 environmental chemicals, mostly pesticidal actives, through the ToxCast™ program. Liver histopathology data from chronic rodent studies on 171 chemicals were collected using ToxRefDB. 141 chemicals activated multiple human NRs in combinations that correlated with rodent liver lesions of increasing severity leading to neoplasms. Cellular pathways regulated by NRs led to altered hepatocellular phenotypes. To determine if these findings can be extrapolated to humans, we further examined a subset of 20 ToxCast™ chemicals and mined the literature to determine the cellular pathways regulated by NRs that lead to altered hepatocellular phenotypes and histpathologic lesions. This was accomplished through an integrated experimental and computational effort that generated quantitative data on molecular and cellular endpoints. The establishment of the Virtual Liver Knowledgebase (vLiverKB™) will enable the development of a systems model of NR-mediated hepatic effects that can provide screening level information on the potential for an adverse hepatic outcome through activation of a NR-dependent mode of action.



2606