**Comparison of Models of Hepatic Lobules at Varying Levels of Detail**

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Normal liver function and xenobiotics-induced liver damage often show zonal patterns. The local dose of both endogenous and exogenous compounds can vary spatially within the liver due to both compound-dependent factors (e.g., diffusion, transport and metabolism) and compound-independent factors (e.g., the complex hepatocyte-sinusoid architecture and heterogeneous blood flow rates).

In this study, we develop mechanistic models to identify possible spatial patterns of simulated hepatic exposure to compounds and investigate how the interplay between spatial and compound dependent factors can give rise to alternative hepatic exposures. The degree of variation in localized intra-hepatic exposures may guide the selection of a coarser (e.g., a simple model with a single “well-stirred” compartment) versus a more complex model with detailed vasculature architecture and blood flow representations based on estimates of factors such as the rate of uptake and metabolism of the compound of interest. We examine three representative architectures for the liver lobule. (1) A simple single well-stirred compartment model similar to standard PBPK representations of the liver. (2) A linear sinusoidal blood vessel lined with hepatocytes and (3) a multi-cell virtual liver lobule composed of hepatocytes, complex microvasculature and hydrodynamic simulation of blood flow. For each of the three models we simulated active and passive transport of compound at the hepatocyte-sinusoid interface and metabolism of the compound within individual hepatocytes, or for the first model the single hepatocyte compartment.

We found that interactions between passive (diffusive) transport, transporter-mediated active transport and metabolism, in the context of a complex liver sinusoid architecture and blood flow distribution, leads to three basic patterns of hepatic exposure within the virtual liver lobule: lobular-wise uniform, radially varying and both radially and azimuthally varying. We propose to use these emergent patterns of exposure as a reference for selection of the most suitable model representation for a particular compound based on compound-specific estimates of passive and active transport and metabolism. In some cases, models of type 1 are adequate to represent the liver compartment and more complex simulations (models of type 2 or 3) do not provide additional information. In other cases models of type 1 are incapable of reproducing the complex local microdosimetry that may be critical in understanding both metabolism in, and toxicity to, the liver.