

# Evaluating the Influence of Environmental Chemicals on the Regulation of Genes Governing the Pharmacokinetics of Morphine in the Human Liver

Dohyun Kim, Katherine Otersen, Moriah Anthony, Tingying Xie, Luigi Brunetti  
Rutgers, The State University of New Jersey

Over 70% of morphine is metabolized in the liver by the UDP-glucuronosyltransferase 2B7 (UGT2B7) to form glucuronide conjugates, which are excreted into bile via efflux transporters, Multidrug Resistance Protein 1 (MDR1) and Multidrug Resistance-associated Protein 2 (MRP2). The uptake transporter Organic Cation Transporter 1 (OCT1) facilitates morphine entry into the liver. Perfluorooctanoic acid (PFOA), a widespread environmental contaminant found in human serum at concentrations up to 12  $\mu\text{M}$  in the U.S., inhibits HNF4 $\alpha$  and activates NRF2 signaling, leading to downregulation of UGT2B7 and OCT1, and upregulation of MDR1 and MRP2. This study aimed to quantify changes in expression of UGT enzymes and drug transporters in HUH7 human hepatoma cells after exposure to PFOA. Cells were exposed to 12 concentrations of PFOA (0.1–100  $\mu\text{M}$ ) for 24, 48, and 72 hours to identify the impact of dose and duration of exposure on cell viability using CCK8 assay. These data were then used to identify the optimal dose and exposure for quantitative PCR studies focused on mRNA expression of UGT2B7, OCT1, MDR1, and MRP2. At both acute and chronic exposure to the selected PFOA doses consistent with reported human serum concentrations, no significant reduction in cell viability was observed. We expect a time-dependent downregulation of UGT2B7 and OCT1, and an upregulation of MDR1 and MRP2 at physiologically relevant PFOA levels. These findings will improve our understanding of how PFAS chemicals interfere with hepatic clearance of morphine and may support the use of PFOA exposure levels as a potential biomarker for personalized drug dosing. Supported by the Rutgers School of Graduate Studies and Ernest Mario School of Pharmacy..

