



Figure S4

The incorporation of tolerance development improved the goodness of fit to the observed plasma citrulline profiles after multiple doses of irinotecan to rats. The observed and model simulated plasma citrulline concentration-time profiles were plotted after multiple administrations of irinotecan (25 mg/kg in BIW and 7.2 mg/kg in QD) in rats by the system toxicology model A) with tolerance development or B) without it. In each panel, symbols, error bars and lines represent the mean observed data (n=3), standard deviation and the model predicted population mean, respectively. The purple and orange arrows on the x-axis represent dose timing.