A biologically based model to quantitatively assess the role of the nuclear receptors liver X (LXR), and pregnane X (PXR) on chemically induced hepatic steatosis

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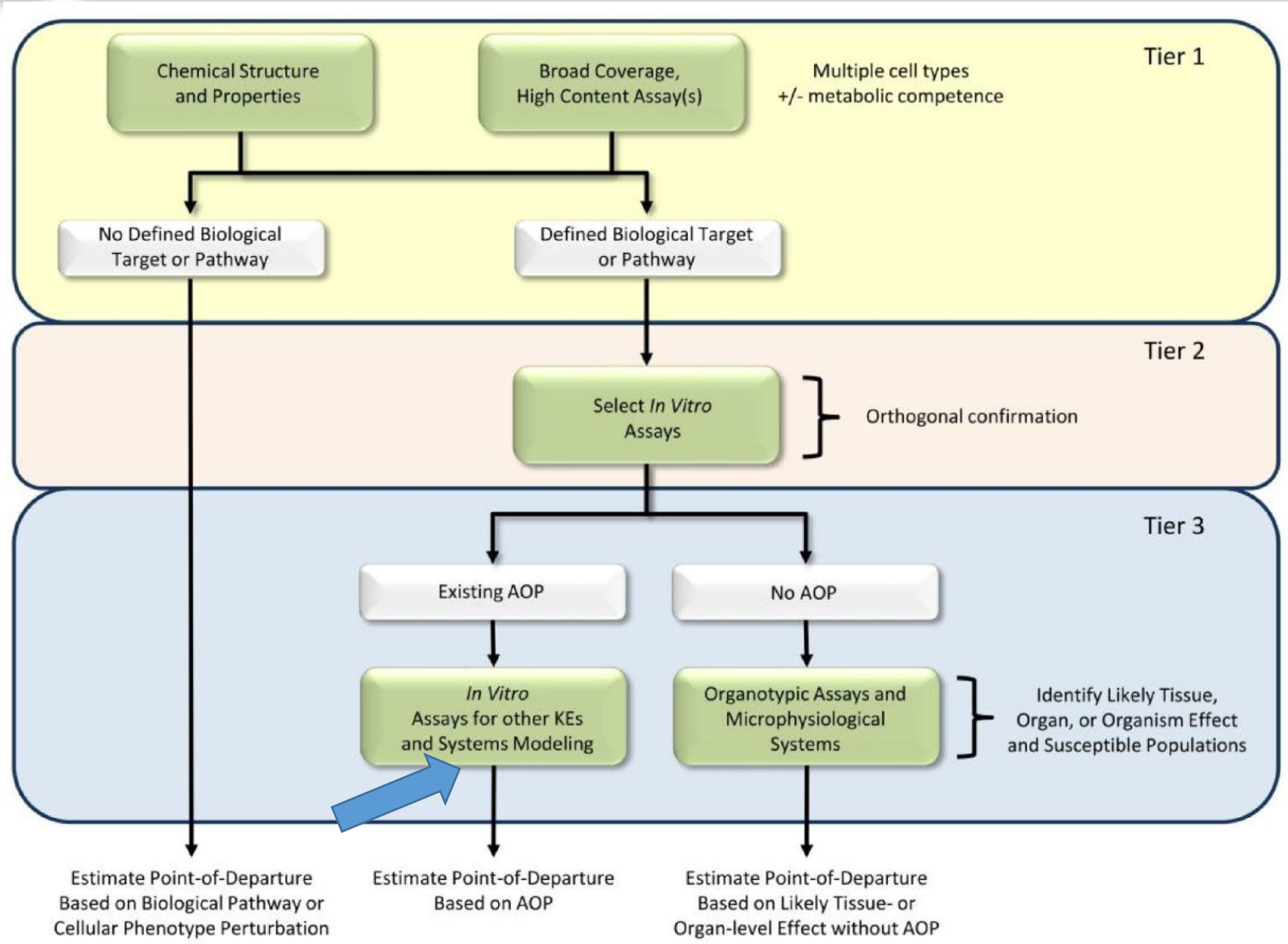
The Next Generation Blueprint of Computational Toxicology. *Thomas et al. 2019*



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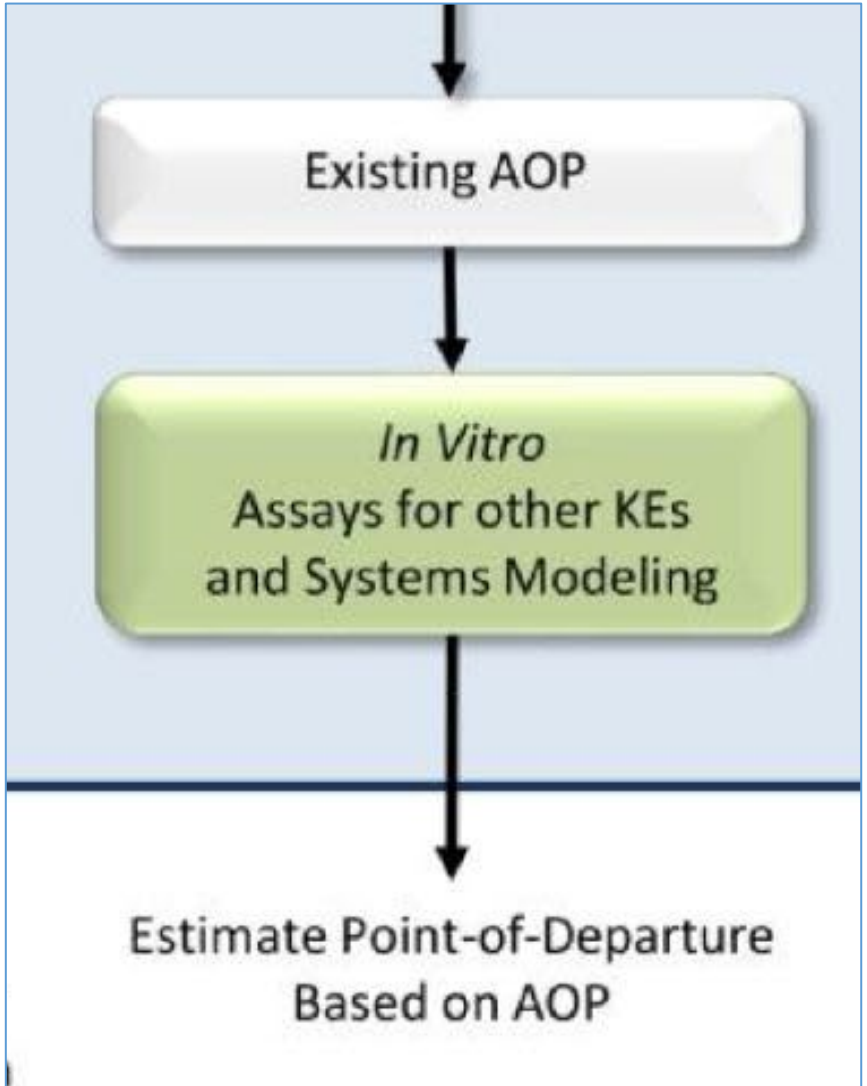
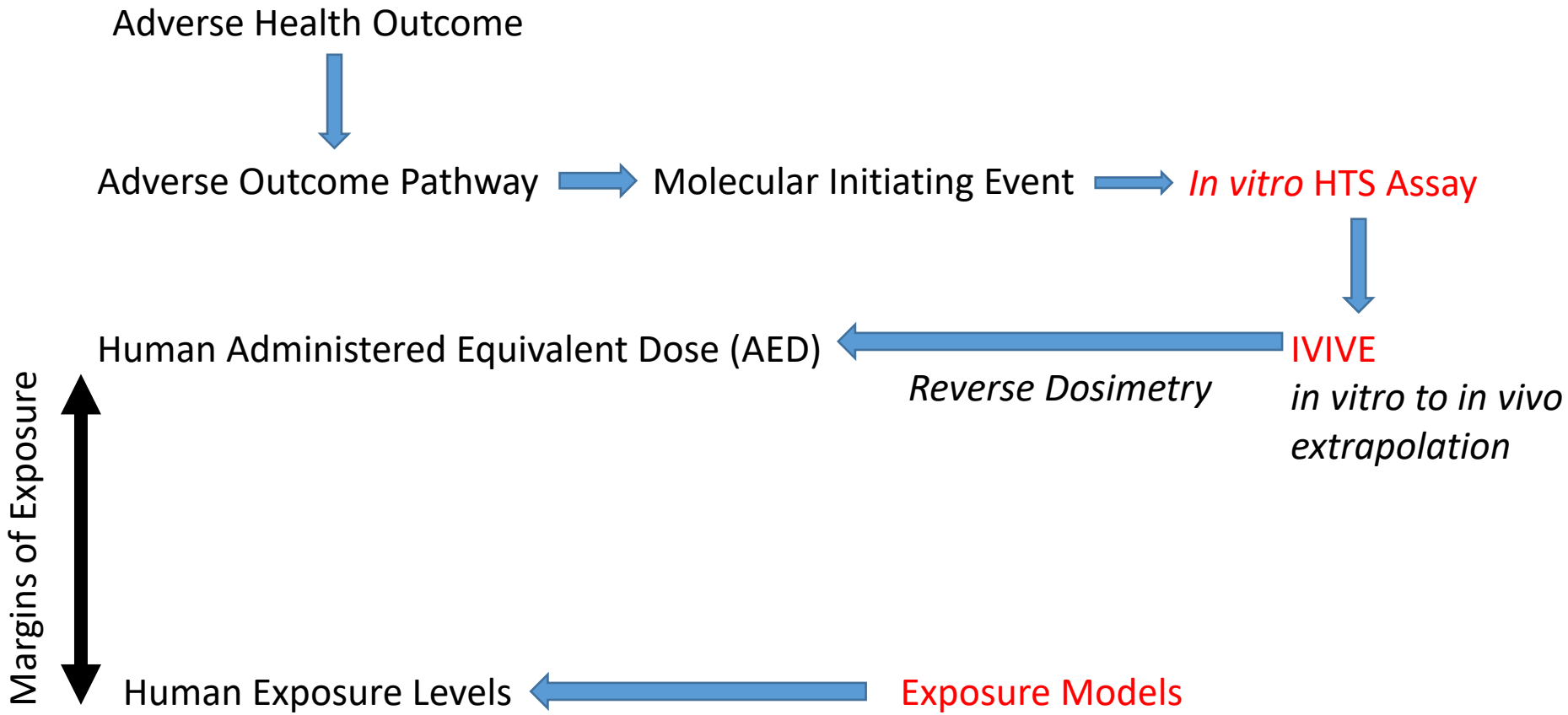


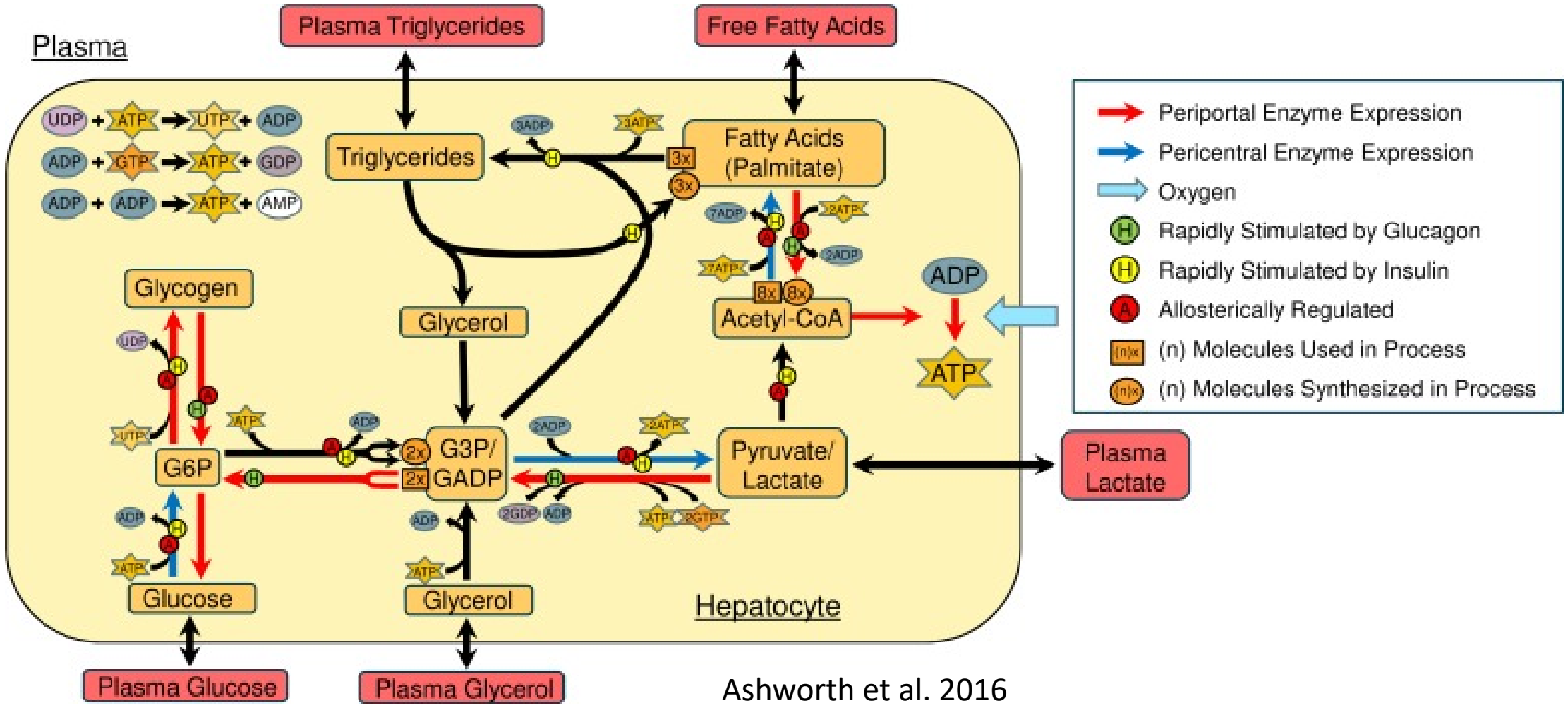
Estimation of AOP-Based Margin of Exposures



Hepatic Fatty Acid Accumulation

- Fatty liver disease affects 20 %–30 % of the population.
- Hepatic steatosis is characterized by intracellular increase of free fatty acids (triglycerides).
  - Contributors include alcohol and environmental chemicals.
- Non-alcoholic fatty liver disease (NAFLD) is defined by fat accumulation to >5% of the liver weight
- Mechanisms of lipid accumulation include *de novo* synthesis (glucose) and transport from blood (fat tissue)

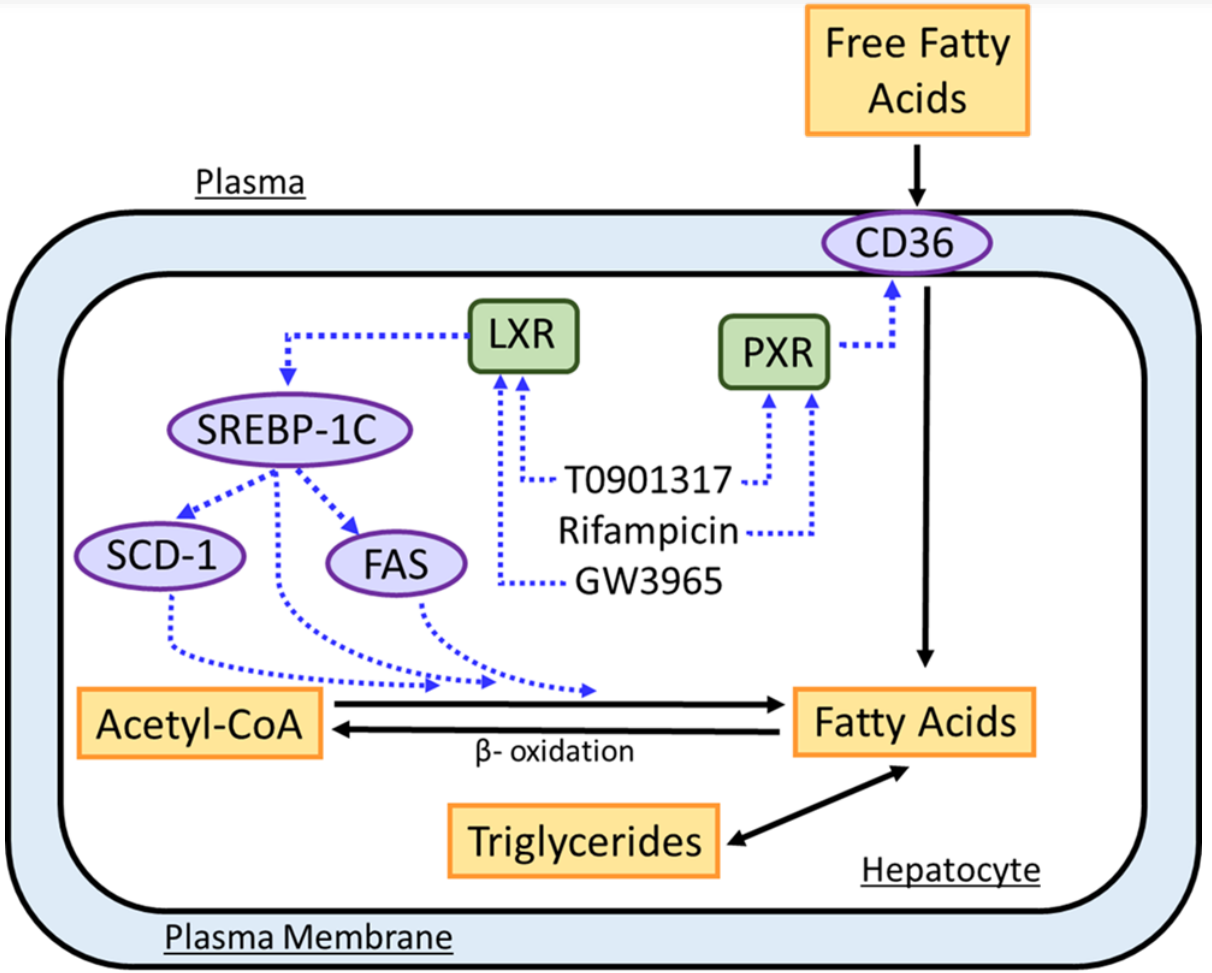
Hepatic Steatosis Mechanisms and Model



Ashworth et al. 2016
PLoS Comput Biol. 2016 Sep; 12(9): e1005105.
Published online 2016 Sep 15. doi:10.1371/journal.pcbi.1005105

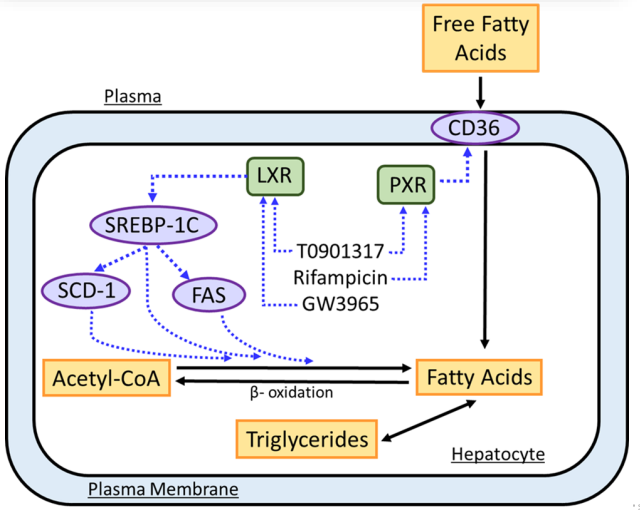
Nuclear Receptors

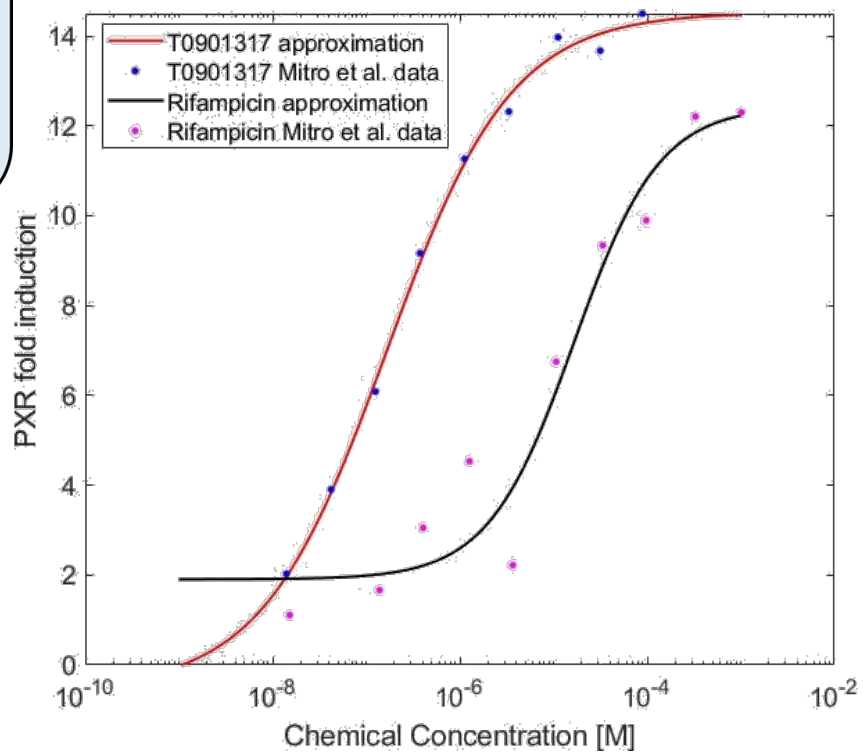
- Nuclear receptors are related to synthesis of hepatic free fatty acids (FFAs) and their liver uptake.
- Synthesis and uptake are mediated through the liver X (LXR) and pregnane X (PXR) receptors, respectively.

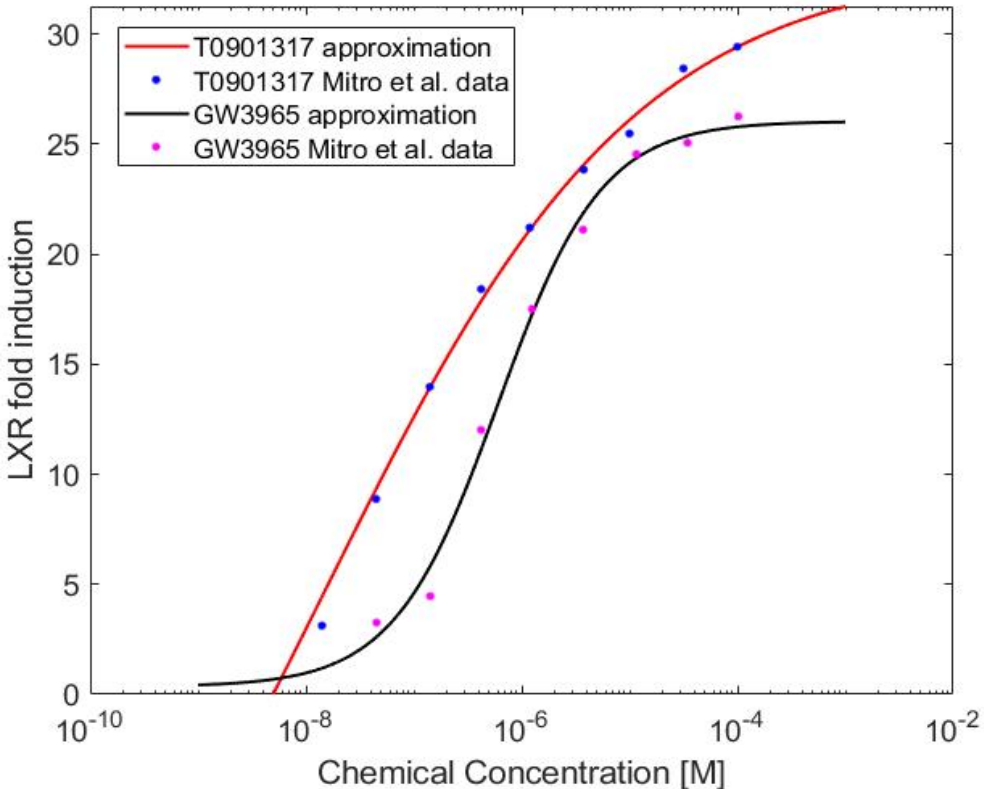


T0901317-LXR/PXR
GW3965-LXR
Rifampicin-PXR

Model Development and Parametrization







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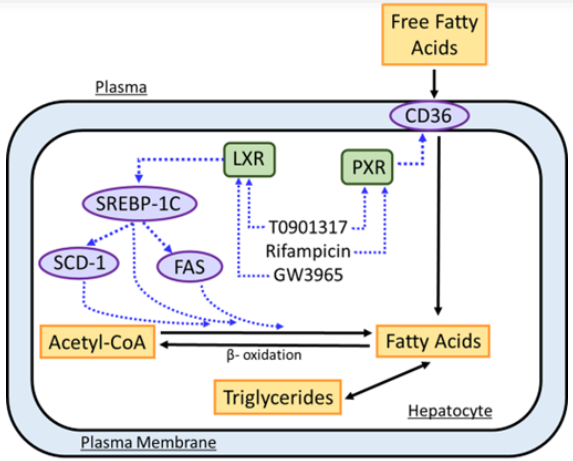
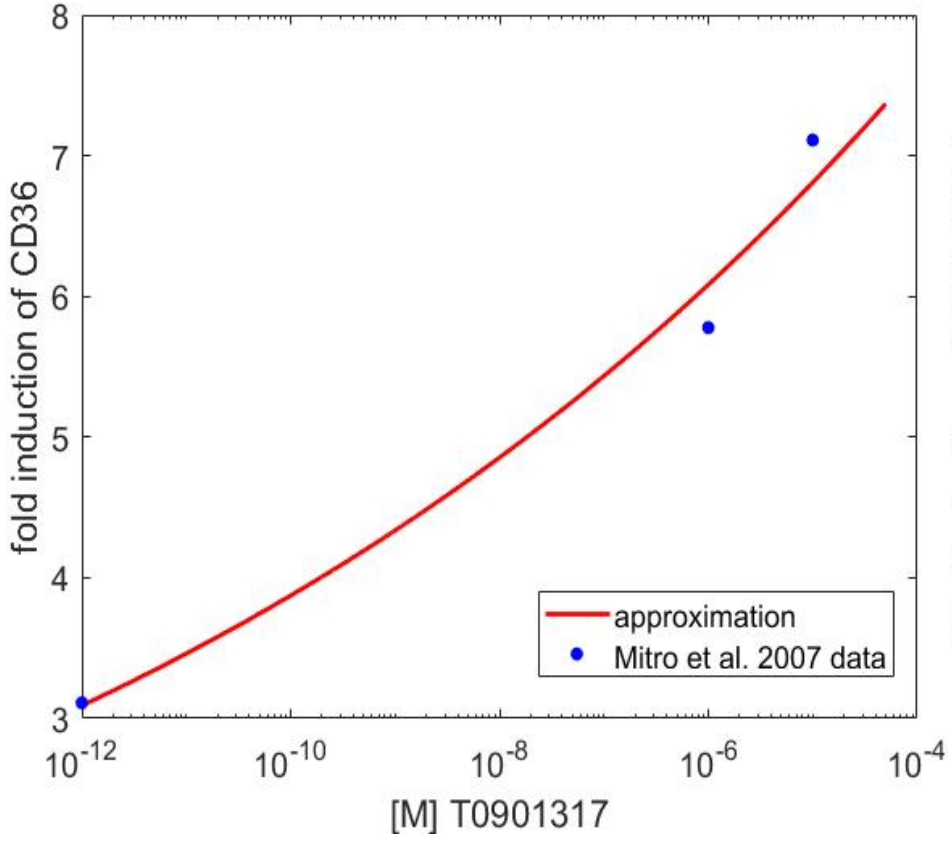
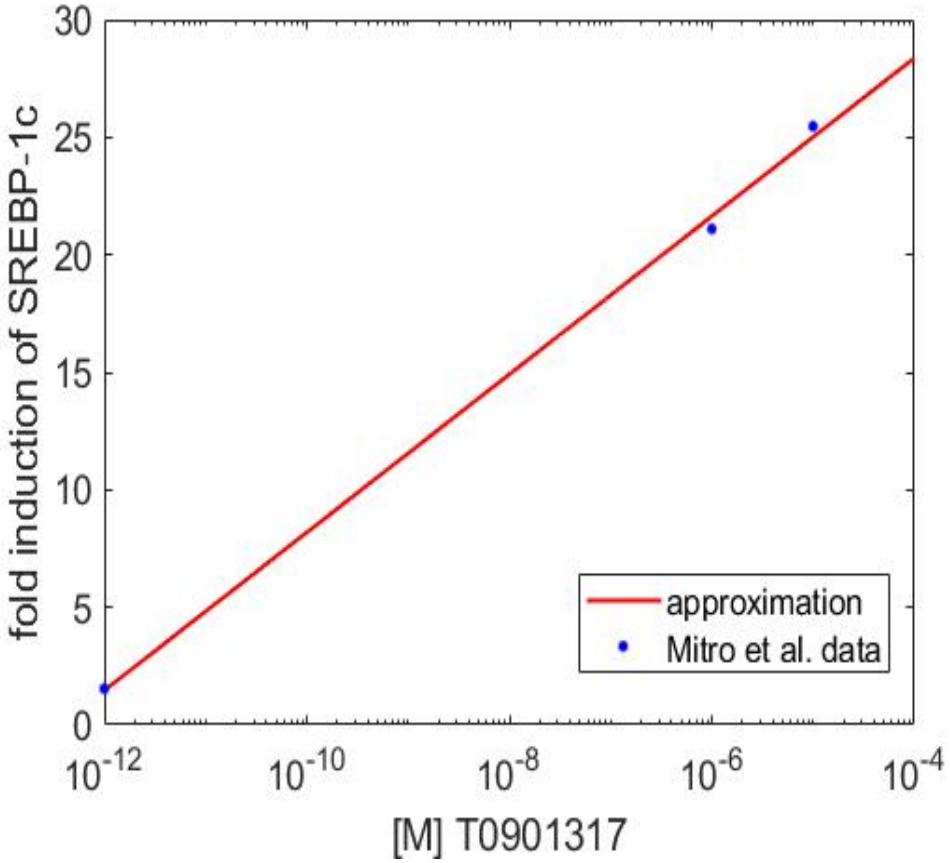
Model Development and Parametrization







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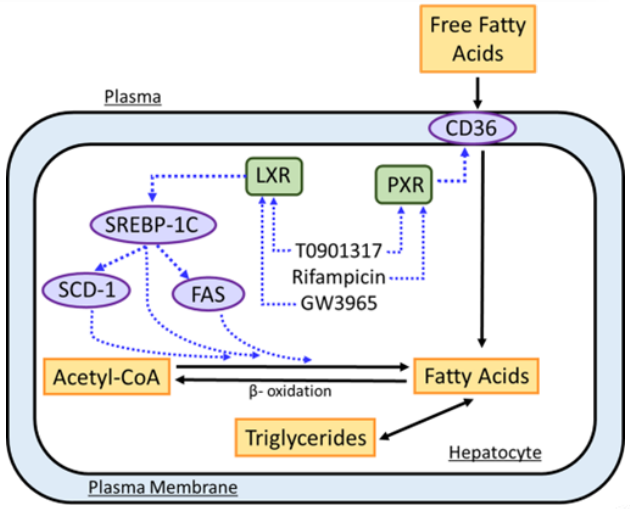

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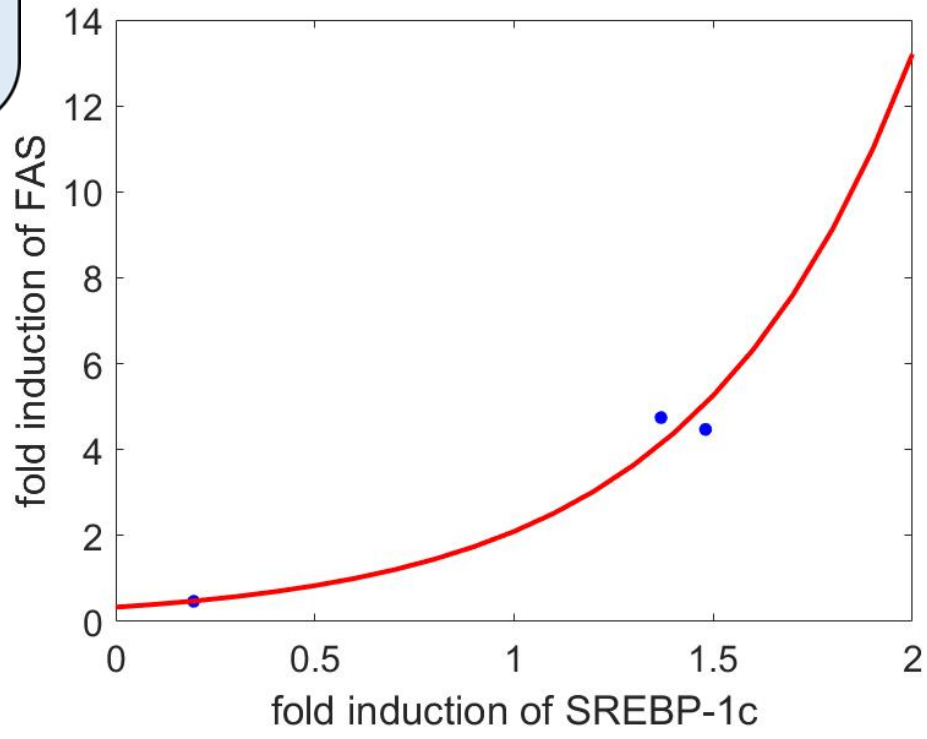

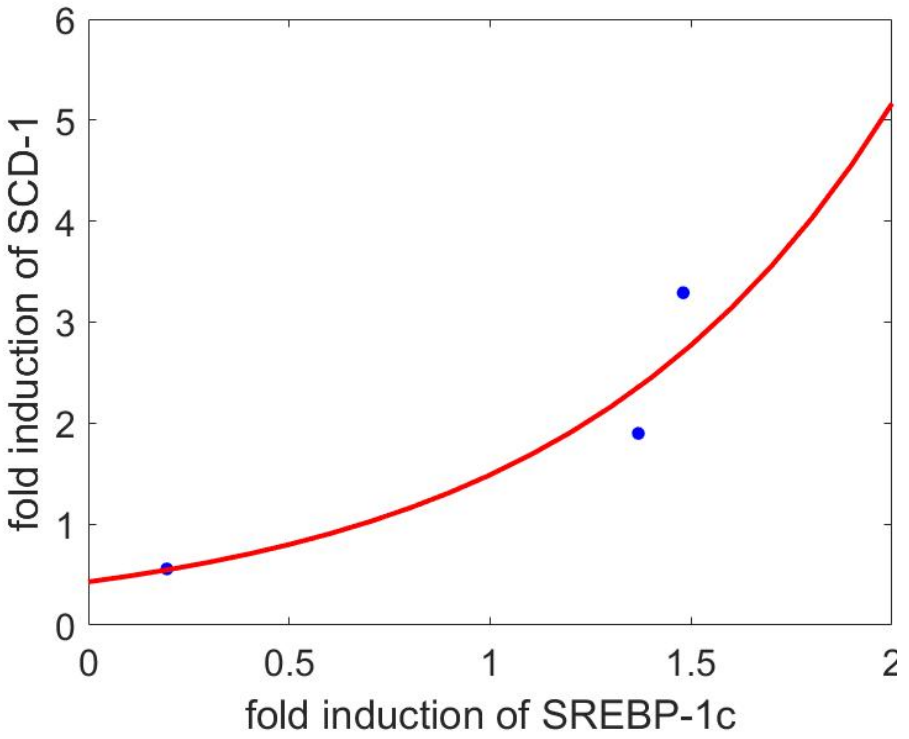

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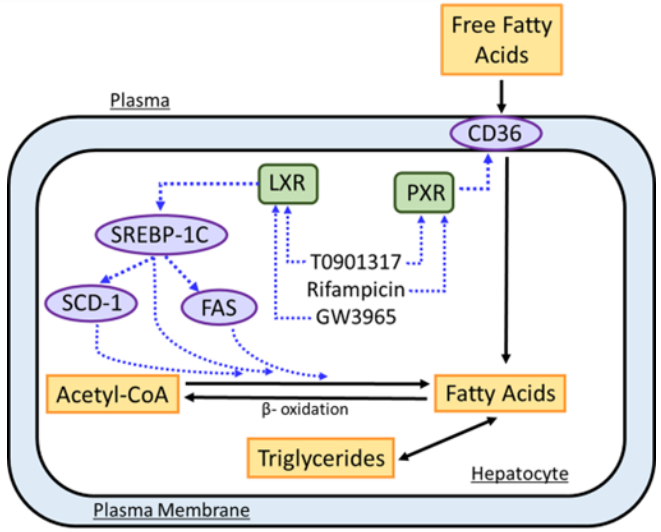

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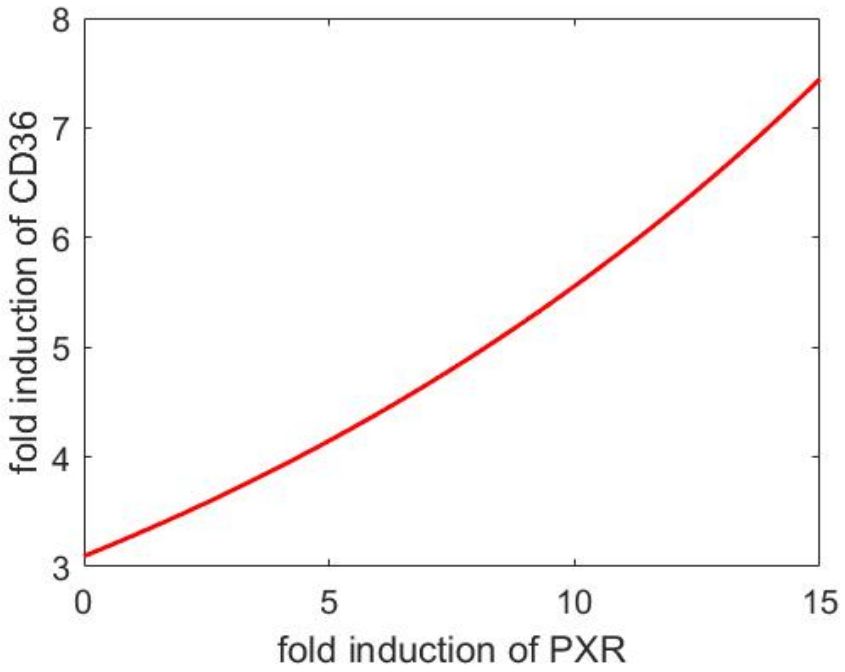
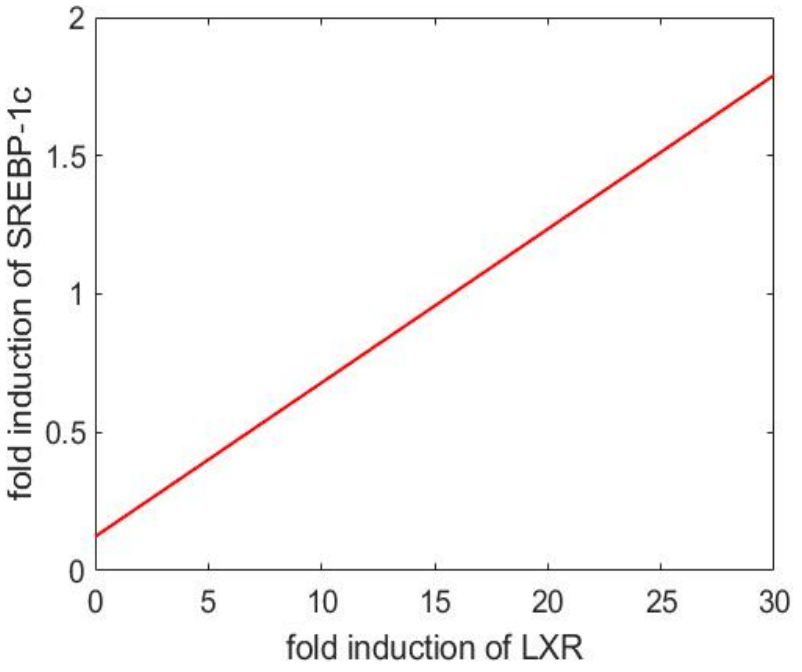
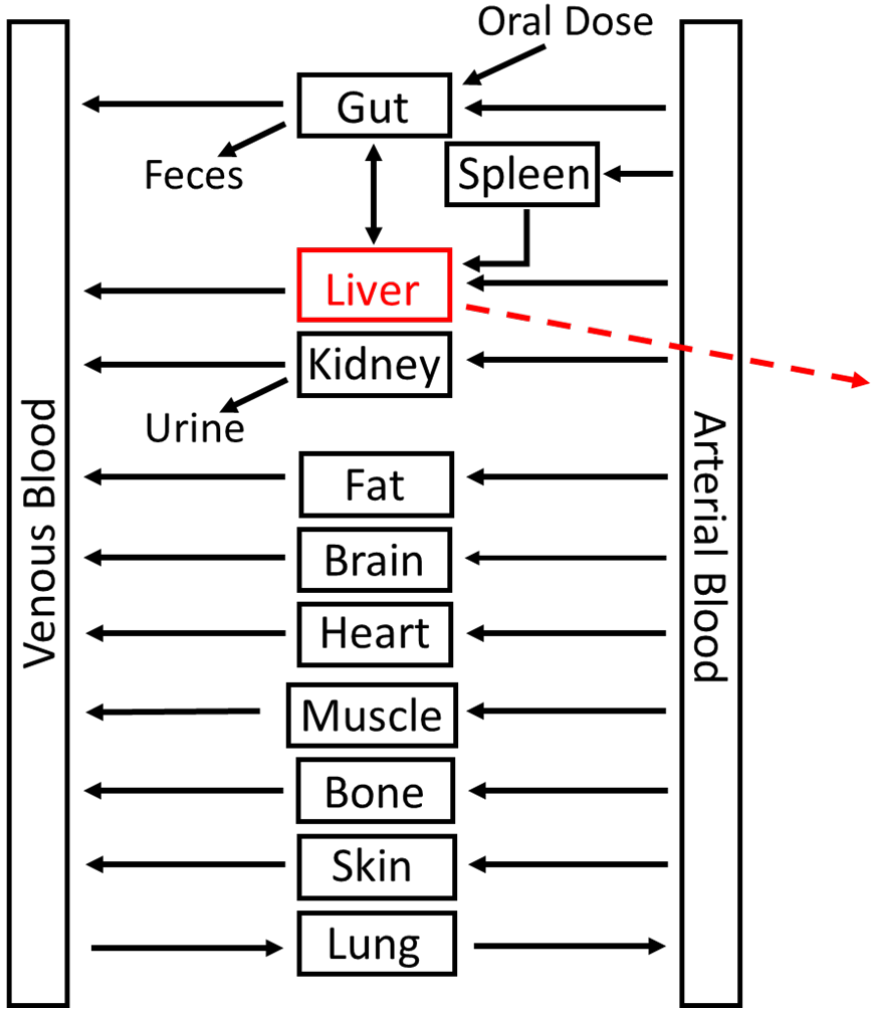
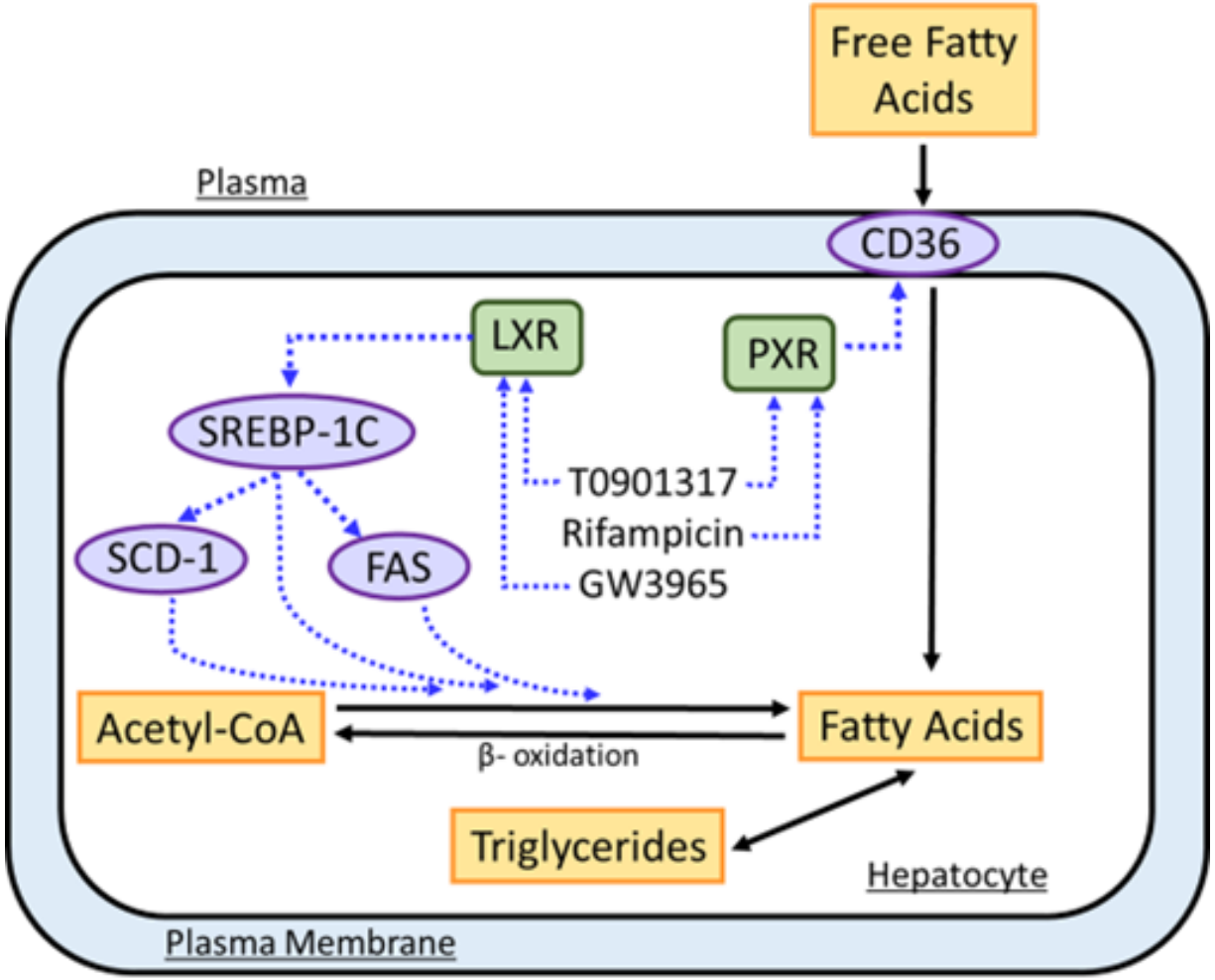




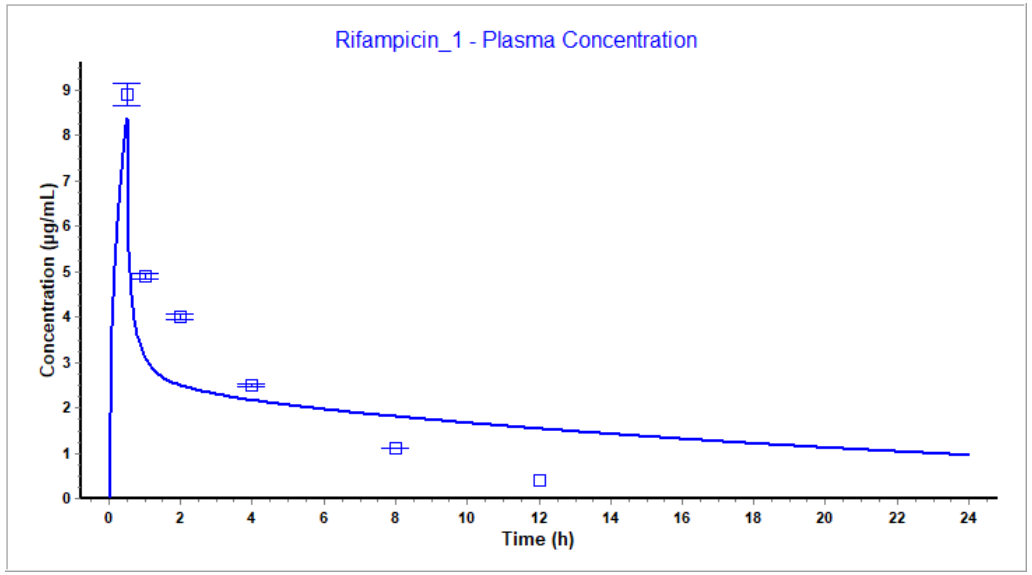
Nuclear Receptors LXR and PXR

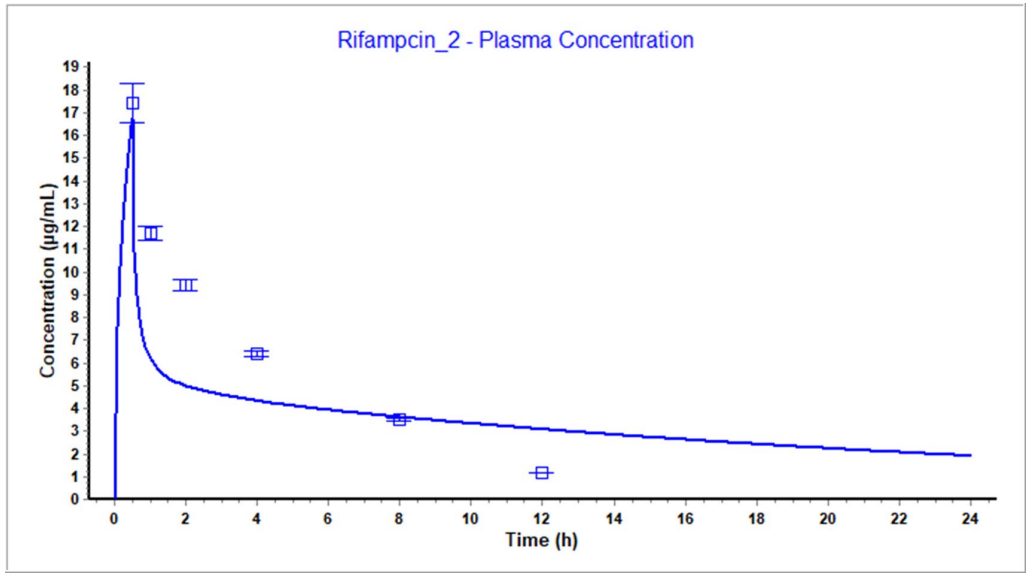




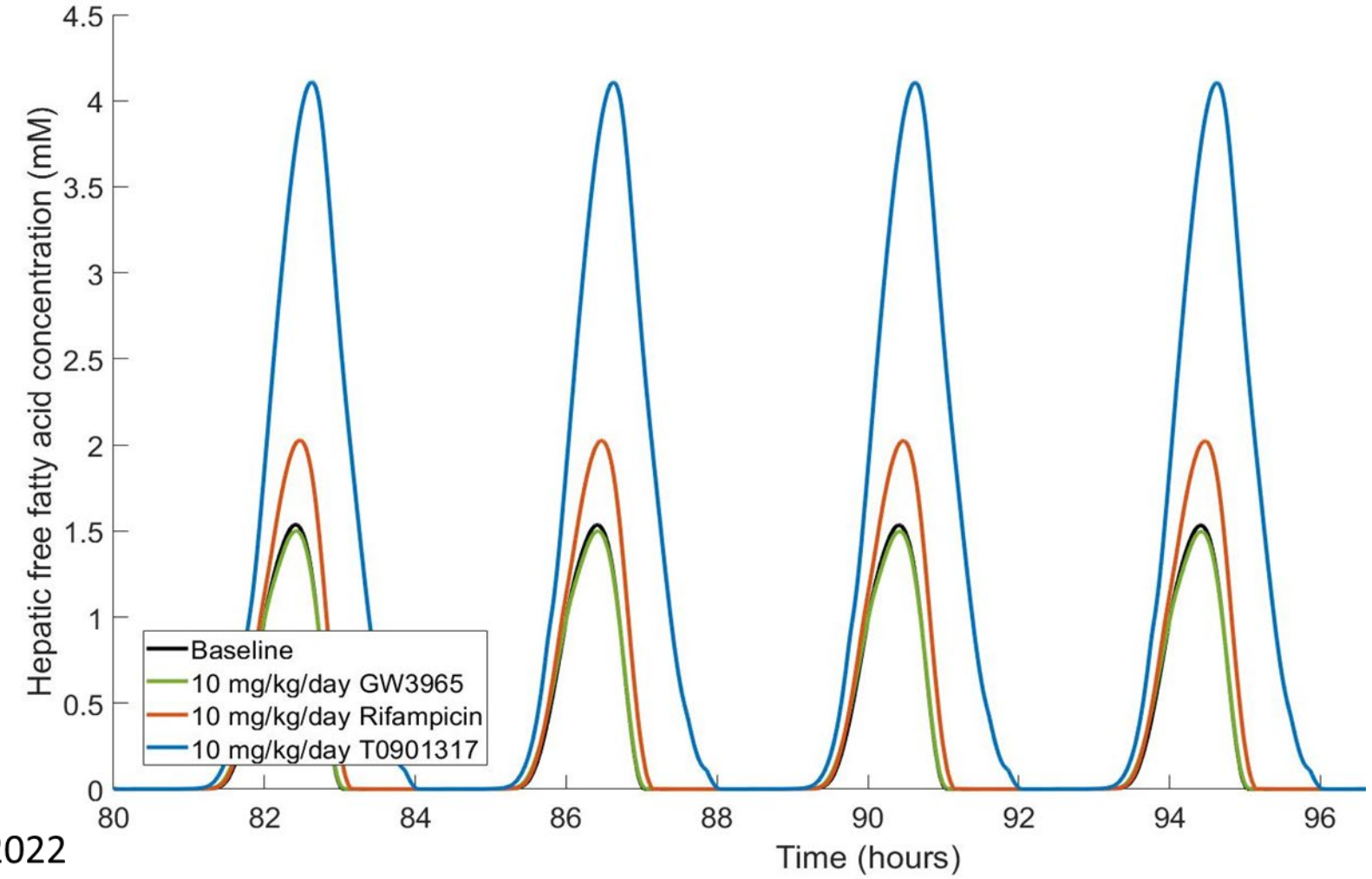
Chemical PBPK Modeling-SimulationsPlus

- Used GastroPlus and AdmetPredict to develop PBPK model for Rifampicin, GW3965 and T0901317
- Rifampicin Model was calibrated against human data obtained from literature





Fatty Acids Transport vs. Synthesis



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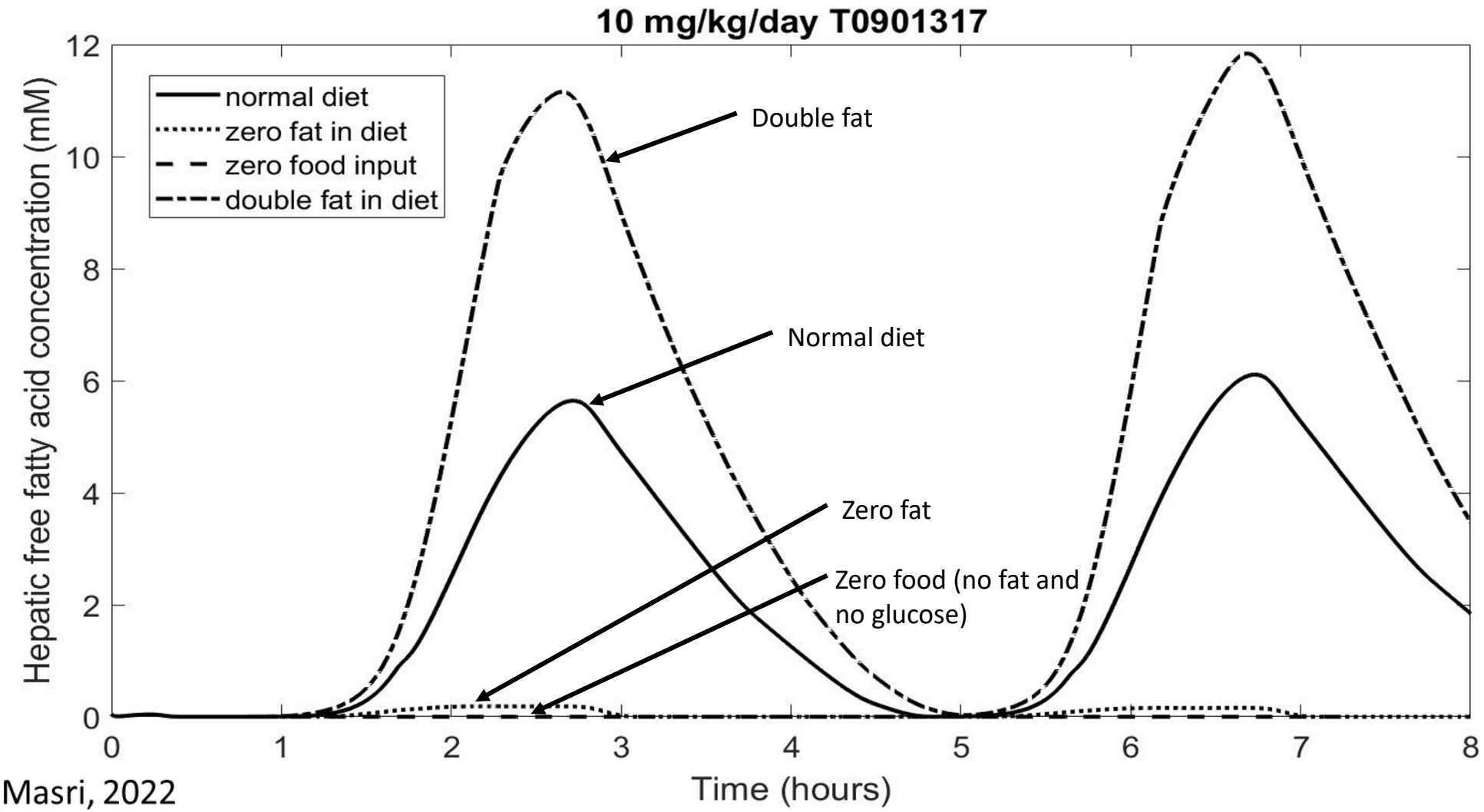
Impact of Fatty Diet



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Conclusions

- Developed an integrative overall PBPK-hepatic lipids quantitative AOP (qAOP) model for in vivo hepatic lipid content via nuclear receptors.
- PBPK-qAOP Modeling approach provides insights into mechanistic dose-response relationships in view of chemical exposure to Humans
    - Literature data mining, epidemiological information, targeted experiments, and modeling using high throughput/IVIVE kinetic and ADME commercial software
    - Identify and quantify health risks to humas
- Fatty lipid accumulation in the liver is more driven by transport of fatty acids from blood
    - Role of fat tissue and obesity
- Co-Exposure to chemicals can enhance hepatic fatty build-up leading to steatosis.

Thank you!!

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