Quantitative Systems Toxicology (QST) Model for Hepatic Steatosis Induction by Carbon Tetrachloride (CCl_4)

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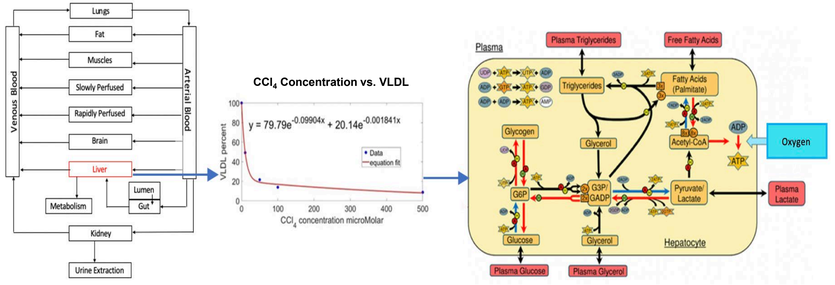
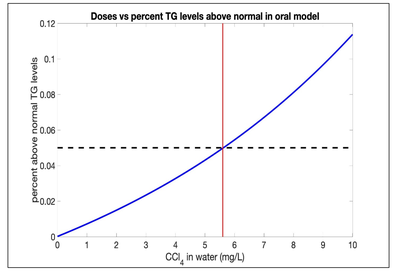
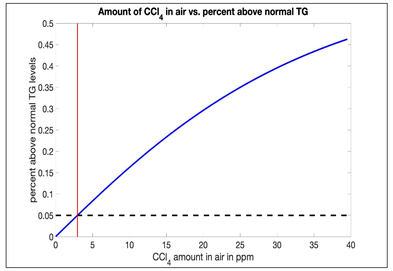
Introduction

Approximately 25-30% of the US population are impacted by nonalcoholic fatty liver disease (NAFLD). Hepatic steatosis, defined by an increase of more than 5% of lipid content in the liver, is the initial manifestation of NAFLD. Hepatic steatosis is manifested though the complex biological mechanisms that disrupts lipid homeostasis in hepatocytes as described by four apical key events central to the hepatic lipid retention: hepatic fatty acid (FA) uptake, de novo FA and lipid synthesis, FA oxidation, and lipid efflux. Hepatic steatosis can be initiated by lifestyle factors, diet and exposure to many environmental chemicals such as carbon tetrachloride (CCl_4). Experimental in vitro research has shown that CCl_4 decreased the levels of hepatic very low-density lipoprotein (VLDL), a major carrier of lipids efflux from liver to general blood circulation. This mechanism was included in an overall quantitative systems toxicology (QST) model to simulate the impact of ingesting or inhaling CCl_4 on the hepatic levels of triglycerides, as a product of free fatty acids.



Oral CCl_4 PBPK Model Data obtained from Ash Becker, E., et al. 1987. Adapted from Ashworth et al. 2016.



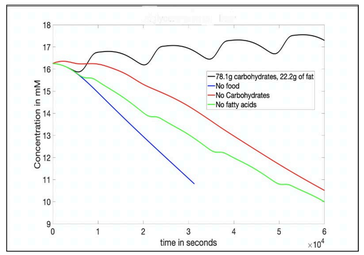


Methods

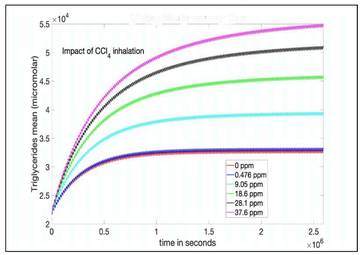
- The QST model consisted of an oral or inhalation of a physiologically based pharmacokinetic (PBPK) model for CCl_4 that was connected to a published hepatic steatosis model via the disruption of VLDL.
- The overall PBPK models (for both oral and inhalation) were tested using literature in vivo data from rats exposed to CCl_4. The calibrated model was then scaled to a human one to establish dose-response relationships for CCl_4 toxicity regarding hepatic steatosis.
- For the oral PBPK model, nonlinear minimization was used to estimate the absorption constant and the metabolites rate in the liver.
- The CCl_4 amounts in the liver, obtained from the simulation of the PBPK, were substituted into an equation that describes the relationship between CCl_4 concentration in liver and the percentage of VLDL present. This was done in order to reflect the changes of VLDL levels due to the presence of in vivo hepatic levels of CCl_4
- The impacted VLDL levels were substituted into a mechanistic model describing the cascading biological events leading to formation of free fatty acids (FFA) and triglycerides (TG) in the liver.
- Liver compartment, in the mechanistic model, is separated into 8 hepatocyte sections with 8 corresponding hepatic blood sections where metabolites, hormones, oxygen, etc. can be transported to the liver tissue. Within each hepatocyte section is a series of biological processes involved in hepatic fatty acid and triglycerides synthesis, transport and metabolism.

Results

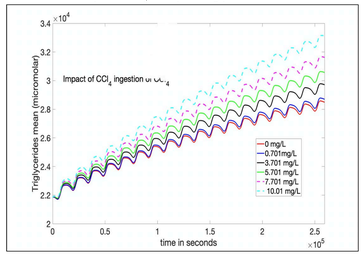
Impact of Diet on Hepatic triglycerides



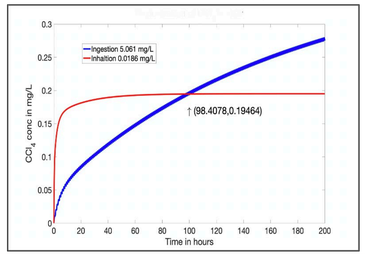
Impact of CCl_4 on hepatic triglycerides



Impact of CCl_4 on hepatic triglycerides



Hepatic Concentration of CCl_4



Discussion

- When the food intake is zero, the levels of triglycerides in the liver keep decreasing. A similar trend appears when the diet consists of no glucose or fat.
- Exposure to CCl_4 leads to an increase of triglycerides in the liver. The amount of triglycerides increases is dependent on the amount of CCl_4 present in the liver.
- Since the VLDL percentage change approaches zero as the CCl_4 concentration keep increasing, TGs concentrations in liver eventually level off to a horizontal asymptote.
- In the oral ingestion model, it takes a concentration of 5.061mg/L in water for TGs to be above 5% of normal levels as a marker of hepatic steatosis. However, it only takes 2.954 ppm when the CCl_4 is inhaled to reach the same level of hepatic TGs.

References

- Ashworth, W. B., Davies, N. A., & Bogle, I. D. (2016). A Computational Model of Hepatic Energy Metabolism: Understanding Zonated Damage and Steatosis in NAFLD. PLoS Comput. Biol, 12(9), pp. 304
- Becker, E., et al. “Two Mechanisms of Cc14-Induced Fatty Liver: Lipid Peroxidation Or Covalent Binding Studied in Cultured Rat Hepatocytes.” *Free Radical Research Communications*, vol. 3, no. 1-5, 1987, pp. 299–308, doi:10.3109/10715768709069797.