Implications of non-linear PK in toxicity testing and interpretation of dose response data

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Symposium Webinar
Opportunities and Challenges in Using the Kinetically Derived Maximum Dose Concept to Refine Risk Assessment
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Understanding how nonlinear kinetics influences external-internal dose relationship

- Many kinetic processes involve enzyme or carrier-mediated systems, and these processes may become saturated at high doses, resulting in nonlinear external-internal dose relationship
- The nonlinear external-internal dose relationship may be illustrated with a curve that has an inflection point, which is considered a KMD, or a smooth curve without an inflection point
- To better define a KMD, we need to better understand the external-internal dose relationship that reflects saturable kinetics

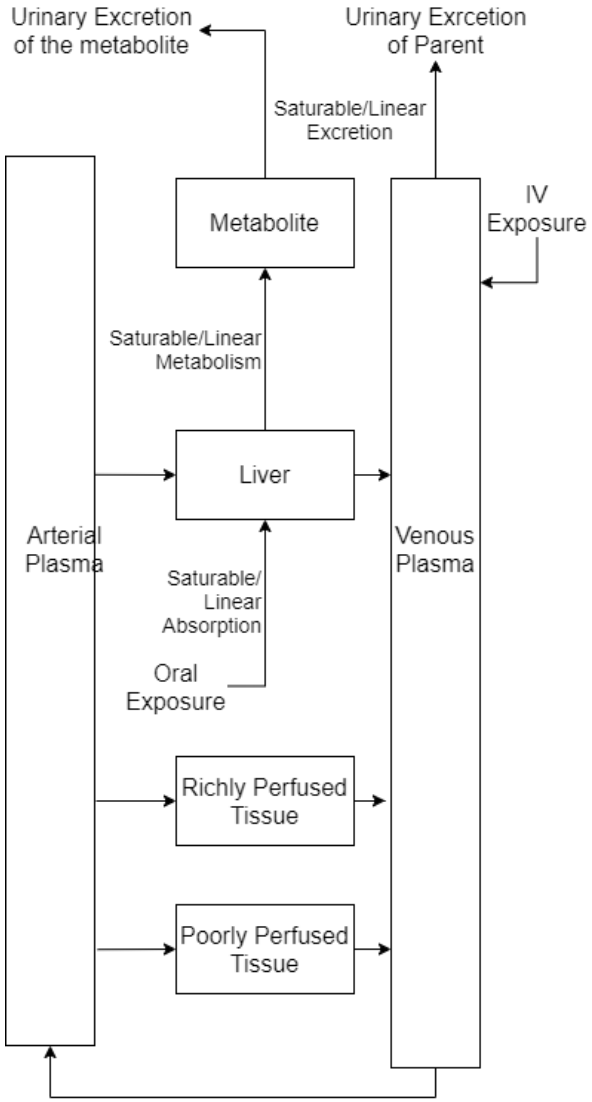
How we decided to address this issue

- Create a PBPK model with saturable kinetic processes
- 8 chemicals with different excretion, metabolism and absorption characteristics, based on realistic values
- Only one metabolite is generated from the parent compound
- The toxic moiety may be the parent only, the metabolite only, or both
  - For all scenarios, the AUCs of parent, metabolite, and both will be plotted against external dose to understand how internal doses of potential toxic moiety change with increasing external doses
- Toxic response is assumed linear with AUC of toxic moiety

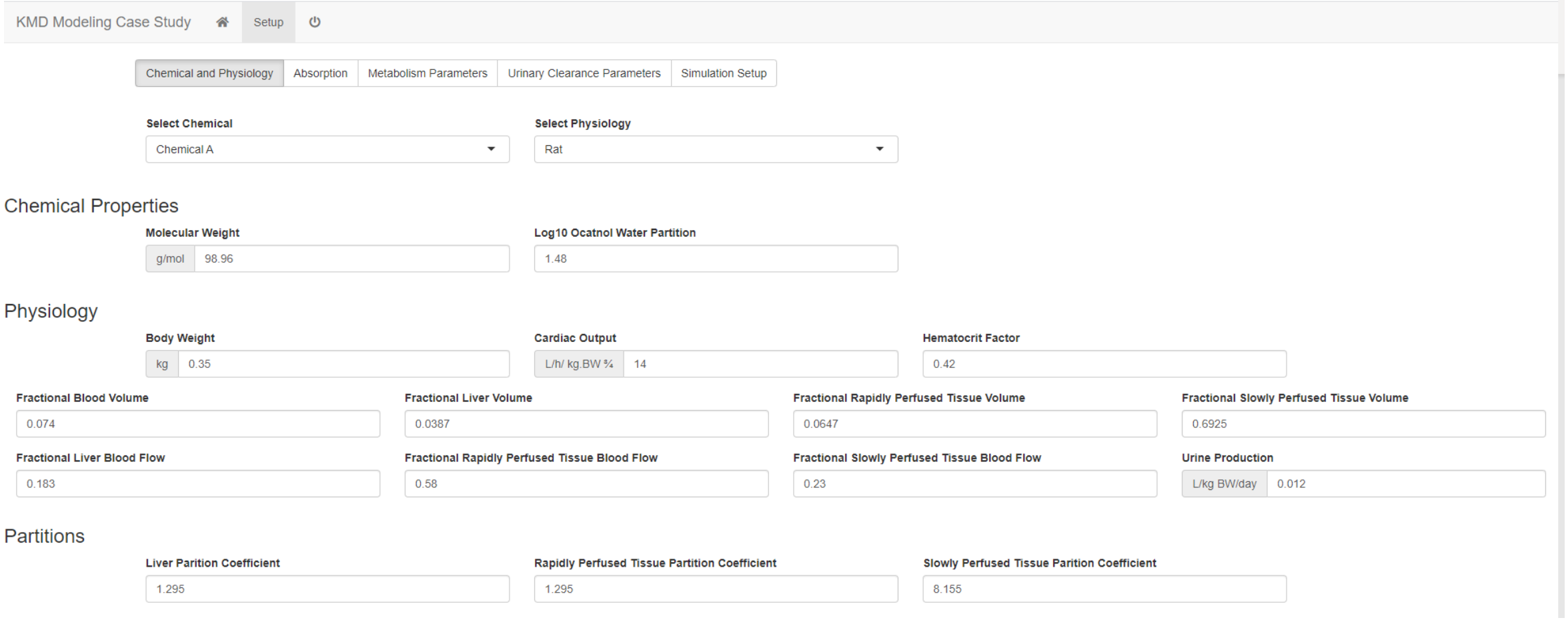
Modeling platform

- PLETHEM – open source, customizable
- Rat model for this case study
- 3-compartment model – liver, slowly perfused tissues, rapidly perfused tissues
- Flow-limited model
- Infusion and oral routes of exposure
- Model is created using MCSIM and then integrated within a shiny interface for simulation
- Model is also coded in Magnolia for QA check
- Model simulated for 2160 h with daily oral dosing or 24 h IV infusion

Minimal PBPK model used in the case studies



PLETHEM interface for running the model



https://scitovation.shinyapps.io/HESI_PBPKModel_KMD/

Case studies investigating different saturable processes

Limiting PK Process	Dosing	Parent absorption	Parent clearance	Metabolite clearance
Saturable clearance of the parent	IV infusion	NA	Michaelis-Menten Kinetics	Michaelis-Menten Kinetics
Saturable clearance of metabolite	IV infusion	NA	Michaelis-Menten Kinetics	Michaelis-Menten Kinetics
Saturable absorption of parent	Oral gavage	Michaelis-Menten Kinetics	First-order Kinetics	First-order Kinetics

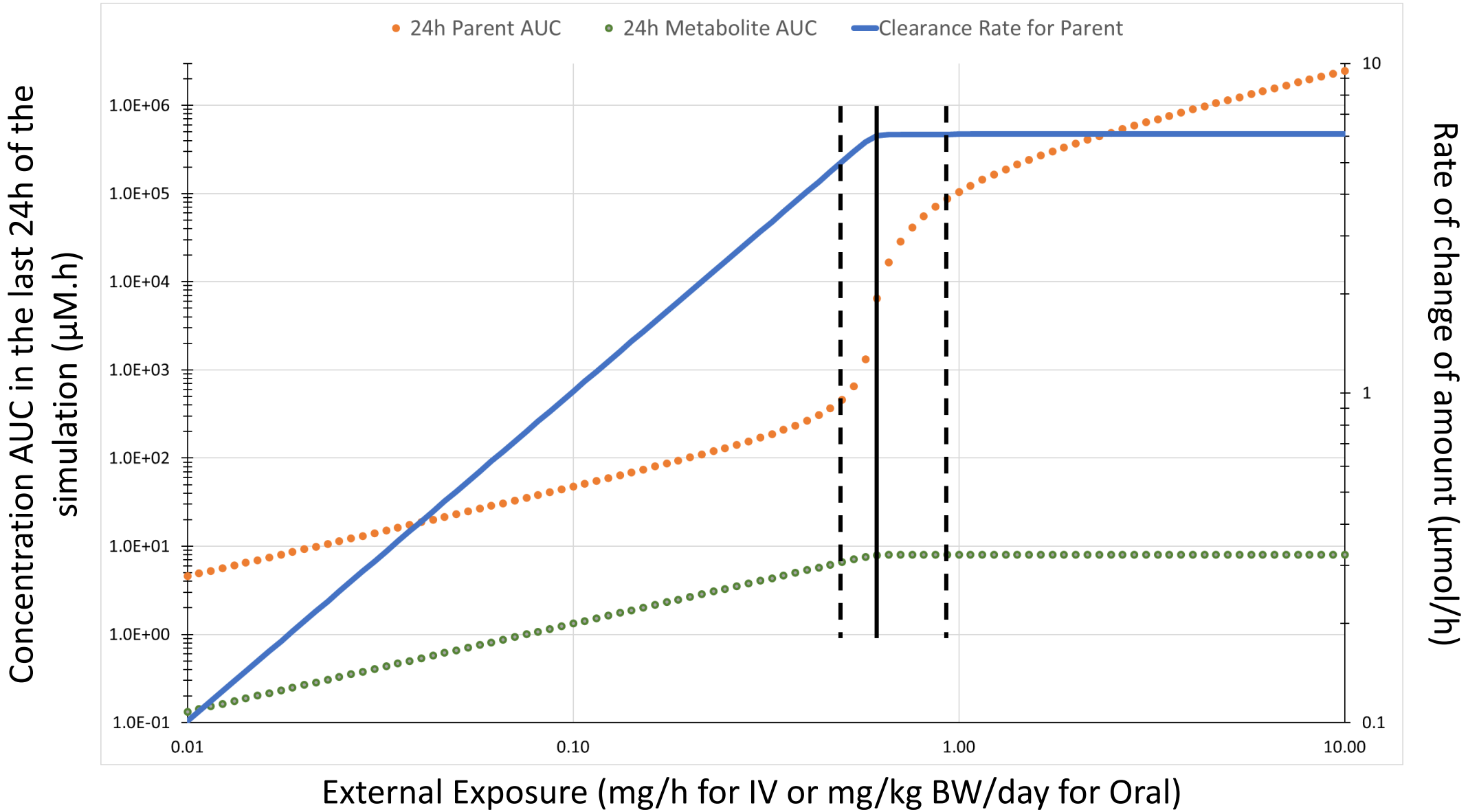
- 3 chemicals from the 8 used for the case studies.
- For the first two case studies, the parent and metabolite clearance was modeled using a Michaelis-Menten kinetics. Saturation of clearance happened as a result of the relative values of Vmax and Km to plasma concentration.

Chemicals used in simulations for this talk

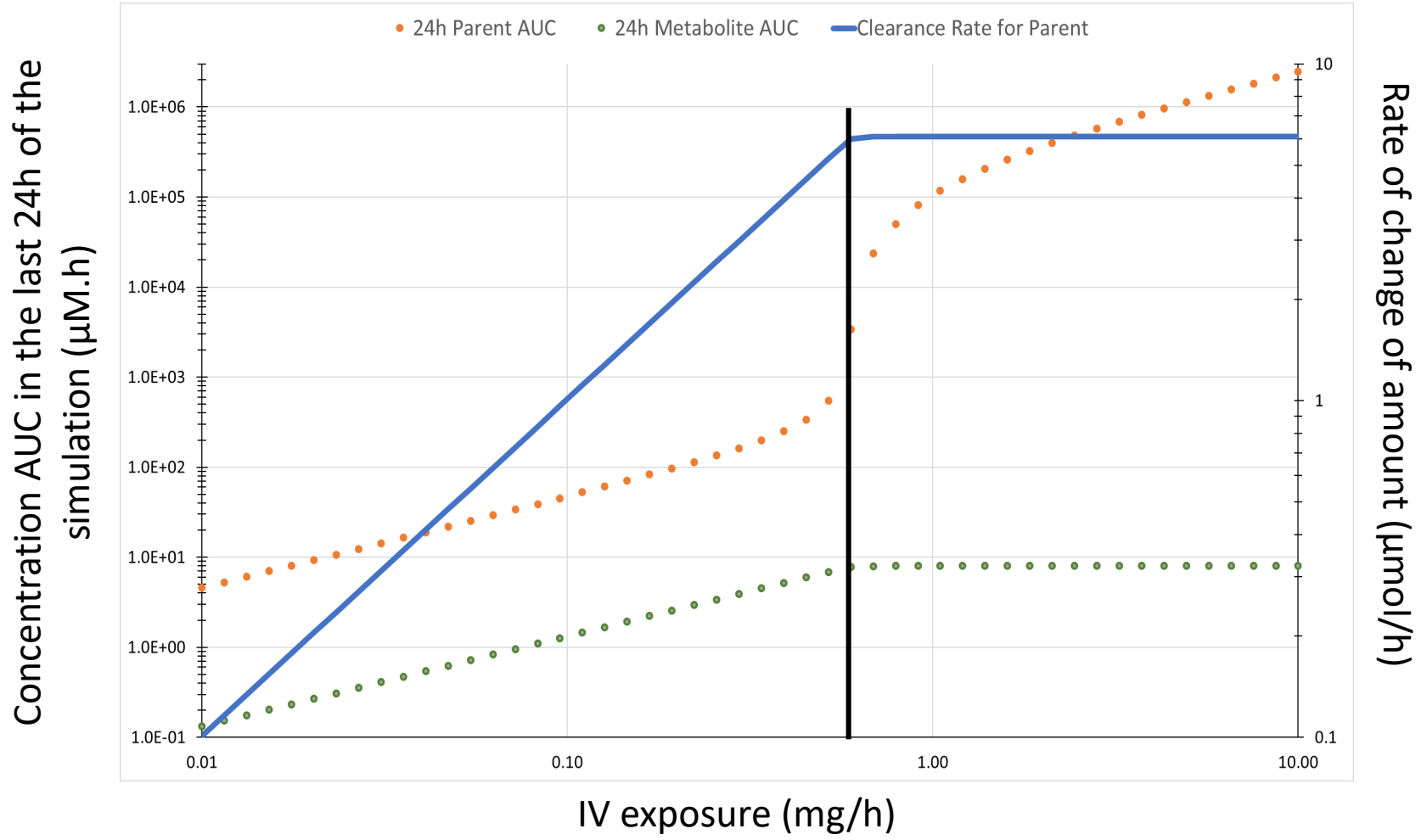
Chemical	Parent Clearance Rate – Vmax (µmol/h)	Parent Clearance – Km (µM)	Metabolite Clearance Rate – Vmax (µmol/h)	Metabolic Clearance Km (µM)
Chemical A : Saturable Clearance of the Parent	6.09525	2.5	2194	120
Chemical E : Saturable Clearance of the Metabolite	528.255	180	60.55	1470
Chemical B: Saturable Oral Absorption	189.63	1100	189.63	500

- Oral absorption was modeled as a saturable process for Chemical B with Vmax = 10 /h and Km = 2 µmols

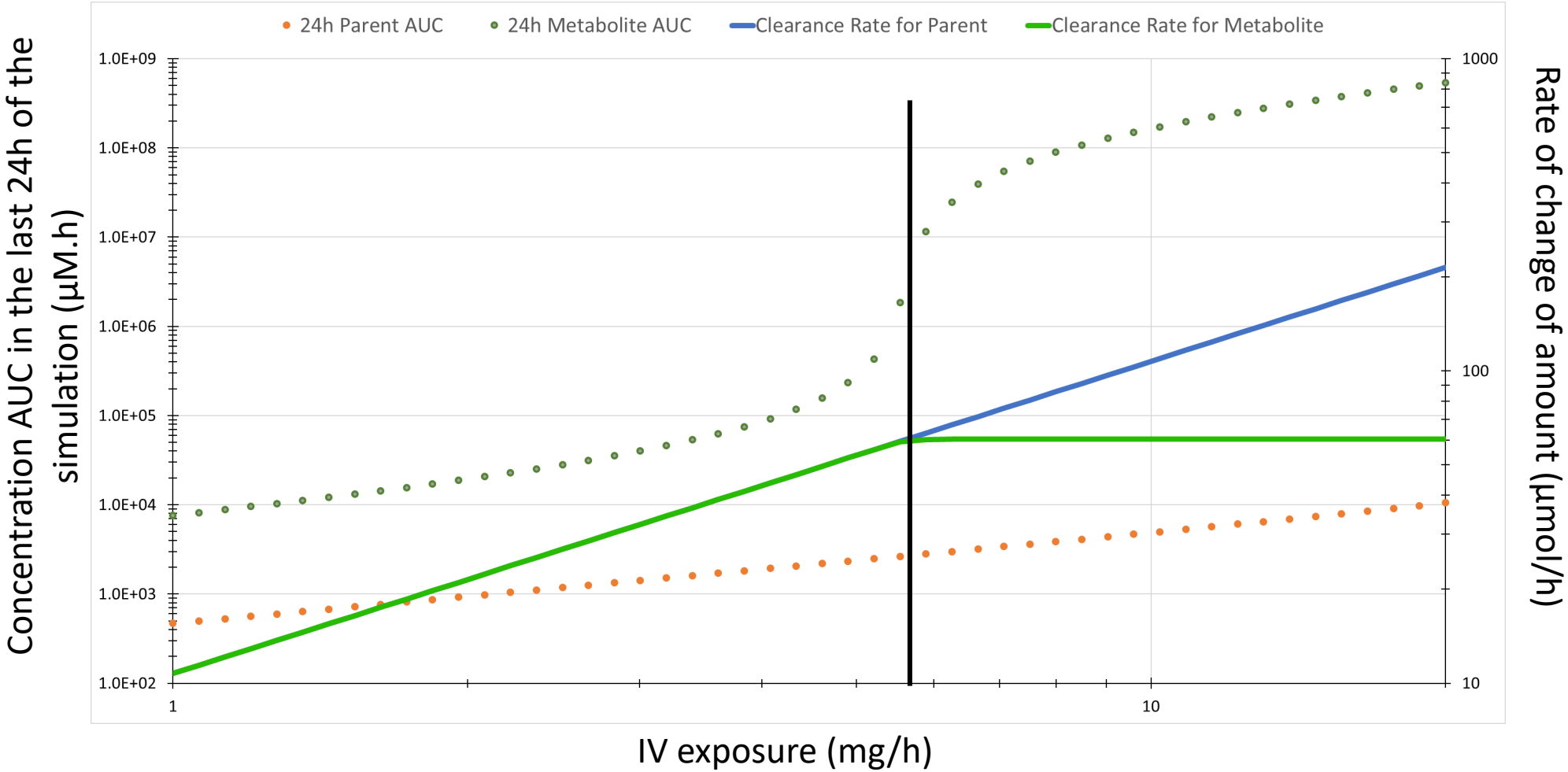
Before we start looking at simulation results…



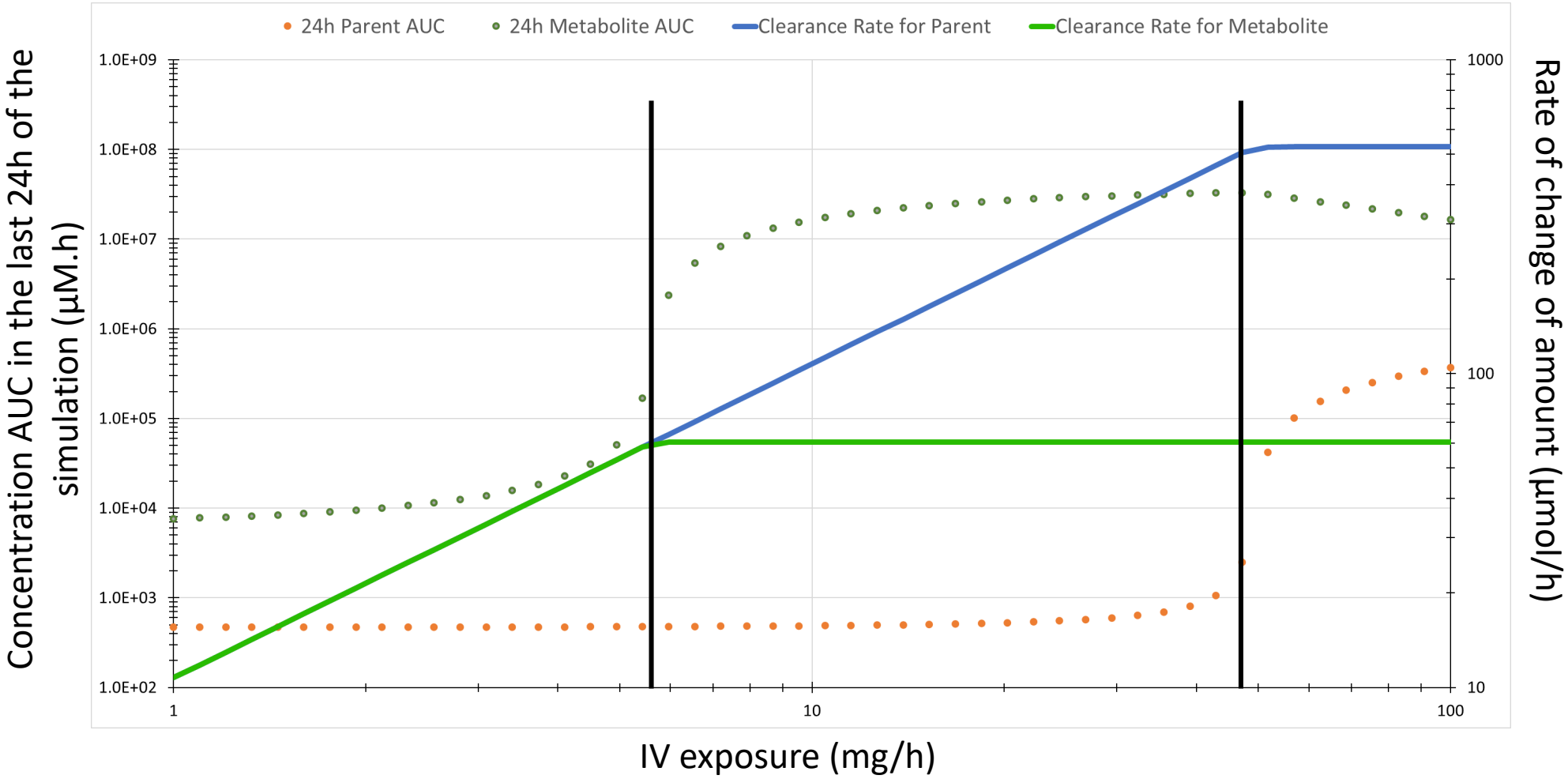
Case Study 1 – Saturation of parent clearance (Chemical A)



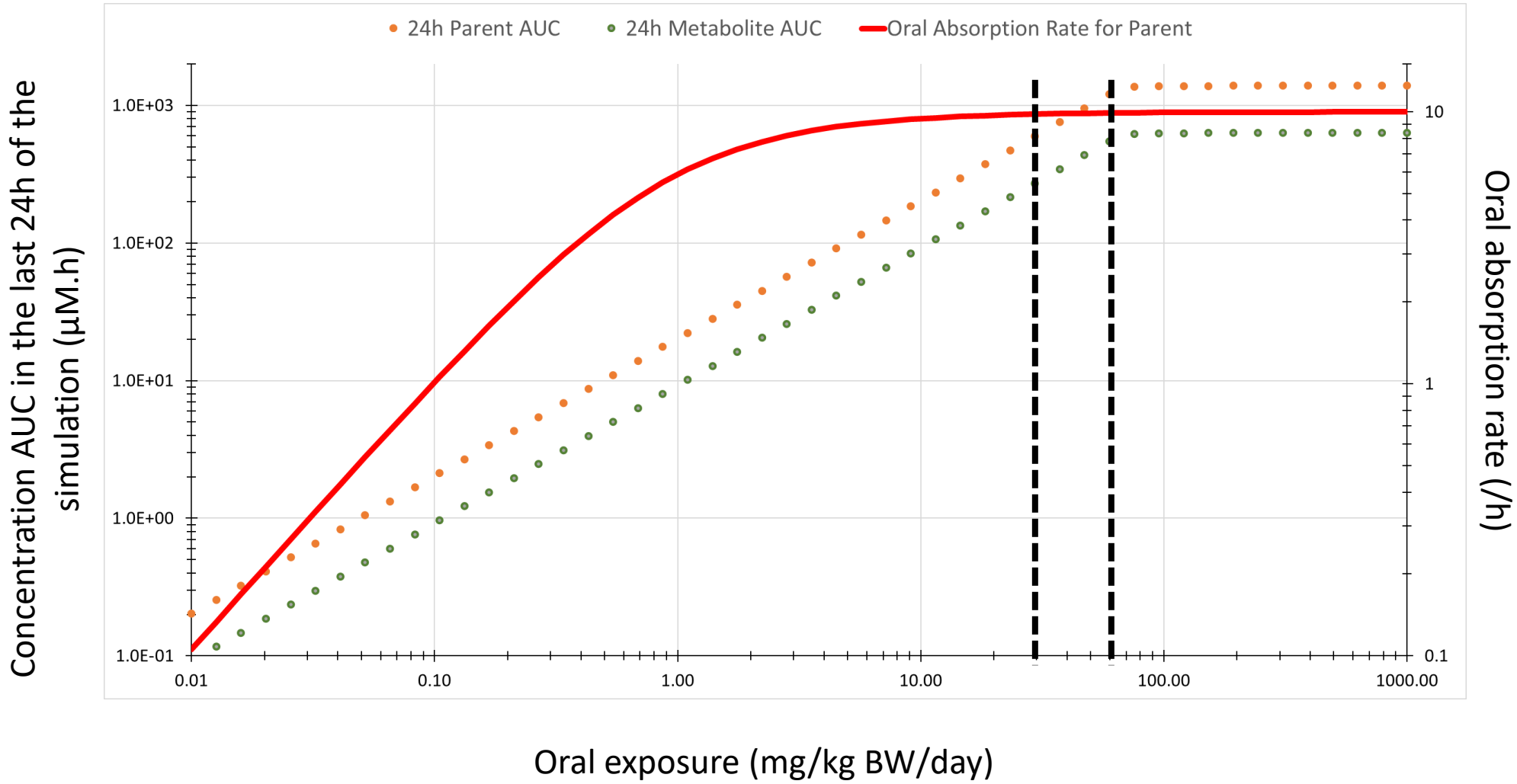
Case Study 2- Saturation of metabolite clearance (Chemical E)



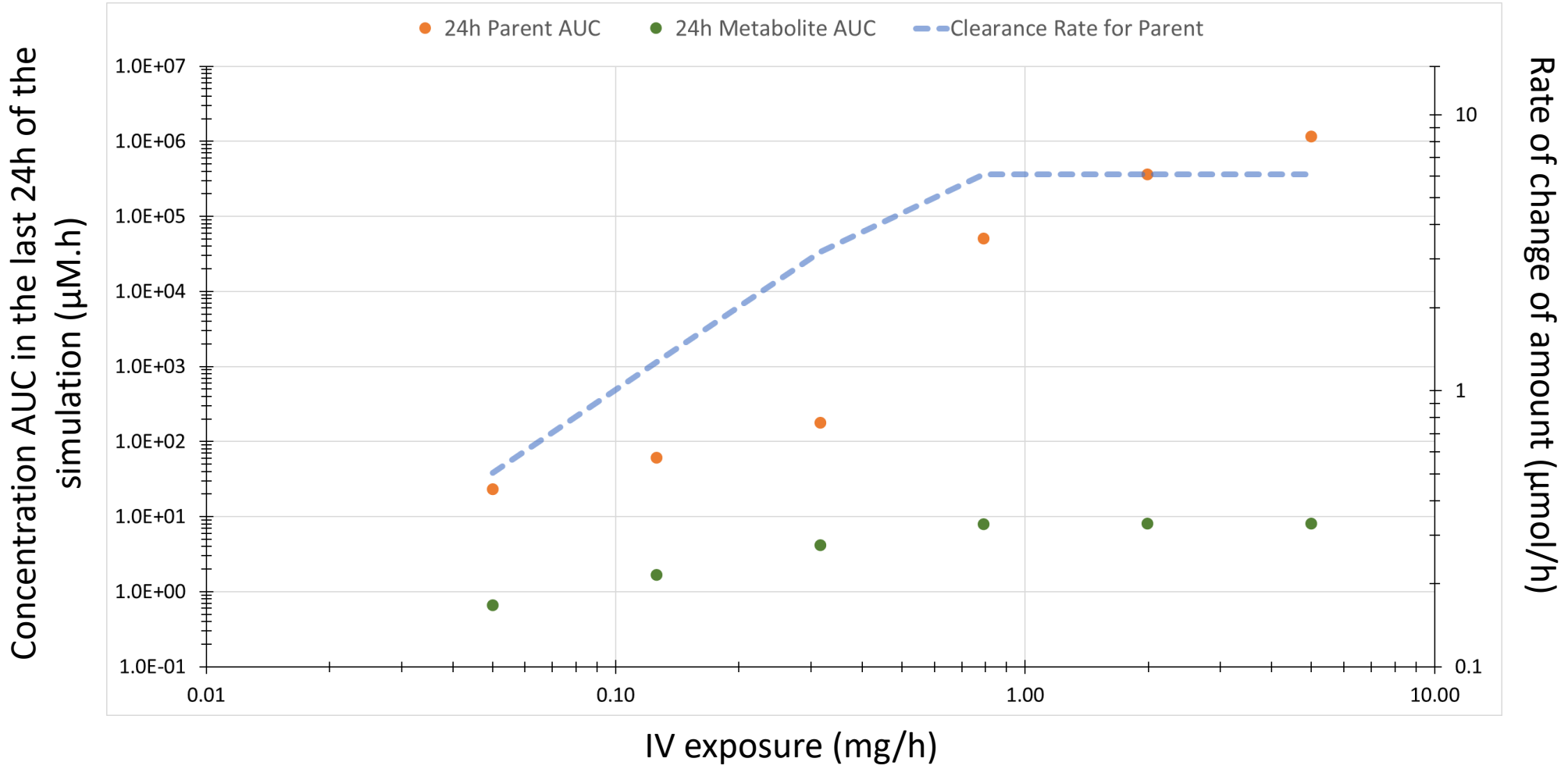
Testing the same chemical at a higher exposure…



Case Study 3 – Saturable oral absorption for parent (Chemical B)



More plausible dose response data



Points to consider

- The internal-external dose (IED) response can be quite complex and may appear linear at different regions along the response curve
- Understand the toxic moiety is important to application of KMD.
- Usually KMD is determined based on sparse IED data. Using in vitro methods and computational modeling, we may be able to simulate a dense IED relationship.
- Species extrapolation using PBPK modeling can be used to account for PK differences between human and animal. KMD can then be compared to human exposure

Summary

- Simulation illustrates different dose-response for parent and metabolite for different chemicals that should be considered for KMD
- Different saturating process impact the dose-response curves in different ways

Next Steps:

- Extend the simulations to include more saturating process to investigate more complex PK profiles
- We can sample the dense dose-response curve at different points to create datasets that can be used to test different approaches to fitting dose-response curves

Through some of the talks today we will…

- Look at statistical techniques that can be used to determine the point of non-linearity in a dose response curve
- Discuss how to incorporate knowledge of other biological processes that may lead to a non-linearity in the dose response curve.
- Understand the role of human exposure estimation in the use of KMD.

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