EPA's Concentration *versus* Time Database: A Resource for Extrapolating Toxicokinetic Trends Across Chemicals

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1 Expansion of the Concentration *versus* Time Database

1a) What is the CvTdb?

- The Concentration *versus* Time Database (CvTdb) is a database of standardized time-course data of chemical compound concentrations measured *in vivo* from hundreds of diverse publications. It serves as a platform for assessing PK/TK models on a large set of data. (Sayre, Grulke, and Wambaugh, 2020).

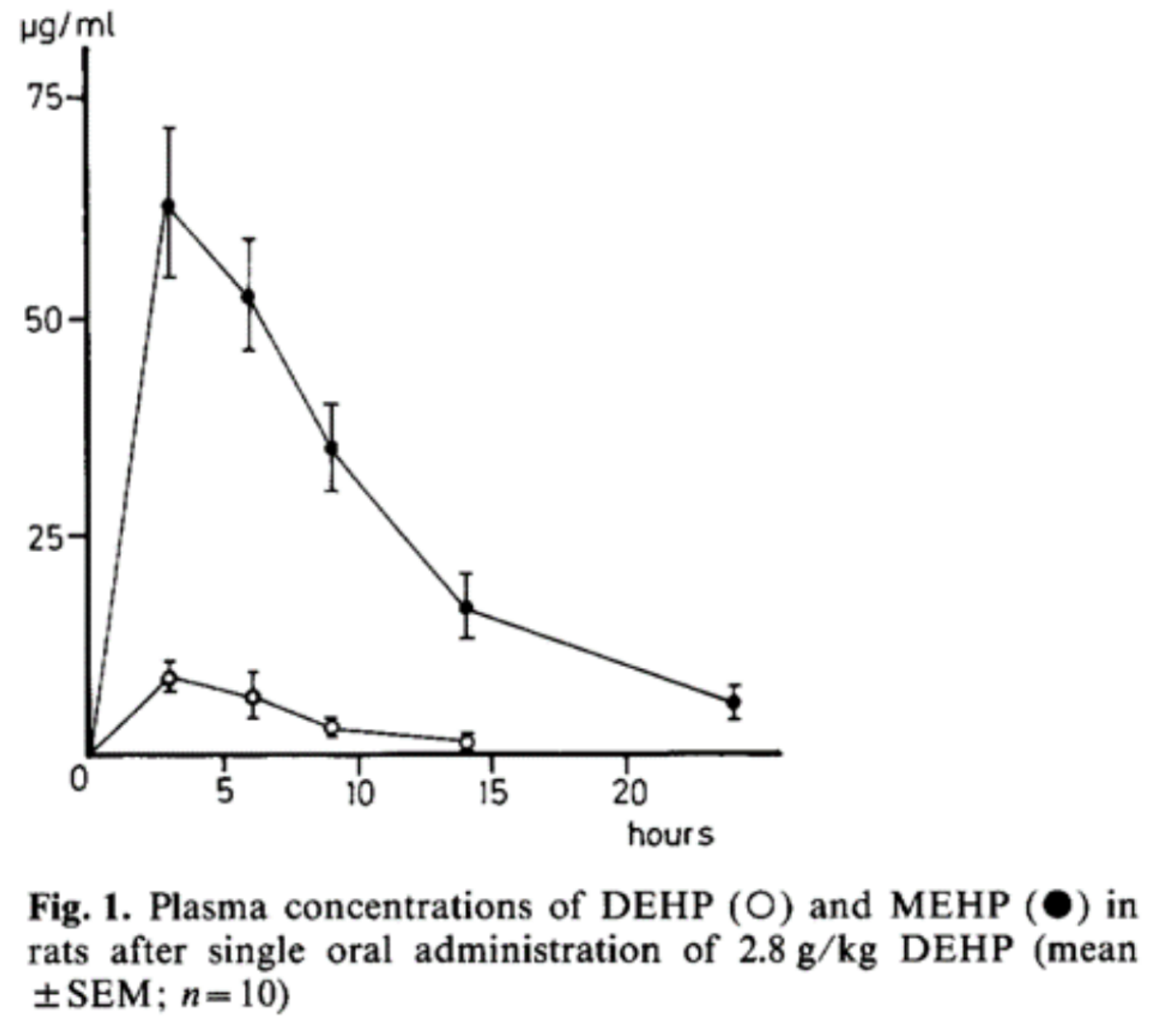


Fig. 1. Plasma concentrations of DEHP (○) and MEHP (●) in rats after single oral administration of 2.8 g/kg DEHP (mean ±SEM; $n = 10$)

Figure 1: Typical plot from which CvT data is extracted. From Sowa and Steibert (1985).

- The CvTdb contains 389 unique chemicals, including 70 pharmaceuticals (~30%). 101 analytes are present in EPA's ToxCast dataset (~53%).

1b) Integration of Data Shared by Other Institutions

- Showa Pharmaceutical University shared CvT data consisting of over 200 unique compounds (Kamiya *et al.*, 2020; Kamiya *et al.*, 2021).
- If YOU have CvT data, please consider collaborating with us! Visit https://github.com/USEPA/CompTox-PK-CvTdb or email Wambaugh.John@epa.gov

2 Toxicokinetic Trends Across Chemicals

- We can explore trends across chemicals and references using the CvTdb.
- "In PBPK modeling, predictions that are, on average, within a **factor of 2** of the experimental data have frequently been considered adequate" (WHO, 2010).
- In Figure 2, 85.1% of replicate timepoint data in the CvTdb is within a factor of two of their respective mean. The "factor of two" rule may not be appropriate if the data itself is spread beyond a factor of two.

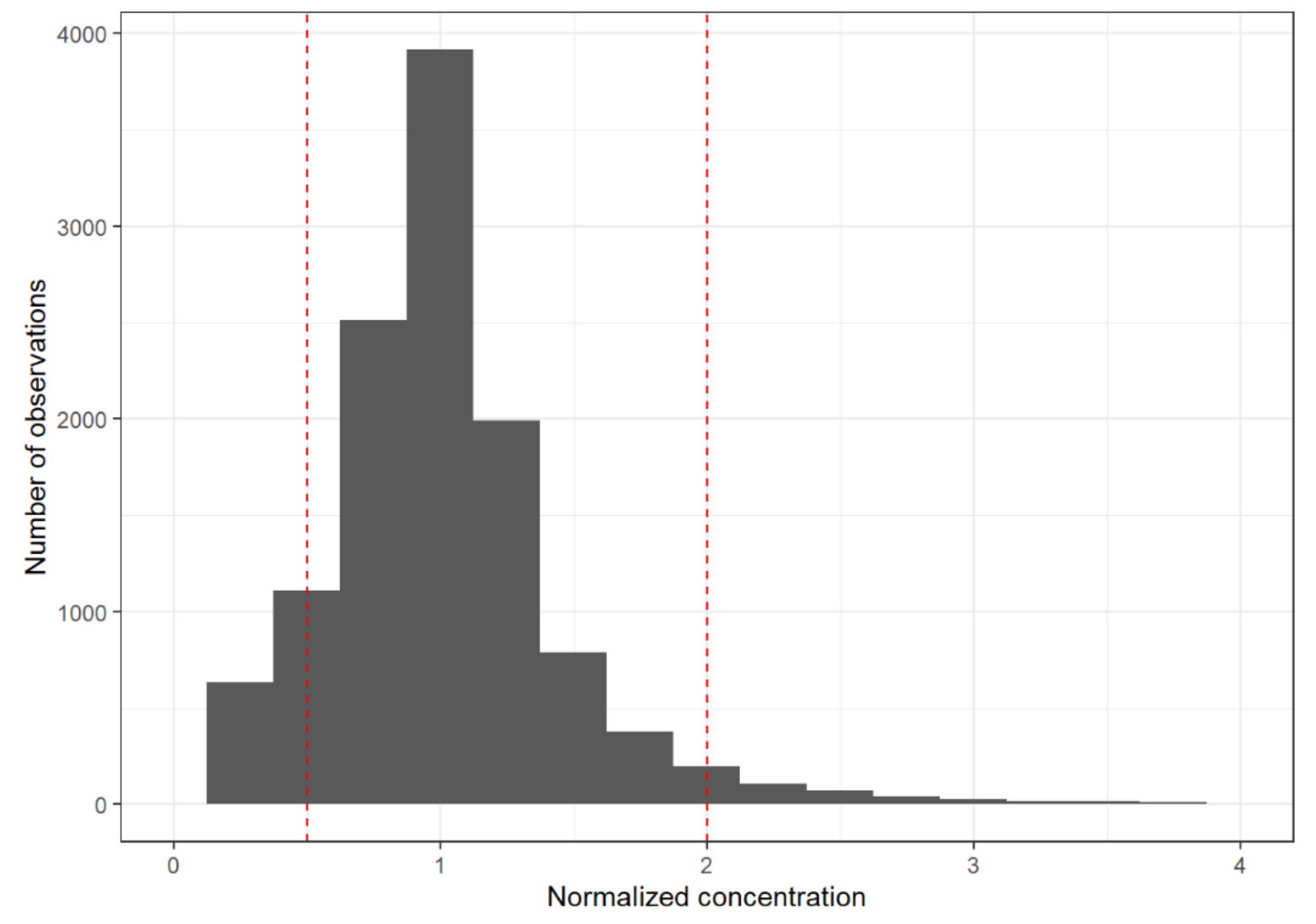
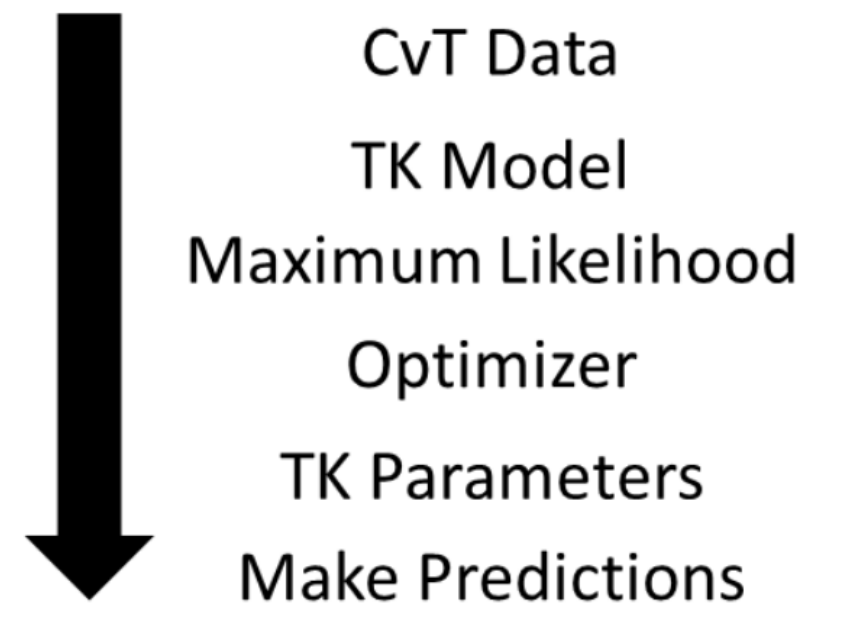


Figure 2: The CvTdb data was grouped into unique combinations of compound/reference/route/dose/timepoint. Groups without replicate timepoints were removed. If all replicate timepoints corresponded to non-detect concentration values, those data were removed. If some, but not all replicate timepoints corresponded to non-detect concentration values, those values were set to equal 0.45 of the minimum value. Each concentration was normalized by the mean concentration of each group.

3 Introducing *invivoPKfit*

3a) What is *invivoPKfit*?

- R package that fits 1- and 2- compartment models to CvT data and extrapolates TK parameter values (e.g., half-life, elimination rate, and volume of distribution)



CvT Data
TK Model
Maximum Likelihood
Optimizer
TK Parameters
Make Predictions

Figure 3: *invivoPKfit* workflow.

3b) TK Model Descriptions

1-Compartment Model

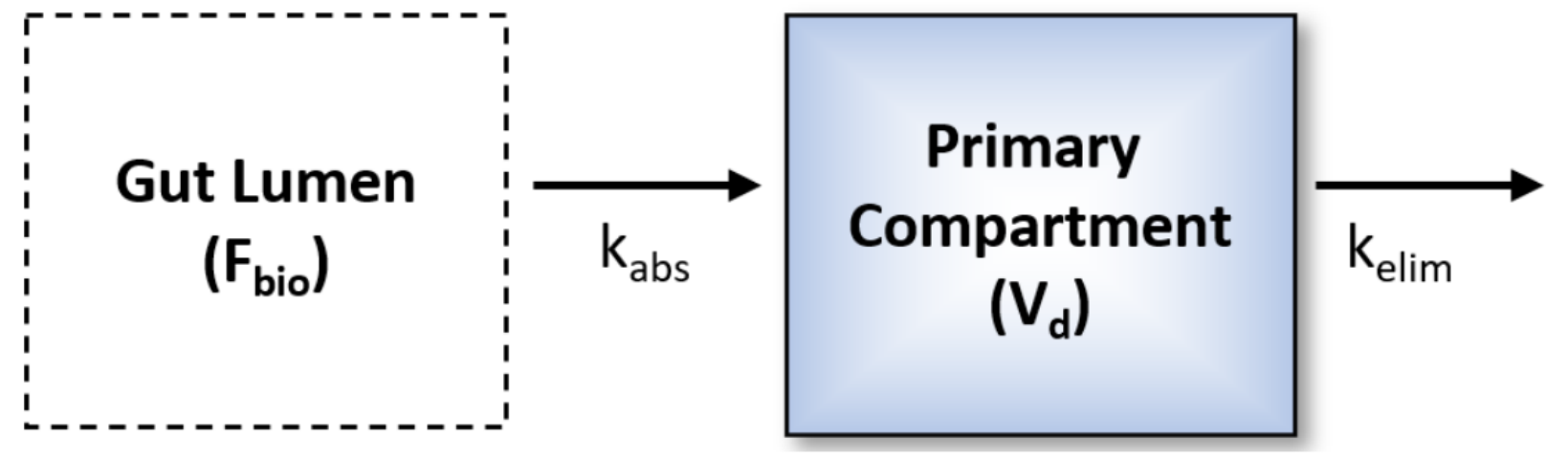


Figure 4: 1-Compartment Model. Adapted from Wambaugh et al. (2018).

$$C_{iv}(dose,\ t)\ =\ \frac{dose}{V_d}e^{(-k_{elim}\,*\,t)}$$

$$C_{oral}(dose,\ t)\ =\ \frac{F_{bio}\ *\ dose}{V_d}\ *\ \frac{k_{abs}\ *\ (e^{-k_{elim}\,*\,t}\ -\ e^{-k_{abs}\,*\,t})}{k_{abs}\ -\ k_{elim}}$$

- Parameters include V_d (volume of distribution), k_{elim} (elimination rate), k_{abs} (absorption rate; oral only), and F_{bio} (fraction bioavailable; oral only).

2-Compartment Model

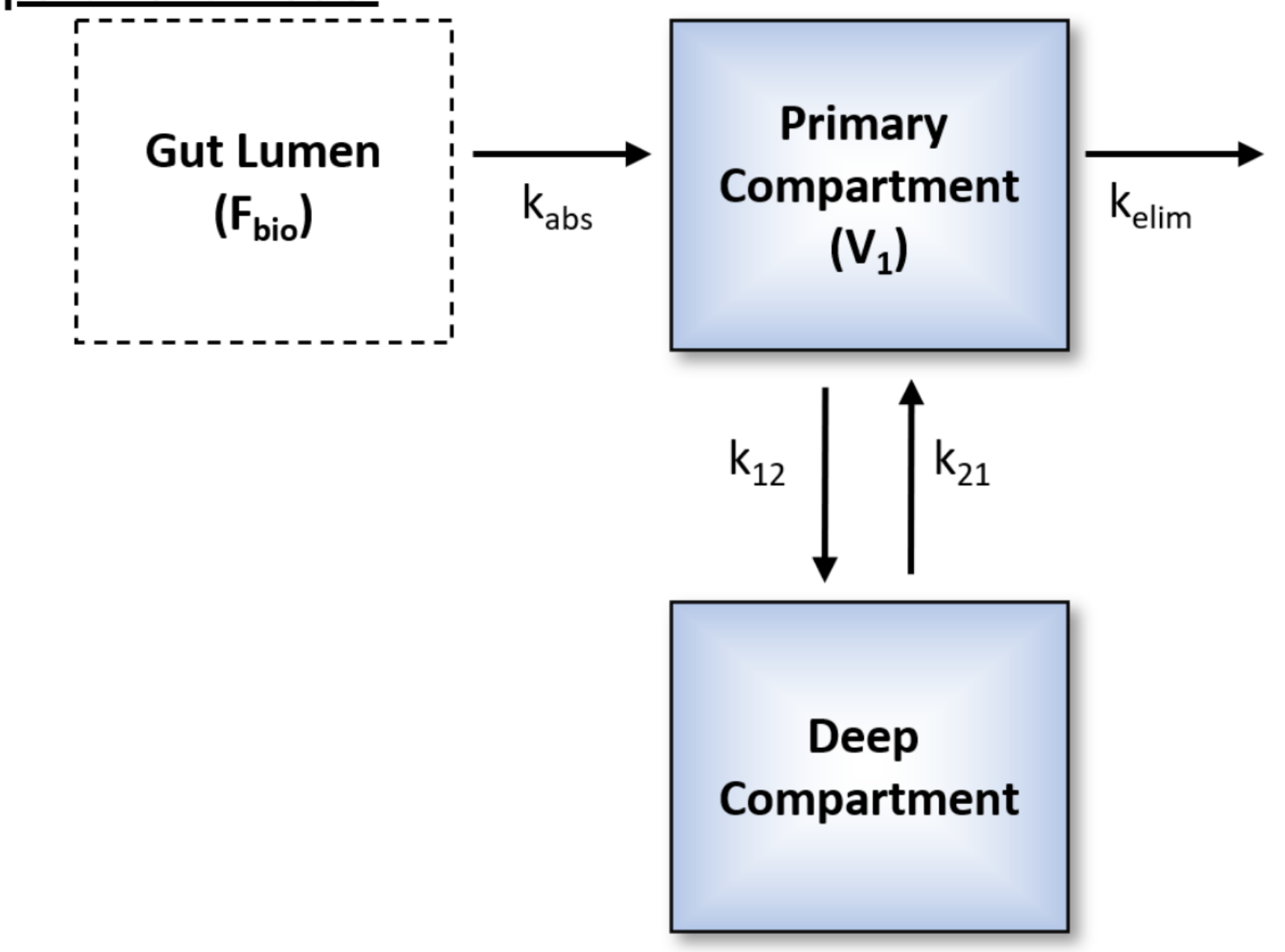


Figure 5: 2-Compartment Model. Adapted from Wambaugh et al. (2018).

$$C_{iv}(dose,\ t)\ =\ A\ *\ e^{-\alpha\,*\,t}\ +\ B\ *\ e^{-\beta\,*\,t}$$

$$C_{oral}(dose,\ t)\ =\ A\ *\ e^{-\alpha\,*\,t}\ +\ B\ *\ e^{-\beta\,*\,t}\ +\ C\ *\ e^{-ka\,*\,t}$$

- Parameters include $V1$ (volume of primary compartment), k_{elim}, k_{12} (distribution rate to deep compartment), k_{21} distribution rate from deep compartment), k_{abs} (oral only), F_{bio} (oral only).

3c) Statistical Model Description

- *invivoPKfit* calculates the probability of C_{obs} given a PK model $M(p,\ t)$ and a statistical model $S(\sigma)$, where $P\ =\ L(C_{obs},\ M,\ S)$, and assumes that C_{obs} are log-normally distributed around the concentrations predicted by $M(p,\ t)$ (Cox and Hinkley, 1979).

$$ln\ L(x,\ \mu,\ \sigma)\ =\ \Sigma_{i=1,n} ln\frac{1}{x\sigma\sqrt{2\pi}}e^{-\frac{1}{2}\left(\frac{ln\ x\ -\ \mu)}{\sigma}\right)^2}$$

$$ln\ L(x,\ \mu,\ \sigma)\ =\ \Sigma_{i=1,n} ln\frac{1}{C_{obs,i}\sigma\sqrt{2\pi}}e^{-\frac{1}{2}\left(\frac{ln\ C_{obs,i}\ -\ M(p,t_i)}{\sigma}\right)^2}$$

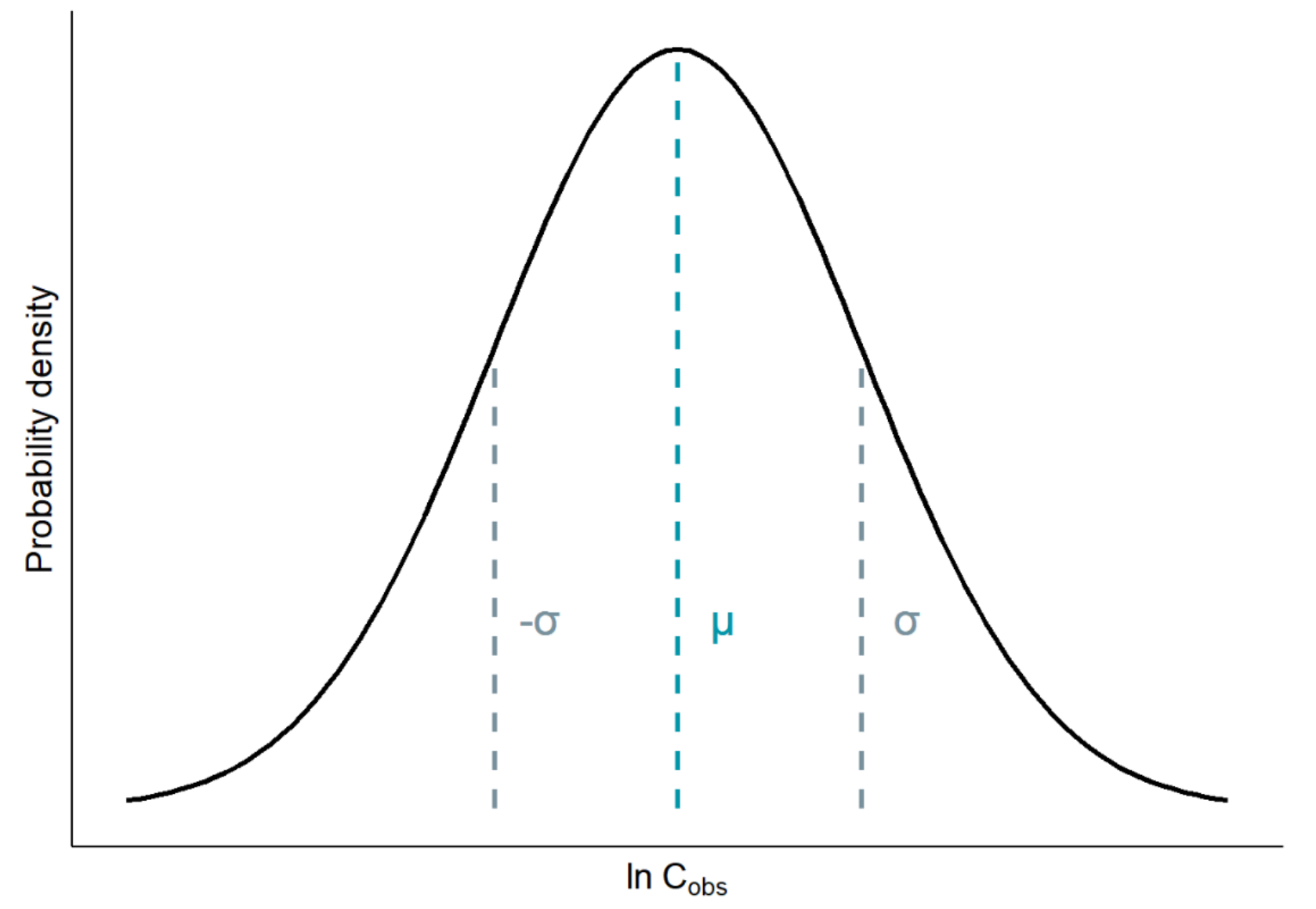


Figure 6: Log-Normal Distribution

- The R package, *optimx* (Nash and Varadhan, 2011; Nash, 2014) optimizes the log-likelihood equation and estimates p and σ.
- We used the Hessian of the likelihood function to estimate standard deviations of the log parameter (Dovi, 1991).

4 *invivoPKfit* Analyses

4a) Predicted Concentrations

- 63.3% of 16,675 concentrations predicted by the 1-compartment model fit within a factor of two of the observed concentrations.
- 69.1% of 13,097 concentrations predicted by the 2-compartment model fit within a factor of two of the observed concentrations.

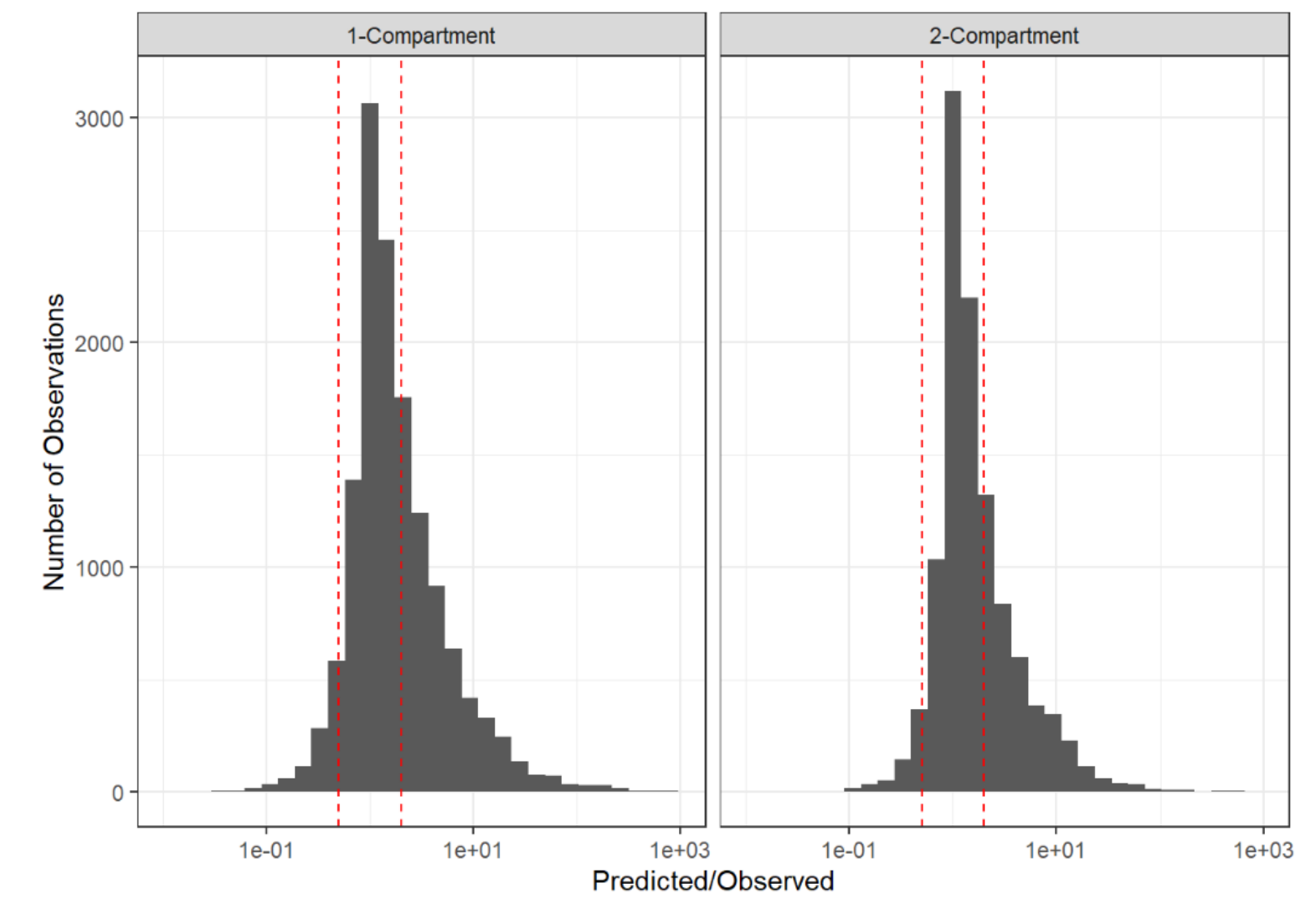


Figure 7: Concentrations were predicted using the estimated model parameters. Predicted concentrations were normalized by observed concentrations, such that C_{pred} / C_{obs} . The red dashed lines mark the 'factor of two' bounds. This plot does not include 'Joint Analysis' fits.

4b) *invivoPKfit* Performance *versus* Data Variability

- Can start to gauge how data variability influences the performance of a model

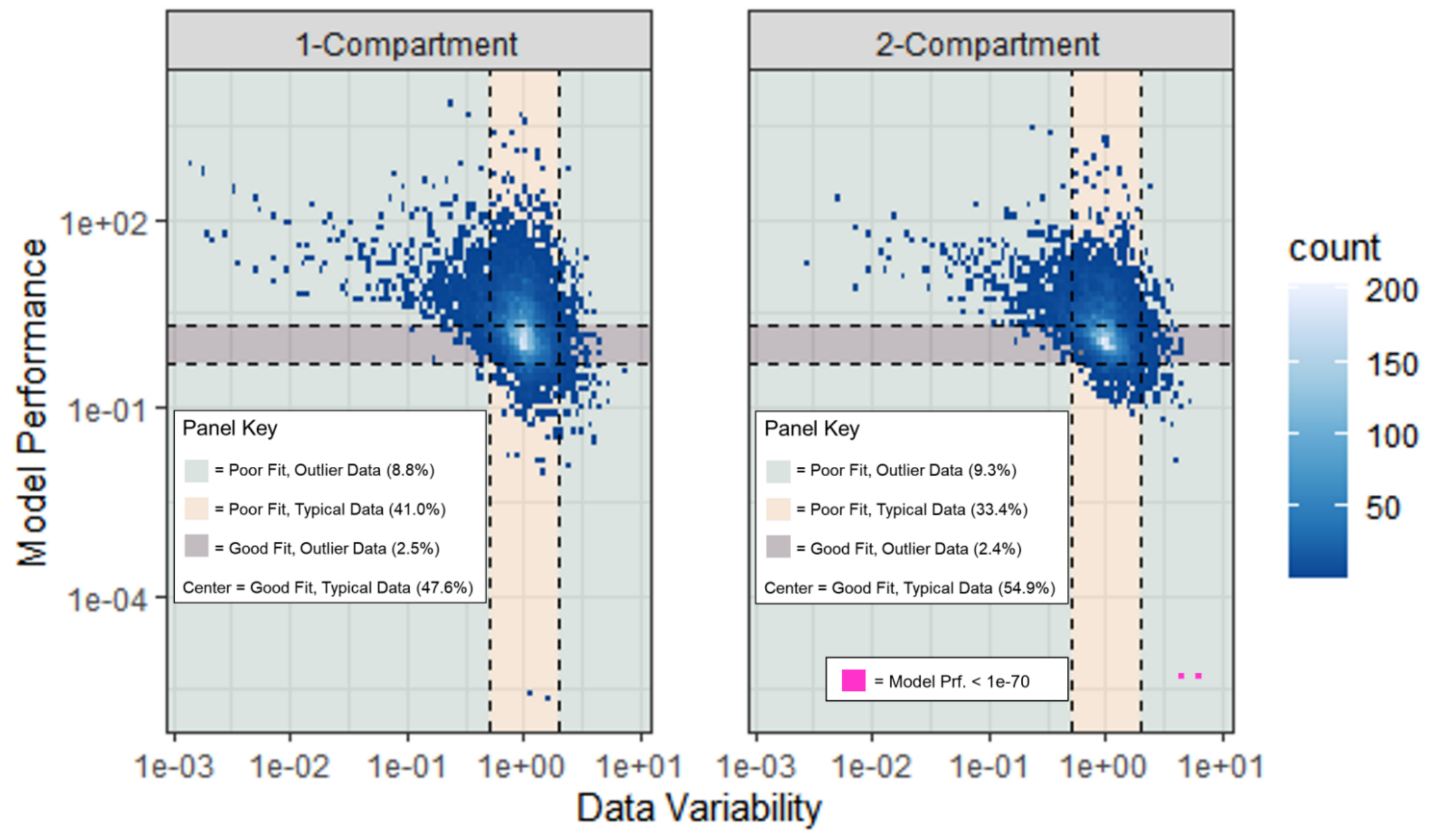


Figure 8: Predicted concentrations were normalized by observed concentrations (see Figure 7), and plotted against observed concentrations normalized by experiment-timpoint specific replicates (see Figure 2). The dashed lines mark the 'factor of 2' bounds for each axis. Sections were assigned based on both the ability of a model to accurately predict an observed concentration and the spread of the observed data. Points colored pink represent concentrations significantly underpredicted by the model.

4c) Diagnosing Poor Fits

- Plotting model predictions against observed data can help determine why a model might fit poorly. A poor fit could indicate 1) a deficiency in the model, 2) an inaccurate curation of data, and/or 3) a deficiency in the experimental collection of data.

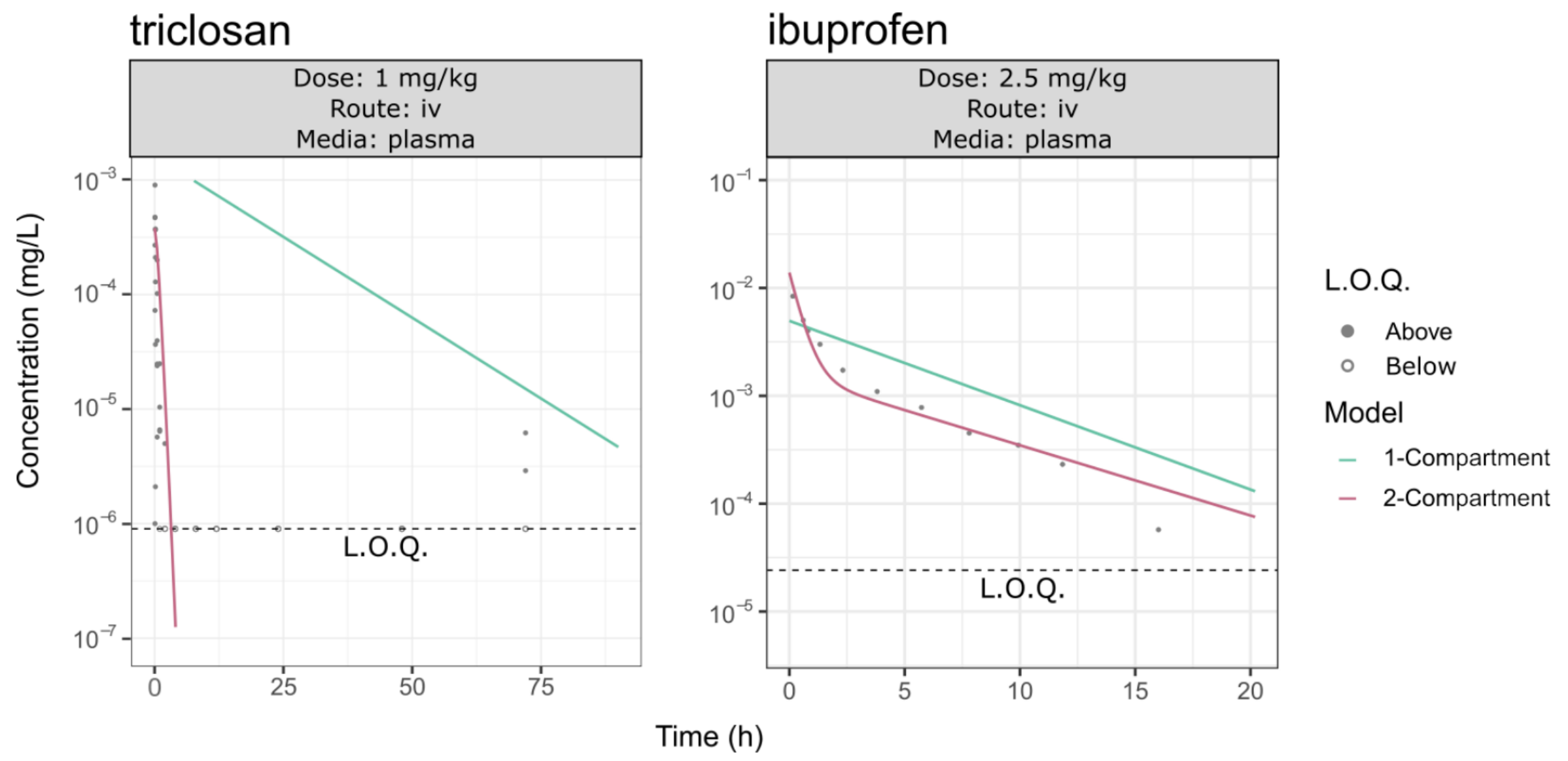


Figure 9: 1-compartment model (green line) and 2-compartment model (red line) fit through CvT data (gray points) Open points represent non-detects that were below the limit of quantitation (L.O.Q.).

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