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).

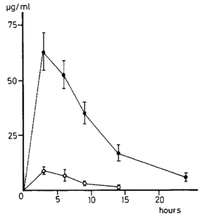

Fig. 1. Plasma concentrations of DEHP (○) and MEHP (●) in rats after single oral administration of 2.8 g/kg DEHP (mean ±SEM; $n = 10$)

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.

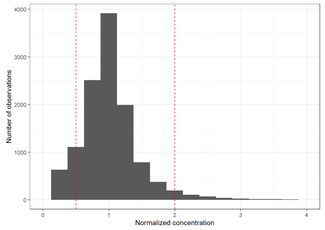

Figure 2: The CvTdb data was grouped into unique combinations of compound/reference/route/dose/timepoint. Groups without replicate timepoints were removed. If all replicate timepoints corresponded to non-detect concentration values, those data were removed. If some, but not all replicate timepoints corresponded 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)

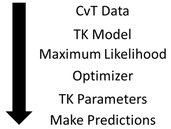

Figure 3: *invivoPKfit* workflow.

3b) TK Model Descriptions

1-Compartment Model

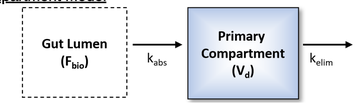

Figure 4: 1-Compartment Model. Adapted from Wambaugh et al. (2018).

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

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

- 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

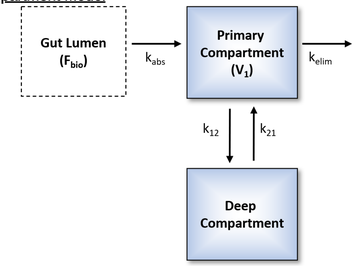

Figure 5: 2-Compartment Model. Adapted from Wambaugh et al. (2018).

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

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

- 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).

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

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

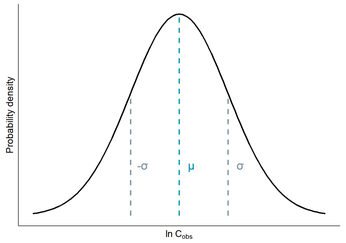

Figure 6: Log-Normal Distribution

- 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.

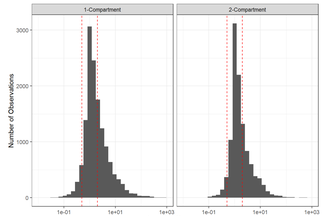

Figure 7: Concentrations were predicted using the estimated model parameters. Predicted concentrations were normalized by observed concentrations, such that C_{pred} / C_{obs} - The red dashed lines mark the 'factor of two' bounds. This plot does not include 'Joint Analysis' fits.

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

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

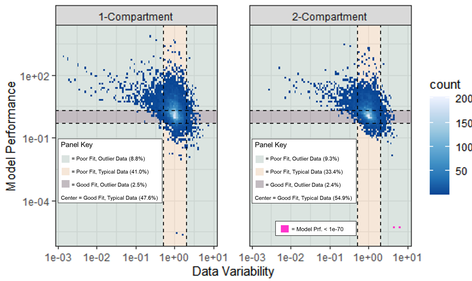

Figure 8: Predicted concentrations were normalized by observed concentrations (see Figure 7), and plotted against observed concentrations normalized by experiment-timpoint specific replicates (see Figure 2). The dashed lines mark the 'factor of 2' bounds for each axis. Sections were assigned based on 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.

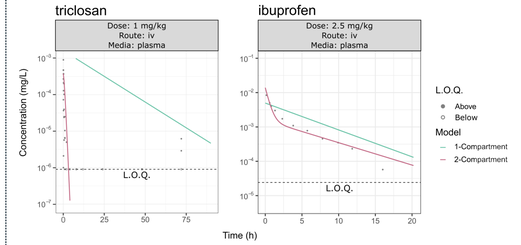

Figure 9: 1-compartment model (green line) and 2-compartment model (red line) fit through CvT data (gray points) Open points represent non-detects that were below the limit of quantitation (L.O.Q.).

References

Boxenbaum, Harold G., Sidney Riegelman, and Robert M. Elashoff. 1974. "Statistical Estimations in Pharmacokinetics." *Journal of Pharmacokinetics and Biopharmaceutics* 2 (2): 123–48. https://doi.org/10.1007/BF01061504.

Cox, D. R., and D. V. Hinkley. 1979. *Theoretical Statistics*. CRC Press.

Dovi, V. G., O. Paladino, and A. P. Reverberi. 1991. "Some Remarks on the Use of the Inverse Hessian Matrix of the Likelihood Function in the Estimation of Statistical Properties of Parameters." *Applied Mathematics Letters* 4 (1): 87–90. https://doi.org/https://doi.org/10.1016/0893-9659(91)90129-J.

Kamiya, Yusuke, Kentaro Handa, Tomonori Miura, Junya Ohori, Makko Shimizu, Masato Kitajima, Fumiaki Shono, Kimito Funatsu, and Hiroshi Yamazaki. 2021. "An Updated in Silico Prediction Method for Volumes of Systemic Circulation of 323 Disparate Chemicals for Use in Physiologically Based Pharmacokinetic Models to Estimate Plasma and Tissue Concentrations After Oral Doses in Rats." *Chemical Research in Toxicology* 34 (10): 2180–3. https://doi.org/10.1021/acs.chemrestox.1c00249.

Kamiya, Yusuke, Shohei Otsuka, Tomonori Miura, Manae Yoshizawa, Ayane Nakano, Miyu Iwasaki, Yui Kobayashi, et al. 2020. "Physiologically Based Pharmacokinetic Models Predicting Renal and Hepatic Concentrations of Industrial Chemicals After Virtual Oral Doses in Rats." *Chemical Research in Toxicology* 33 (7): 1736–51. https://doi.org/10.1021/acs.chemrestox.0c00009.

Kudo, Naomi, Masanori Katakura, Yasunori Sato, and Yoichi Kawashima. 2002. "Sex Hormone-Regulated Renal Transport of Perfluorooctanoic Acid." *Chemico-Biological Interactions* 139 (3): 301–16. https://doi.org/10.1016/s0009-2797(02)00006-6.

Nash, John C. 2014. "On Best Practice Optimization Methods in R." *Journal of Statistical Software* 60 (2): 1–14. https://doi.org/10.18637/jss.v060.i02.

Nash, John C., and Ravi Varadhan. 2011. "Unifying Optimization Algorithms to Aid Software System Users: optimx for R." *Journal of Statistical Software* 43 (9): 1–14. https://doi.org/10.18637/jss.v043.i09.

O'Flaherty, E. J. 1981. *Toxicants and Drugs: Kinetics and Dynamics*. John Wiley & Sons.

Sayre, Risa R., John F. Wambaugh, and Christopher M. Grulke. 2020. "Database of Pharmacokinetic Time-Series Data and Parameters for 144 Environmental Chemicals." *Scientific Data* 7 (1): 122. https://doi.org/10.1038/s41597-020-0455-1.

Sheiner, L. B. 1985. "Analysis of Pharmacokinetic Data Using Parametric Models. II. Point Estimates of an Individual's Parameters." *Journal of Pharmacokinetics and Biopharmaceutics* 13 (5): 515–40. https://doi.org/10.1007/BF01059333.

Thorne, W. Brent. 2019. *Posterdown: An R Package Built to Generate Reproducible Conference Posters for the Academic and Professional World Where Powerpoint and Pages Just Won't Cut It*. https://github.com/brentthorne/posterdown.

Wakefield, Jon, Leon Aarons, and Amy Racine. 1999. "The Bayesian Approach to Population Pharmacokinetic/Pharmacodynamic Modeling." https://doi.org/10.1007/978-1-4612-1502-8_4.

Wambaugh, John F., Michael F. Hughes, Caroline L. Ring, Denise K. MacMillan, Jermaine Ford, Timothy R. Fennell, Sherry R. Black, et al. 2018. "Evaluating in Vitro-in Vivo Extrapolation of Toxicokinetics." *Toxicological Sciences : An Official Journal of the Society of Toxicology* 163 (1): 152–69. https://doi.org/10.1093/toxsci/kfy020.

World Health Organization. 2010. "Characterization and Application of Physiologically Based Pharmacokinetic Models in Risk Assessment." WHO Document Production Services, Geneva, Switzerland.

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