

In Vitro to In Vivo Extrapolation (IVIVE) for High-Throughput Prioritization and Decision Making: The Role of Pharmacokinetic Model Evaluation

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Outline

- Background
- Model evaluation
 - Key questions
 - Sensitivity analysis
- Simplified models/limiting cases
- Take away messages
- Question and answer period

Webinar/Workshop Series

- Setting the Stage: Purpose, Definitions, Scope, and Assumptions
 - Barbara Wetmore (The Hamner Institutes), October 7, 2015
 - Webinar slides and recording available online
- Building Fit-for Purpose Pharmacokinetic Models
 - John Wambaugh (US EPA NCCT), November 4, 2015
 - Webinar slides and recording available online
- **The Role of Pharmacokinetic Model Evaluation**
 - **Lisa Sweeney (Naval Medical Research Unit Dayton)**
- Framework for Establishing an Internal Threshold of Toxicological Concern
 - Corie Ellison (Procter & Gamble), January 6, 2016
- Workshop
 - February 17-18, 2016, US EPA, Research Triangle Park, North Carolina

Background/Review

- ToxCast = Toxicity Forecaster
- The purpose of “toxicology” is risk assessment
 - Risk assessment is the synthesis of exposure assessment and hazard assessment
- Those involved in ToxCast/Tox21 efforts recognized the need for context for in vitro effective doses

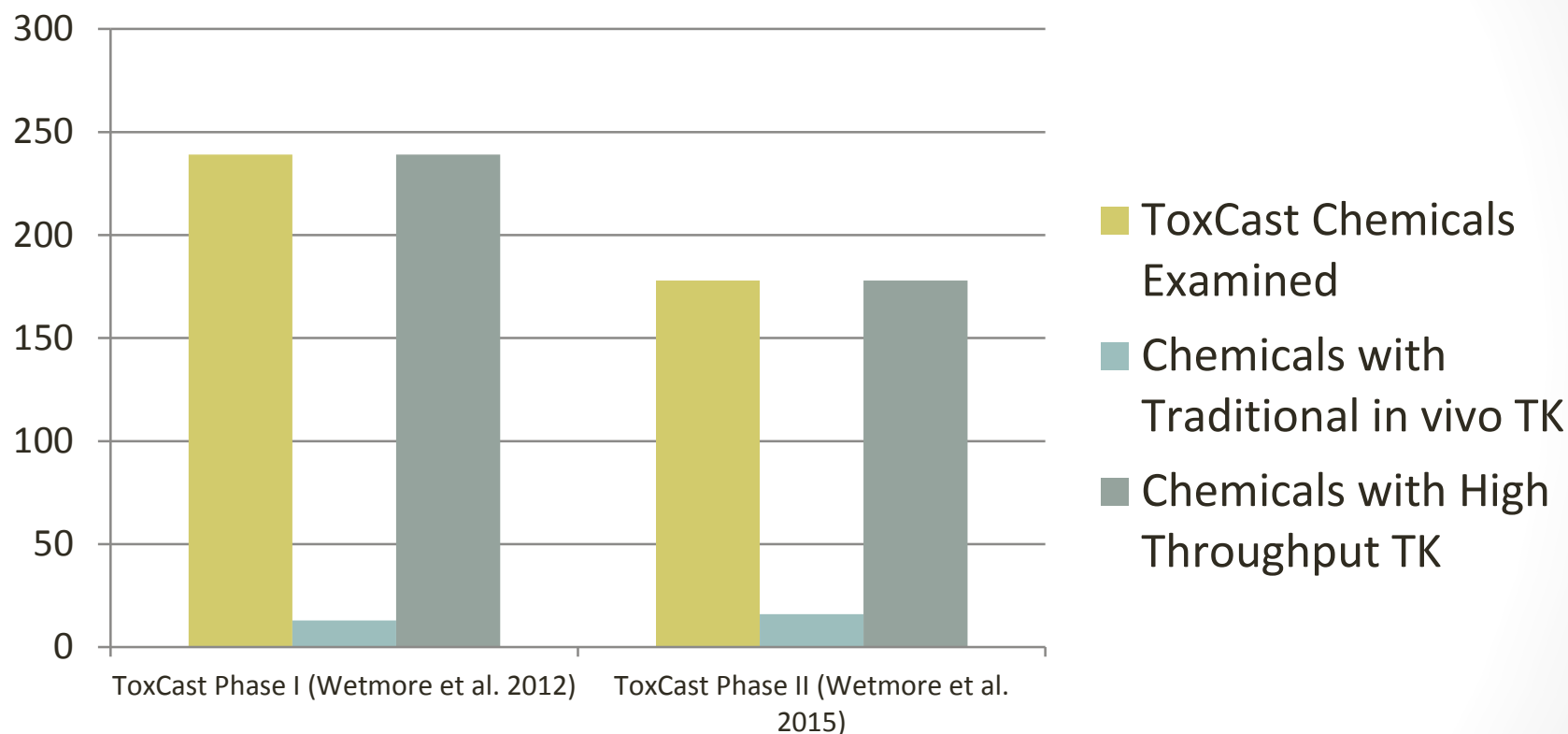
Background/Review

- Dose-response relationships can be divided into pharmacokinetic (PK) and pharmacodynamic (PD) aspects
 - PK: “what the body does to the chemical”
 - PD: “what the chemical does to the body”
- Traditional PK/TK studies are resource intensive
- PK and PD data and models are important in risk assessment because they connect exposure and toxicity



Background/Review

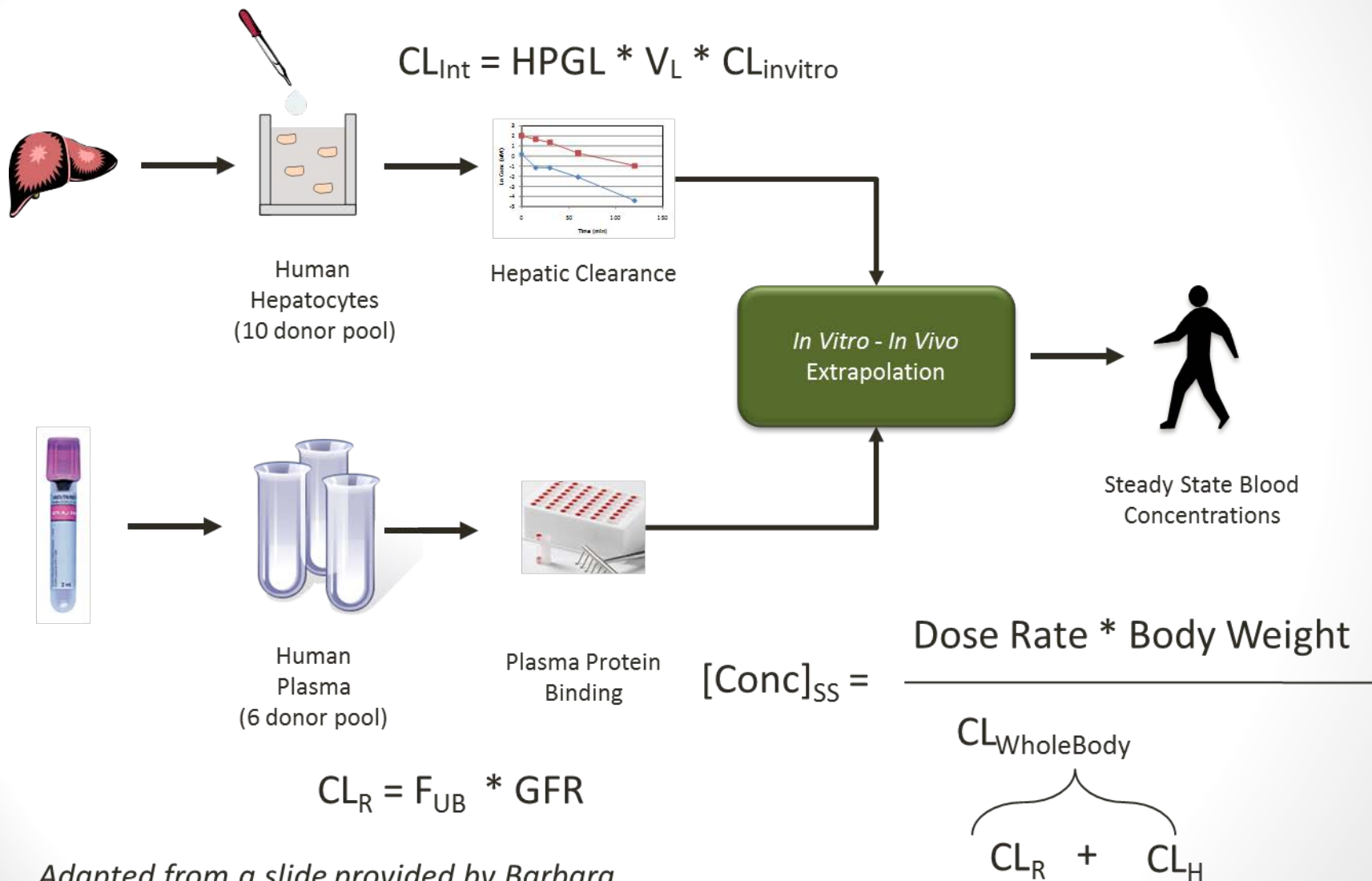
The need for *in vitro* toxicokinetics



- Studies like Wetmore et al. (2012) addressed the need for TK data using *in vitro* methods

Courtesy of John Wambaugh, EPA

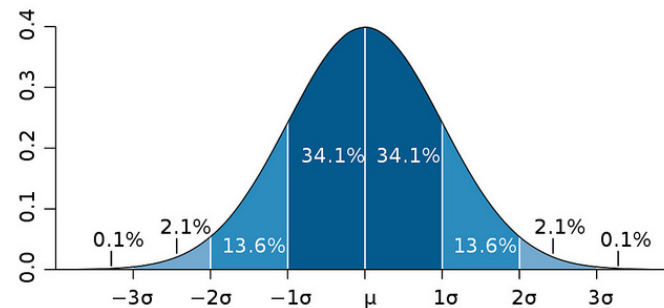
IVIVE in a High-Throughput Environment -- Modeling *In Vivo* Pharmacokinetics Using *In Vitro* Assays



Adapted from a slide provided by Barbara Wetmore, The Hamner Institutes

Background/Review

- Simplistic models are used to estimate oral equivalent dose (OED) for an effective in vitro concentration
 - E.g., dose that in 95% of simulated individuals produces steady-state blood concentrations below the lowest effective in vitro concentration
- OEDs are compared to exposure estimates to prioritize chemicals for research/testing



Model Evaluation: Introduction

- Goal: To assess model confidence for either a specific application or a spectrum of (tiered) applications
 - Prioritization vs. IRIS RfD or slope factor
 - Level of model confidence vs. acceptable margin of exposure
- We will assume a model has already been built
 - Model building is frequently iterative
 - Initial model evaluation may identify modifications required/desired for a particular purpose
- Key questions adapted from McLanahan et al. (2012)

Model Evaluation:

Key questions



- How biologically realistic is the model structure vs. how realistic does it need to be?

- Lumping vs. splitting



- Is the model suitable for intended use? /For what uses is the model suitable?

- Species, exposure route/scenario, suitable metrics

- Simplified, steady-state models may not be suitable for short, dynamic life stages (e.g. pregnancy)



Model evaluation: Key questions



- Are the mathematical description and computational implementation adequately verifiable?
- Reconstruction of a model from a literature description only is often challenging
 - Examples
 - Metabolism based on liver tissue or blood concentration
 - Missing parameter values
 - Lack of clarity regarding scaling
 - Tissue: blood vs. tissue: air partition coefficients

Model evaluation: Key questions



- Is the model verifiable?
 - Can previous simulations be reproduced?
- Evaluate model performance
 - Has model been tested against all (or most) of the appropriate literature data?
 - Not all published models have been comprehensively evaluated
 - How well did the model perform?
 - How good is “good enough”?
 - One recommendation is, on average, within a factor of 2 (IPCS, 2010)
 - How well is the model known/expected to perform in the scenario of interest (e.g., low vs. high concentrations)

Model evaluation: Key questions



- Evaluate parameter values
 - Are values consistent with well-vetted collections?
 - Are values suitable for the scenario of interest?
 - Population: general public, workers, subpopulations, level of activity
 - Timing (e.g., background exposure to Pb has decreased dramatically in 40 years)

Model evaluation: Key questions

- Evaluate parameters (cont'd)
 - Have the variability and/or uncertainty in the parameter values been characterized?
 - Sensitivity analysis may be very helpful in prioritizing parameters for scrutiny and will be further discussed



Model evaluation: Key questions



- Evaluate parameters (cont'd)
 - Are assumptions about parameters supportable?
 - Species/strain/ethnic differences minimal, or substantial?
 - Parallelogram approach (supported by values determined for another species)
 - Read across (supported by values determined for another chemical)
 - If not a “purely” predictive model (e.g., parameters were optimized), can confidence in optimized parameters be judged (“identifiability”)?

Model evaluation: conclusions

- **Assess model applicability and confidence based on answers to previous questions and additional considerations**
- Level of model confidence may limit application or have other implications
 - With higher model confidence, smaller MOEs might be considered acceptable

Sensitivity analysis

- Sensitivity analysis involves determination of how a change in input affects the model output (prediction)
- Analysis can be done using many different approaches
- Reference point should be clearly defined
 - Sensitivity of (metric) (moiety) (compartment) (measured when) (exposed to what, when, how, how much) for what population
 - E.g., Sensitivity of the concentration of Chemical X in the venous blood after 10 years of continuous ingestion of X at the Oral Equivalent Dose by a healthy adult with no other exposure to X

Sensitivity analyses approaches

- Direct comparison of two groups
 - Healthy adults vs. adults with renal failure
 - People exposed for 2 years vs. 20 years
- Local sensitivity analysis
 - E.g., make a 1% change in one input parameter, determine change in output
 - Typically, the results are normalized to starting values (fractional change in output/fractional change in input) = normalized sensitivity coefficient (NSC)

- $$\text{NSC}_{C:P} = \frac{\frac{C_1 - C_0}{C_0}}{\frac{P_1 - P_0}{P_0}}$$

Local sensitivity analysis example

- Example

- $$\text{NSC}_{C:P} = \frac{\frac{C_1 - C_0}{C_0}}{\frac{P_1 - P_0}{P_0}} = 100 \times \left(\frac{C_1}{C_0} - 1 \right)$$

where C_1 = predicted concentration when P_1 is set to $P_0 \times 1.01$, and C_0 = predicted concentration at baseline condition ($P = P_0$)

- If C is directly proportional to P, $\text{NSC}_{C:P} = 1$
- If C is inversely proportional to P, $\text{NSC}_{C:P} = -1$

Global sensitivity analysis (McNally et al., 2011)

- Greater coverage of parameter space
- McNally et al. (2011) propose the following workflow
 - Conduct a screening exercise to identify most important parameters (Morris test)
 - Average of results of multiple local sensitivity analyses
 - Identify time period of interest and perform extended Fourier amplitude sensitivity test
 - Graphical presentation of results (Lowry plot)
 - Visualize the contribution of various parameters to total variance
- Interactions of parameters need to be delineated

Local sensitivity analysis applications

- Reverse dosimetry: The difficulty is that the “dose” is an INPUT, not an OUTPUT, of the model.....

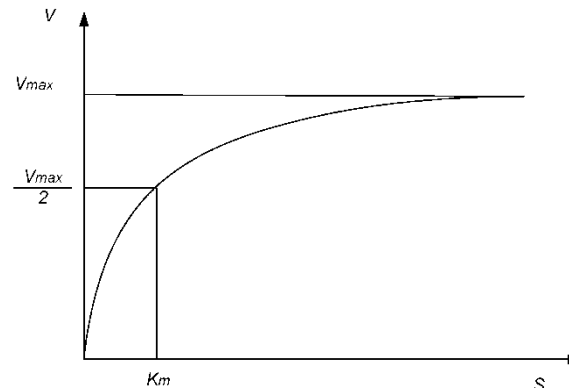
$$\text{However, } NSC_{C:D} = \frac{1}{NSC_{D:C}}$$

And $NSC_{D:P} = NSC_{D:C} \times NSC_{C:P}$, so in a limited range,

$$NSC_{D:P} = \frac{NSC_{C:P}}{NSC_{C:D}}$$

Local sensitivity analysis applications

- Parameter “identifiability” (Key question for parameter value evaluation)
 - For optimized parameters to be identified with confidence from experimental data, the metrics (e.g., blood concentration, fraction of dose exhaled) must be “sensitive” to the value(s) of the parameter being optimized when the scenario in the experiment is simulated.
 - In low dose studies (e.g., most human studies), both V_{max} and K_M may not be uniquely identifiable



Local sensitivity analysis applications

- Prioritize parameters for uncertainty and/or variability analysis
 - Product of sensitivity and variability (or uncertainty) drives the spread of predicted possible outcomes
- Use LSA results in model variability predictions

$$CV_m = \sqrt{\sum_i ((NSC_{m:i})^2 \times CV_i)}$$

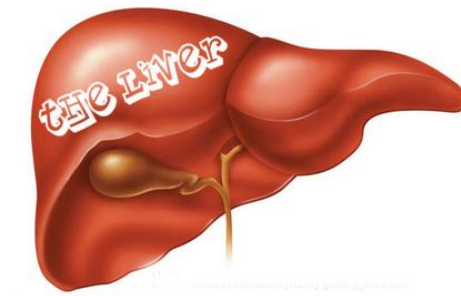
Where CV = coefficient of variation, m= model output, i = model input parameters, and inputs are normally distributed (Licata et al., 2001; Sweeney et al., 2003)

Impact of model sensitivity information on model confidence

- Which parameters are the largest contributors to variability in model predictions?
- If key parameters were optimized/estimated, were they identifiable from fit to TK data?
- If key parameters were estimated, are the estimates supportable, and to what degree?

Simple PK models of Wetmore and co-workers

- Described in Rotroff et al. (2010), Wetmore et al. (2012, 2015) and other publications
- Use metabolic clearance by mixed donor hepatocytes and plasma protein binding
- Predict steady state blood concentrations of administered compound

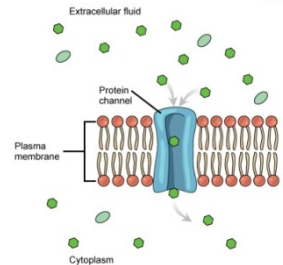


Evaluation of “simple” PK models

- Oral equivalent dose (OED) [=] mg/kg/d
- $OED \times \text{bioavailability} \times \text{body weight} = \text{in vitro POD} \times CL_{WB}$
- $OED = \frac{\text{In vitro POD} \times CL_{WB}}{\text{bioavailability} \times BW}$
 - $CL_{WB} = CL_R + CL_H$
 - $CL_R = GFR \times f_{ub}$
 - $CL_H = \frac{Q_H \times f_{ub} \times CL_{intH}}{Q_H + f_{ub} \times CL_{intH}}$

Evaluation of “simple” PK models

- “Is the model structure (sufficiently) biologically realistic?”
 - Often yes, but not always
 - PCBs (highly lipophilic; may not achieve steady-state)
 - PFCs (ion transporters)
- “Is the model suitable for intended use? /For what uses is the model suitable?”
 - Oral vs. inhalation, dermal
 - Generally suitable for prioritization of large numbers of direct-acting chemicals
 - HTTS and HTTK are not optimized for chemicals acting via metabolite(s)
 - Highly unlikely to be deemed suitable to derive Toxicity Reference Values used as the basis of clean up criteria



Evaluation of “simple” PK models

- “Are the mathematical description and computational implementation adequately verifiable?”
 - Baseline model, definitely
 - Correlated Monte Carlo implementation (Jamei et al. 2009), more challenging
- “Is the model verifiable/reproducible?”
 - Mostly (see Wambaugh et al. 2015)



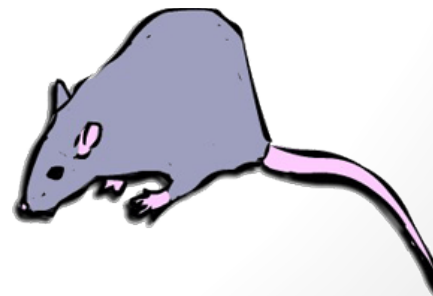
Evaluation of “simple” PK models

- Evaluate model performance
 - “Has model been tested against all (or most) of the appropriate literature data?”
 - Cannot answer; my strategy as a manuscript reviewer would have been to pick a couple of chemicals and do literature searches
 - “How well did the model perform?”
 - Wetmore et al. 2012
 - 13 environmental chemicals evaluated in vivo
 - 6 were “comparable” to predictions (~10x)
 - 5 were significantly overpredicted
 - 2 were underpredicted



Evaluation of “simple” PK models

- Evaluate model performance
 - “How well did the model perform?”
 - Wambaugh et al. 2015 addressed a somewhat different question—how well are the models expected to perform within a chemical space of interest (349 HTTK chemicals)
 - Based on 89 chemicals with in vivo and HTTK data, important descriptors for predictivity were determined (“trriage”)
 - For the HTTK chemical space, the expectations are
 - 140 C_{ss} predictions within 3.2x
 - 102 C_{ss} overpredictions by 3.2x or greater
 - 8 C_{ss} underpredictions by 3.2x or greater
 - 99 for which additional data will be needed
 - While extensive human validation is unlikely, rodent validation could increase confidence



Evaluation of “simple” PK models

- Evaluate model performance
 - “How well is the model known/expected to perform in the scenario of interest”
 - Undetermined; I found no systematic comparison of C_{ss} predictions vs. C in the series of papers
 - In general, extrapolation to lower doses and concentrations is less problematic than extrapolation to higher doses and concentrations
- Evaluate parameter values
 - “Are values suitable for the scenario of interest?”
 - Baseline values are suitable for healthy adult (non-geriatric) humans
 - “Are values consistent with well-vetted collections?”
 - Yes

Evaluation of “simple” PK models

- Evaluate parameter values
 - “Are assumptions about parameters supportable?”
 - “Have the variability and/or uncertainty in the parameter values been characterized?”
 - Yes, but could be more chemical specific
 - Default CV (0.3) for intrinsic and renal clearance (Wetmore et al. 2012)

Sensitivity analysis for Simple PK models of Wetmore and co-workers

- $OED = \frac{In\ vitro\ POD \times CL_{WB}}{bioavailability \times BW}$
- $CL_{WB} = CL_R + CL_H$
 - $CL_R = GFR \times f_{ub}$
 - $GFR = GFR_C \times BW^{0.7}$
 - $CL_H = \frac{Q_H \times f_{ub} \times CL_{intH}}{Q_H + f_{ub} \times CL_{intH}}$
 - $Q_H = QH_C \times QC_C \times BW^{0.7}$
 - $CL_{intH} = CL_{u,in\ vitro} \times HPGL \times V_L$
 - $CL_{u,in\ vitro} = \frac{CL_{in\ vitro}}{f_{uhep}}$
 - $VL = VL_C \times BW$

Sensitivity analysis for Simple PK models of Wetmore and co-workers

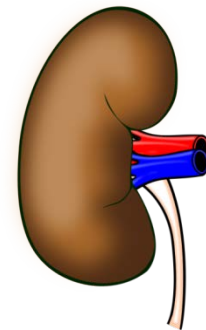
- OED is directly proportional to in vitro POD
 - (NSC = 1)
- OED is inversely proportional to bioavailability
 - (NSC = -1)
- Even with a “simple” model, some sensitivity relationships may not be intuitive
 - Limiting cases may instructive

Sensitivity analysis for Simple PK models of Wetmore and co-workers

- Limiting case: Strictly renal clearance (metabolism = 0)

$$\begin{aligned}
 \bullet \quad OED &= \frac{In\ vitro\ POD \times CL_{WB}}{bioavailability \times BW} = \frac{In\ vitro\ POD \times CL_R}{bioavailability \times BW} \\
 &= \frac{In\ vitro\ POD \times GFR \times f_{ub}}{bioavailability \times BW} = \frac{In\ vitro\ POD \times GFR_C \times BW^{0.7} \times f_{ub}}{bioavailability \times BW} \\
 &= \frac{In\ vitro\ POD \times GFR_C \times f_{ub}}{bioavailability \times BW^{0.3}}
 \end{aligned}$$

- OED is directly proportional to f_{ub}
 - $NSC_{OED:fub} = 1$
- OED is inversely proportional to $BW^{0.3}$
 - $NSC_{OED:BW} = -0.3$
- OED is insensitive to any parameters not in the last OED equation (NSC = 0 for QHC, etc.)



Sensitivity analysis for Simple PK models of Wetmore and co-workers

- Limiting case: metabolism slow relative to hepatic blood flow

$$OED = \frac{In\ vitro\ POD \times CL_{WB}}{bioavailability \times BW} = \frac{In\ vitro\ POD \times (CL_R + CL_L)}{bioavailability \times BW}$$

- $CL_H = \frac{Q_H \times f_{ub} \times CL_{intH}}{Q_H + f_{ub} \times CL_{intH}} = f_{ub} \times CL_{intH} = f_{ub} \times CL_{u,in\ vitro} \times HPGL \times V_L$
- $CL_H = f_{ub} \times CL_{u,in\ vitro} \times HPGL \times VL_C \times BW$

$$OED = \frac{In\ vitro\ POD \times (GFR_C \times BW^{0.7} \times f_{ub} + f_{ub} \times CL_{u,in\ vitro} \times HPGL \times VL_C \times BW)}{bioavailability \times BW}$$

$$OED = \frac{In\ vitro\ POD \times f_{ub} (GFR_C \times BW^{-0.3} + (CL_{in\ vitro} \times HPGL \times VL_C) / f_{uhep})}{bioavailability}$$

- OED is proportional to f_{ub} ($NSC_{OED:fub} = 1$)
- OED is insensitive to QHC, QCC ($NSC_{OED:QHC} = 0$, $NSC_{OED:QCC} = 0$)
- Other NSC depend on fractional contribution of urinary vs. metabolic clearance

Sensitivity analysis for Simple PK models of Wetmore and co-workers

- Limiting case: hepatic metabolism rapid relative to hepatic blood flow

- $$OED = \frac{In\ vitro\ POD \times CL_{WB}}{bioavailability \times BW} = \frac{In\ vitro\ POD \times (CL_R + CL_L)}{bioavailability \times BW}$$

- $$CL_H = \frac{Q_H \times f_{ub} \times CL_{intH}}{Q_H + f_{ub} \times CL_{intH}} = Q_H = Q_{HC} \times Q_{CC} \times BW^{0.7}$$

$$OED = \frac{In\ vitro\ POD \times (GFR_C \times BW^{0.7} \times f_{ub} + Q_{HC} \times Q_{CC} \times BW^{0.7})}{bioavailability \times BW}$$

$$OED = \frac{In\ vitro\ POD \times (GFR_C \times f_{ub} + Q_{HC} \times Q_{CC})}{bioavailability \times BW^{0.3}}$$

- OED is inversely proportion to $BW^{0.3}$
 - $NSC_{OED:BW} = -0.3$
- OED is insensitive to in vitro clearance rate, hepatic binding
- Other NSC depend on fractional contribution of urinary vs. liver blood flow-limited clearance

Summary/Take Home Messages

- Model evaluation principles are applicable to models of varying complexity
- Model evaluation is dependent on having a context for model use/application
- Formal sensitivity analysis can focus model evaluation on key parameters
- Even “simple” models can be challenging to evaluate
- In general, there are good reasons to believe the human HTTK models being generated for IVIVE are sufficiently accurate for the intended application
 - The tendency for these models to err in a conservative direction may not be a significant drawback in that context

References

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Thank you for your interest

- Questions?