High-throughput Pharmacokinetics for Drug Discovery

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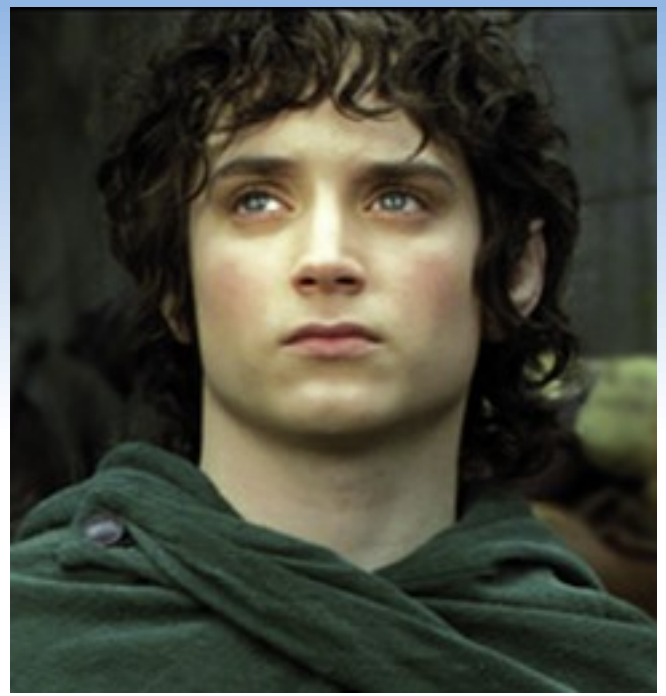
Many Key Properties Can be Estimated Individually *in silico*

- Acid/base dissociation constants (pK_a's) & ionization
- Solubility and tendency to supersaturate
- Lipophilicity
- Intestinal permeability
  - quantitative: passive permeability & local models
  - qualitative: susceptibility to active uptake or efflux on transporters
- Metabolism
  - quantitative: cytochrome P450 (CYP) clearance & local models
  - qualitative: glucuronidation & glutathione conjugation
- Binding to plasma proteins, to red blood cells & within tissues



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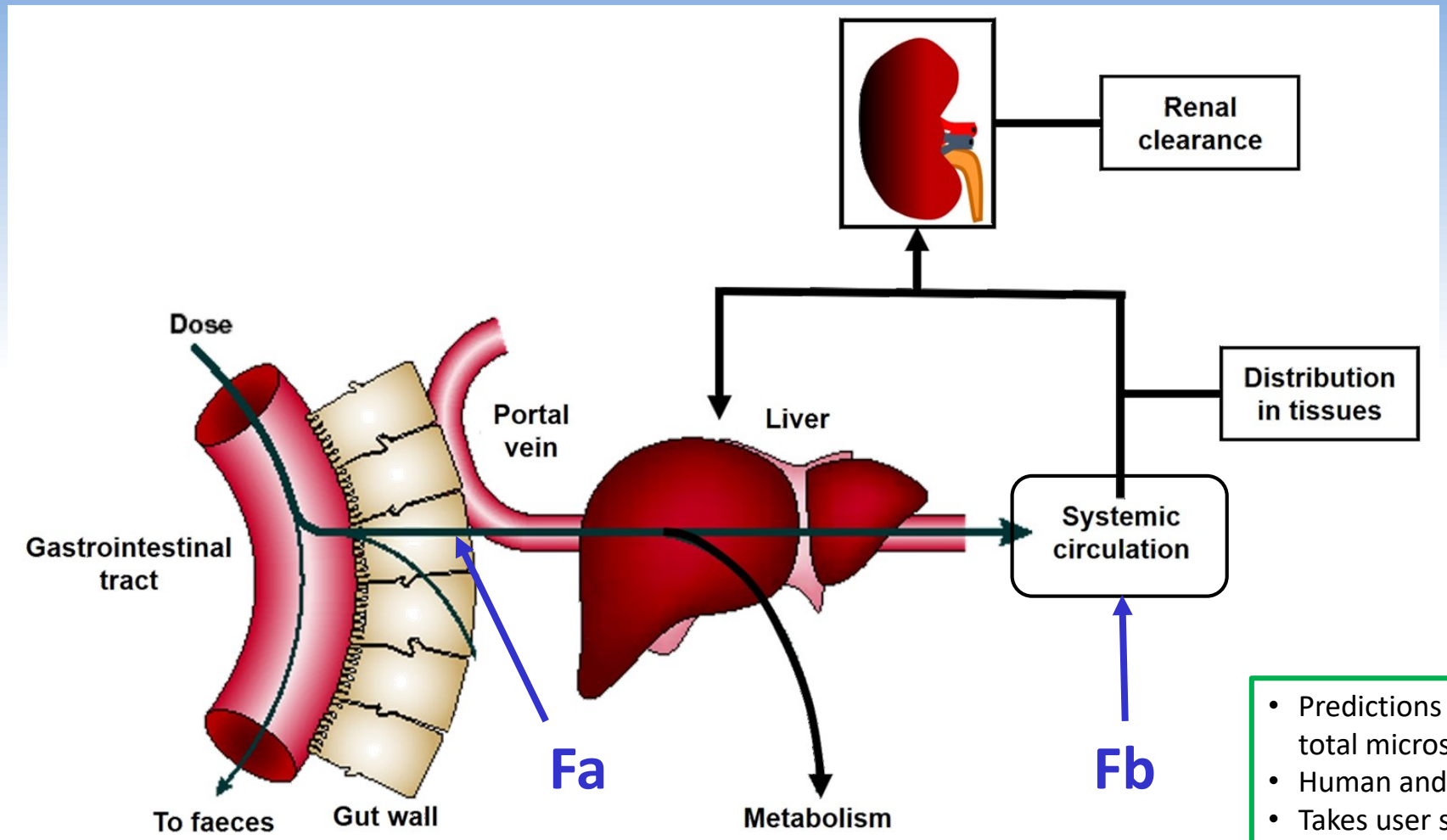
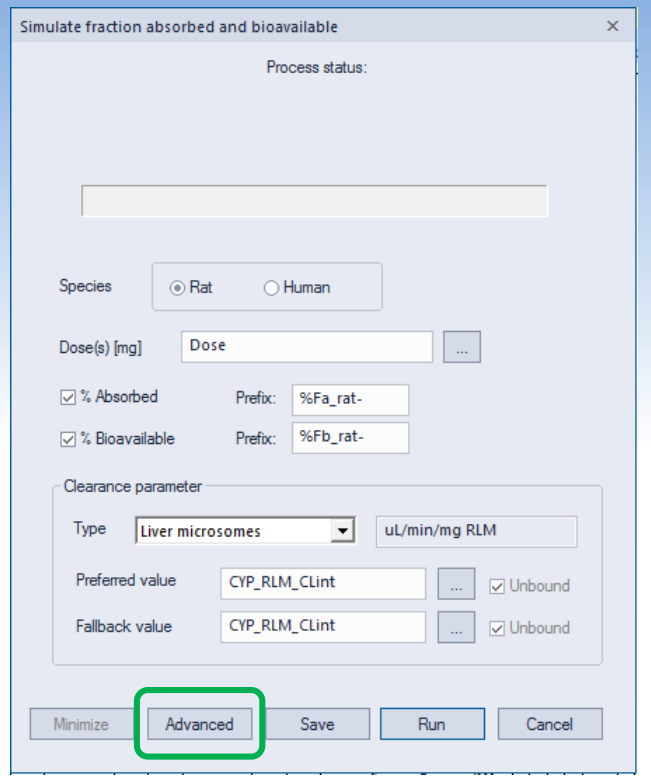
➢ *It takes Physiologically-Based Pharmacokinetic (PBPK) simulation to bind them all.*

HTPK Simulation Is Relatively Simple…





- Predictions provided for physicochemical properties and total microsomal CYP clearance
- Human and rat both supported
- Takes user specified data or predictions where available

"A thing should be made as simple as possible, but no simpler."
- Albert Einstein

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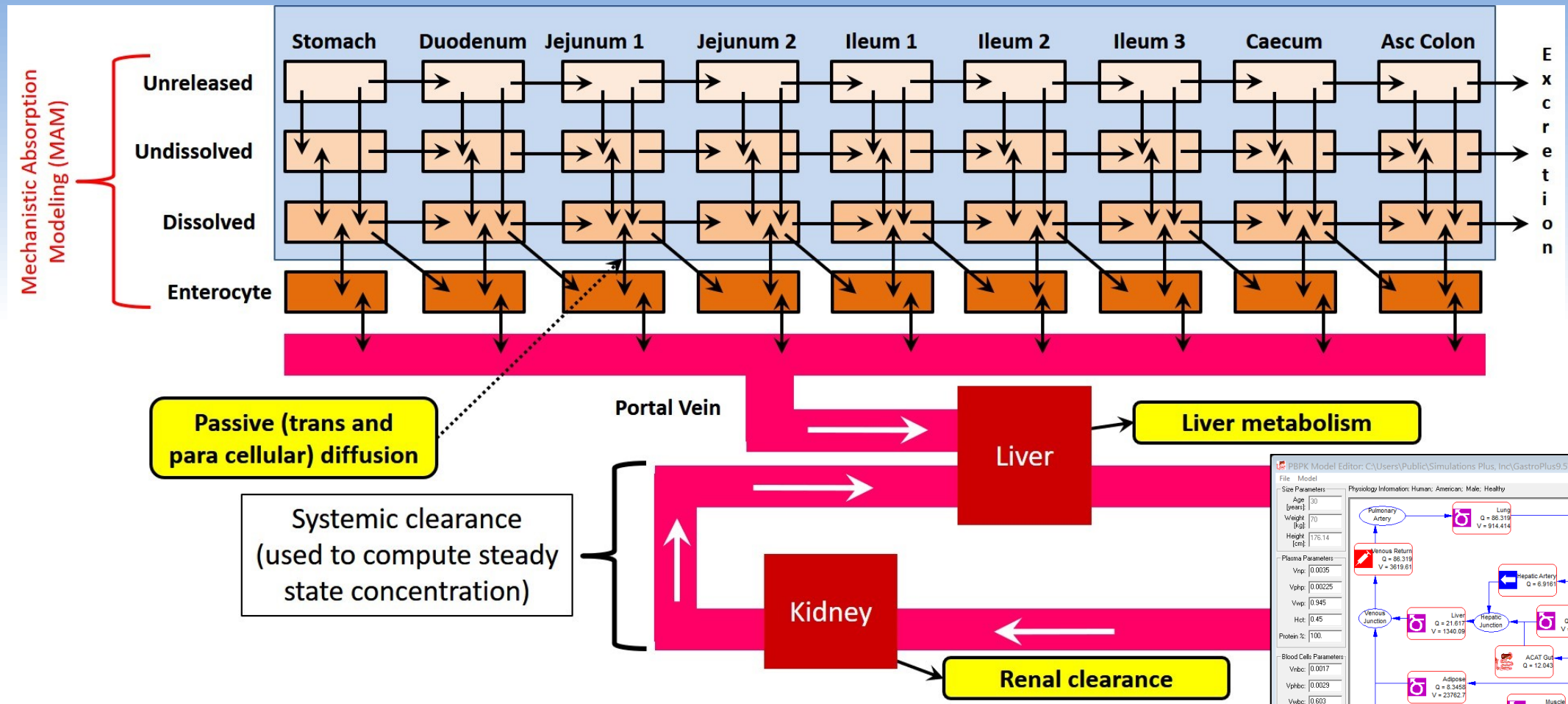
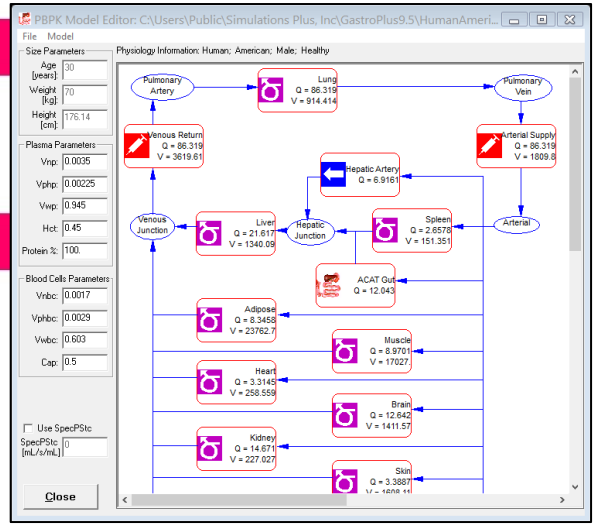
…But Complicated Enough to Get the Job Done

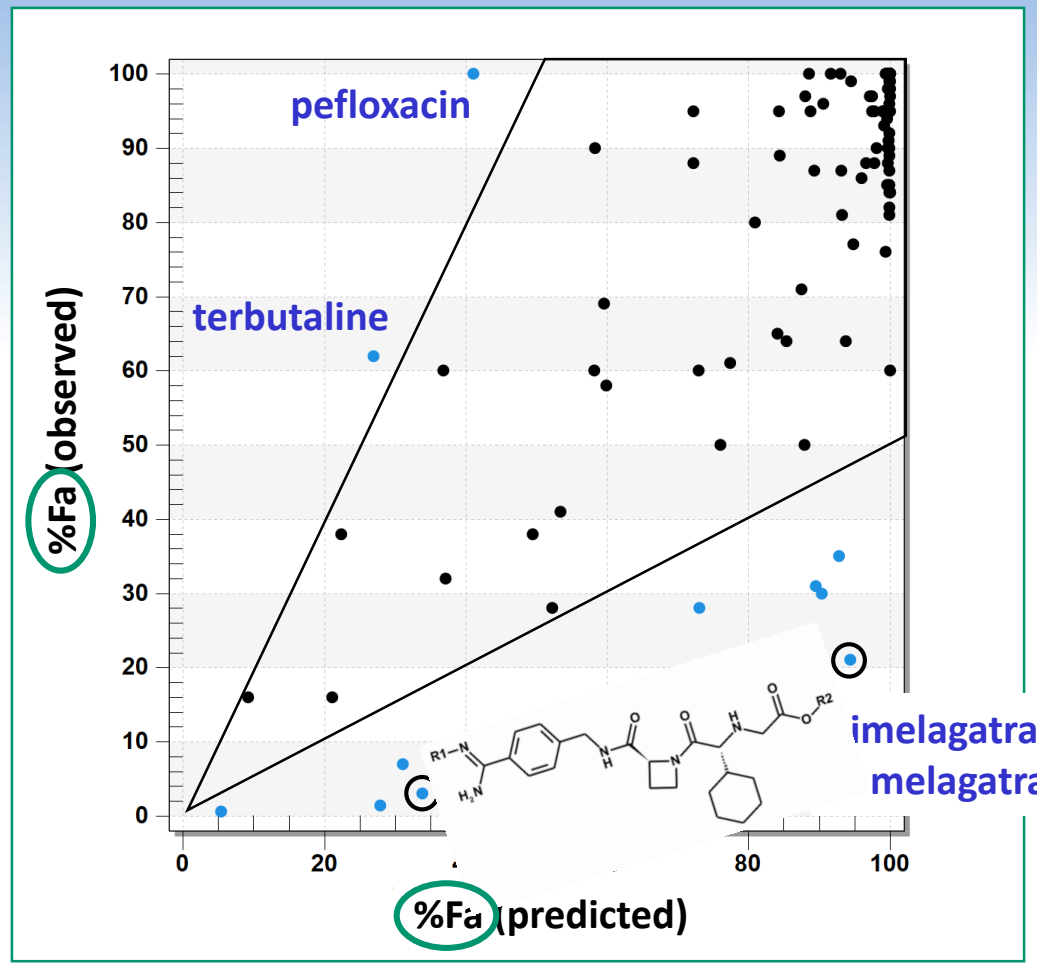




HTPK Simulation in ADMET Predictor™ uses the **A**dvanced **C**ompartmental **A**bsorption and **T**ransit (**ACAT™**) Model from GastroPlus™, lumping everything else other than liver and kidney into a single central compartment.

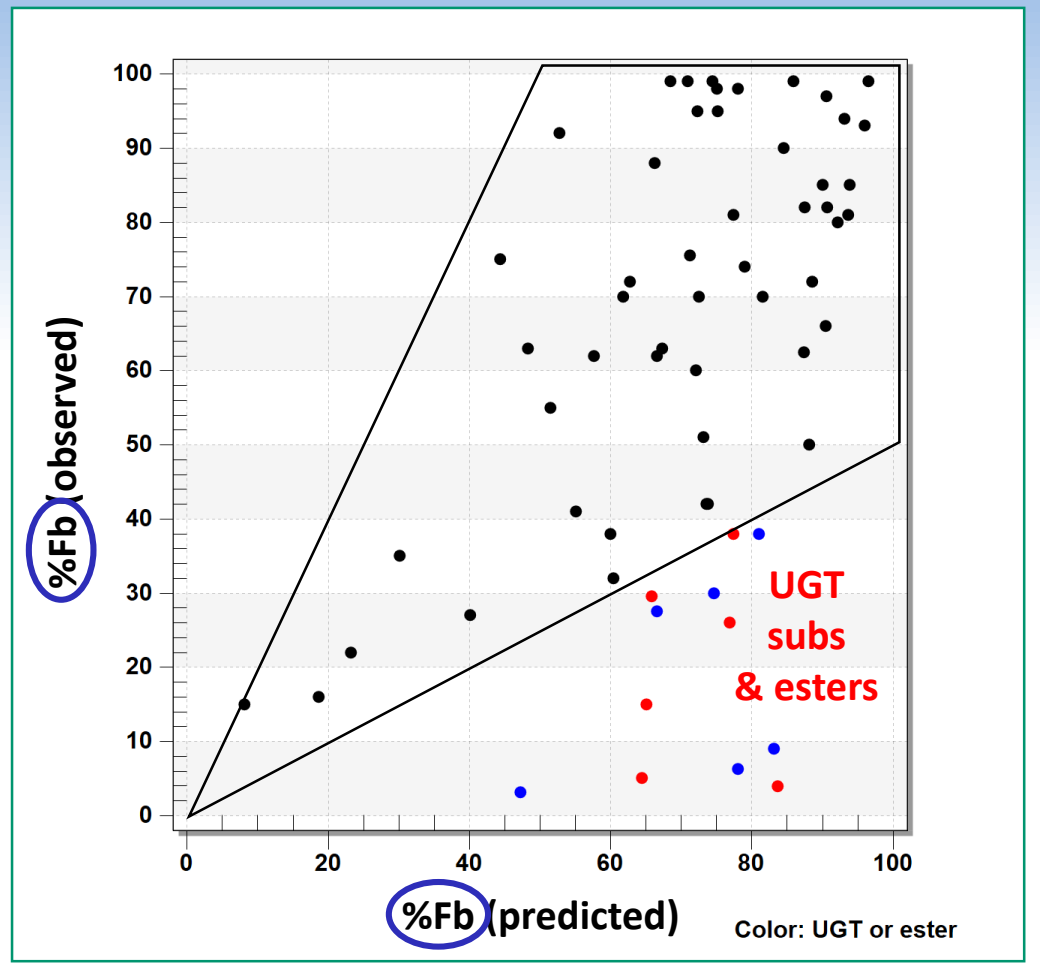
Does HTPK Give Good Enough Answers?

Human %Fa for 115 compounds
(Zhao et al. *J. Pharm. Sci.*, **2001**, 90: 749 and elsewhere)



90% predicted within 2-fold of the reported value.
83% predicted within 1.5-fold.

Human %Fb for 62 CYP-metabolized compounds
(Toshimoto et al. *Drug Metab. Dispos.* **2014**, 42:1811 etc.)



81% predicted within 2-fold of the reported value.
68% predicted within 1.5-fold

Let's Avoid the Streetlight Effect…

Big data's 'streetlight effect': where and how we look affects what we see.
https://theconversation.com/big-datas-streetlight-effect-where-and-how-we-look-affects-what-we-see-58122

Rat Bioavailability: Data Set 1

- Data taken from a survey of all bioavailability enhancement studies published in the *Journal of Medicinal Chemistry* between September 2001 and September 2002
  - rat bioavailabilities for 89 compounds with 20 different targets
  - 1-12 examples from 40 papers

Current Topics in Medicinal Chemistry 2003, *3*, 1269-1288

Molecular Design and Bioavailability

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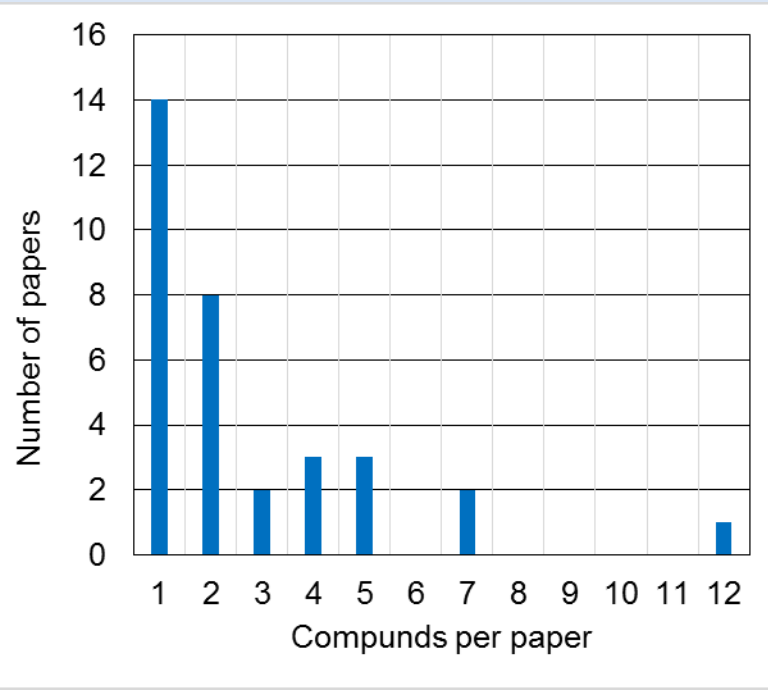
Abstract: A "snapshot" of current medicinal chemistry work on bioavailability is drawn from issues of *J. Med. Chem.* covering the time period between September 2001 and September 2002. An exhaustive compilation of reported absolute oral bioavailability (*F*) values for this period is included, covering 34 structural series and 107 distinct compounds, with data for multiple species in many cases. This is supplemented with a discussion of more qualitative oral bioavailability results, and with illustrative examples addressing clearance, prodrug design, and blood/brain barrier penetration problems. Papers discussing predictions pertaining to one or another aspect of bioavailability are also discussed, and some thoughts on future directions of work on *in silico* prediction in this area are presented.



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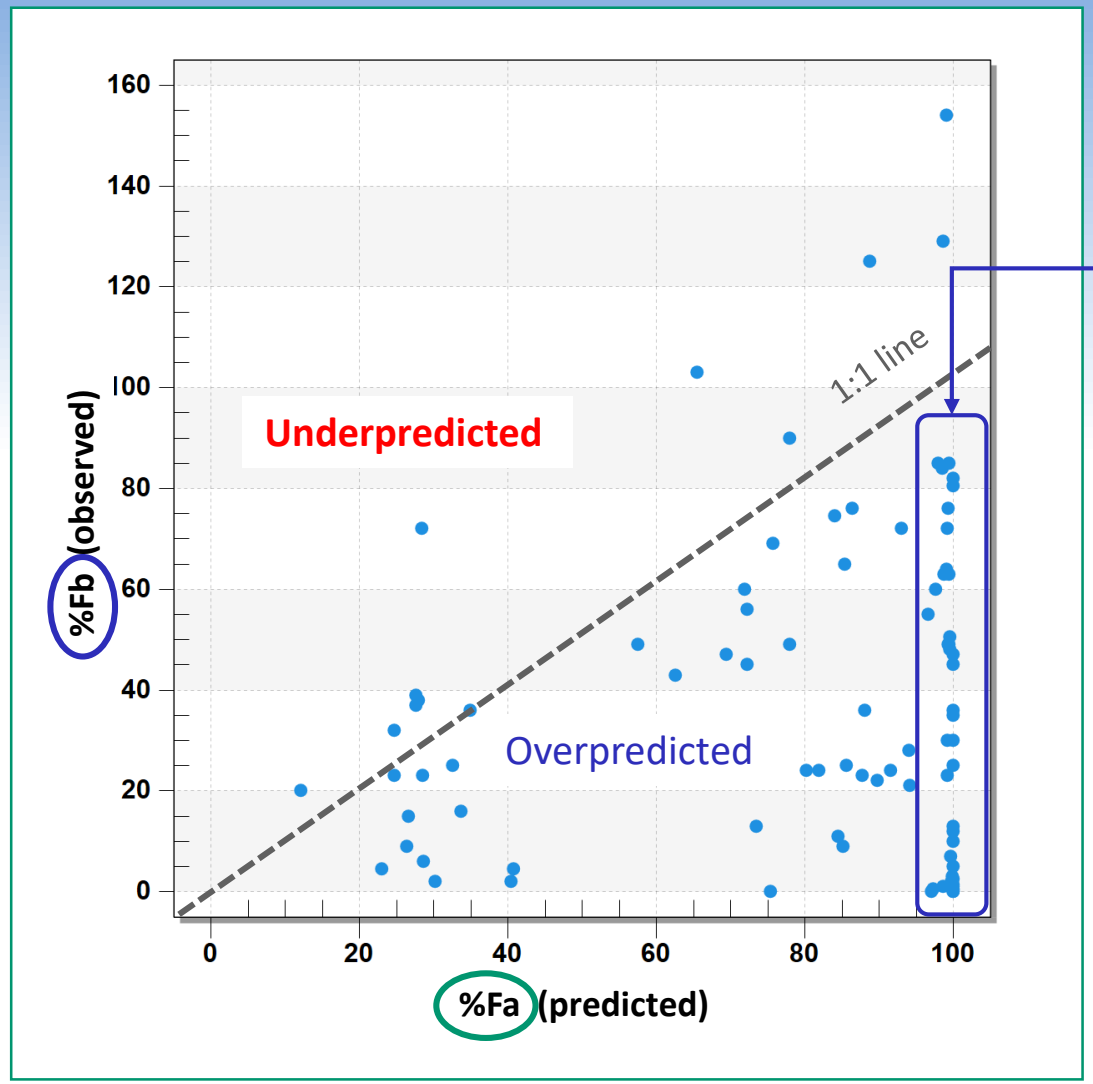
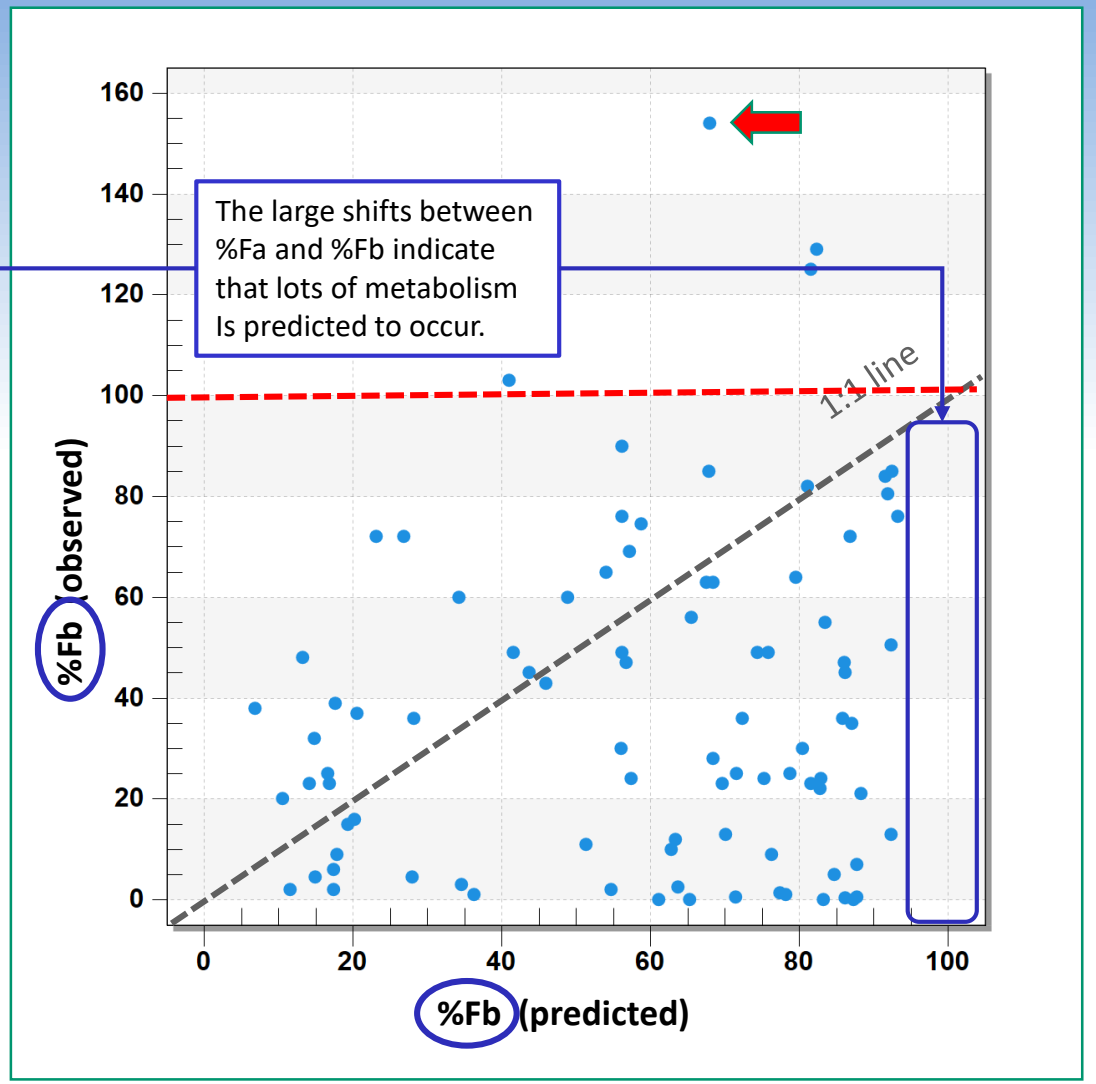
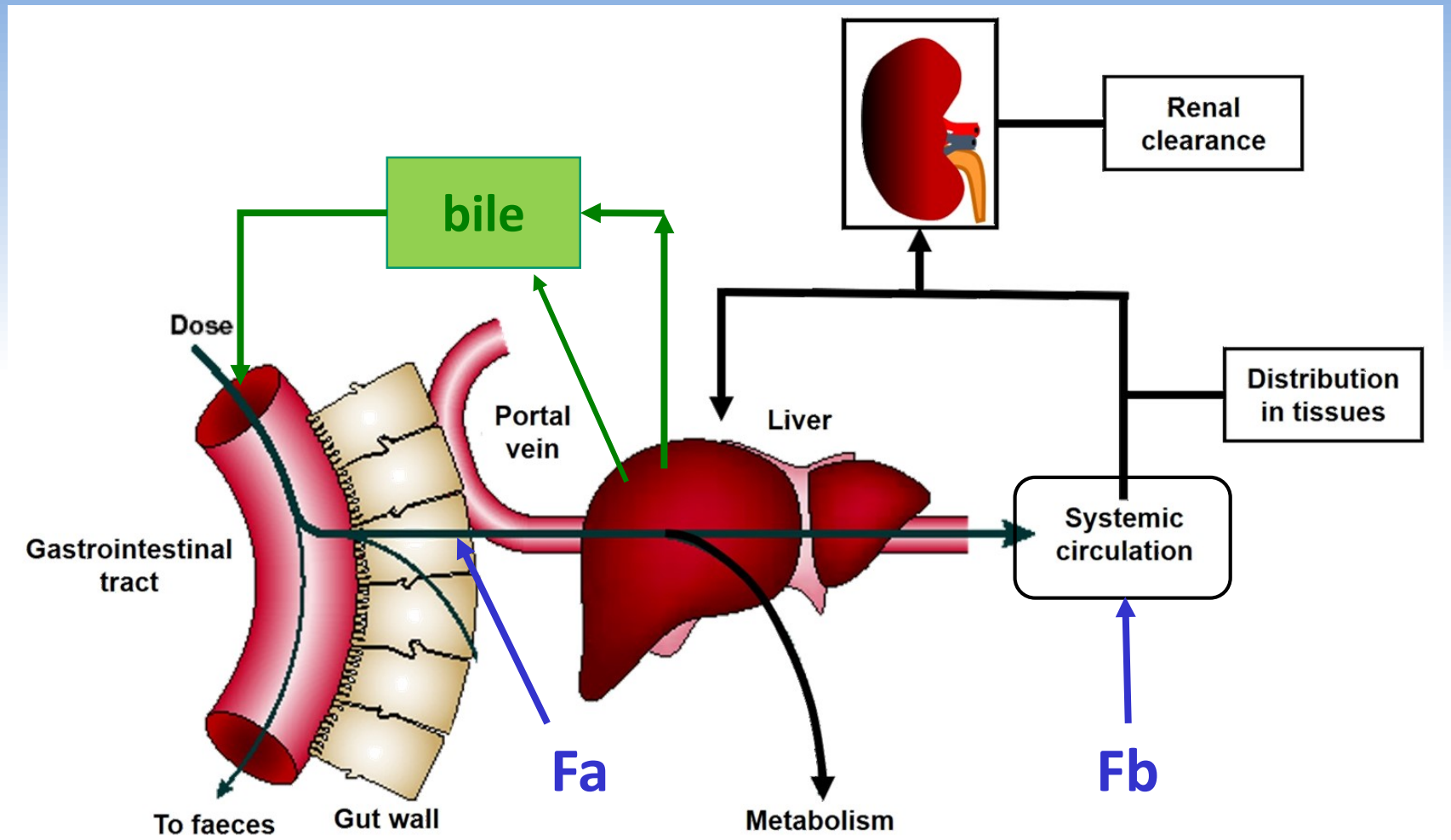
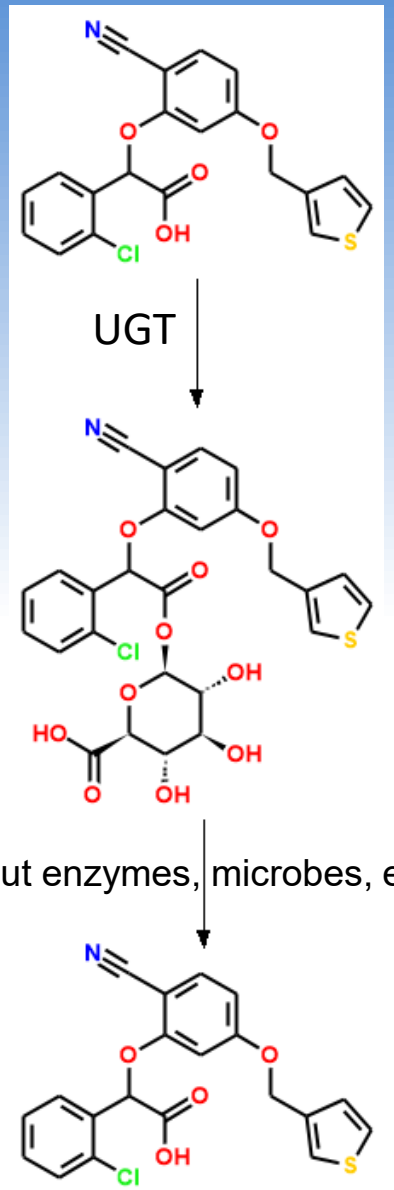
Experimental Fb vs. *in silico* Predictions of Fa and Fb





How Enterohepatic Circulation Works





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- Albert Einstein

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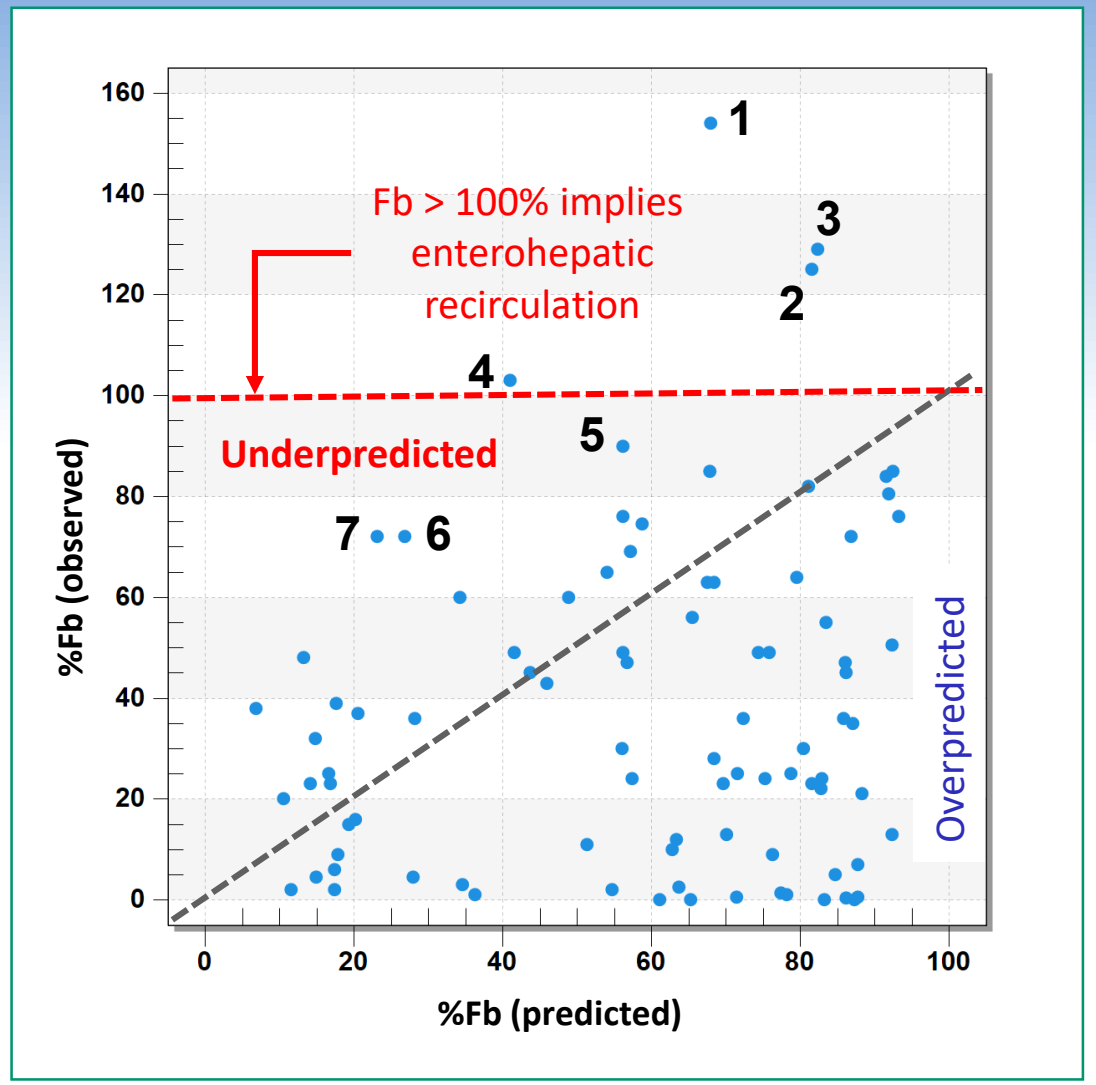
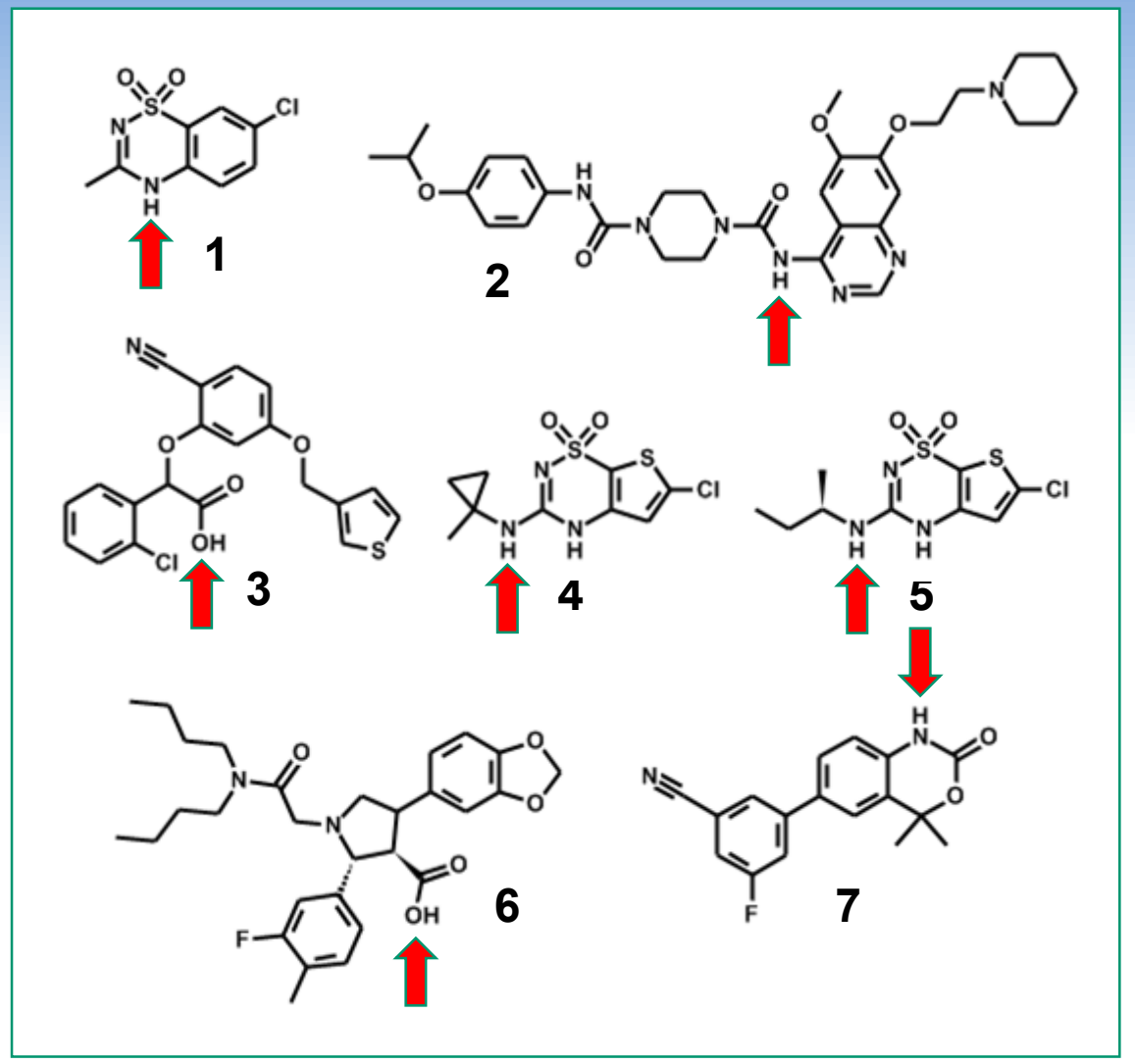
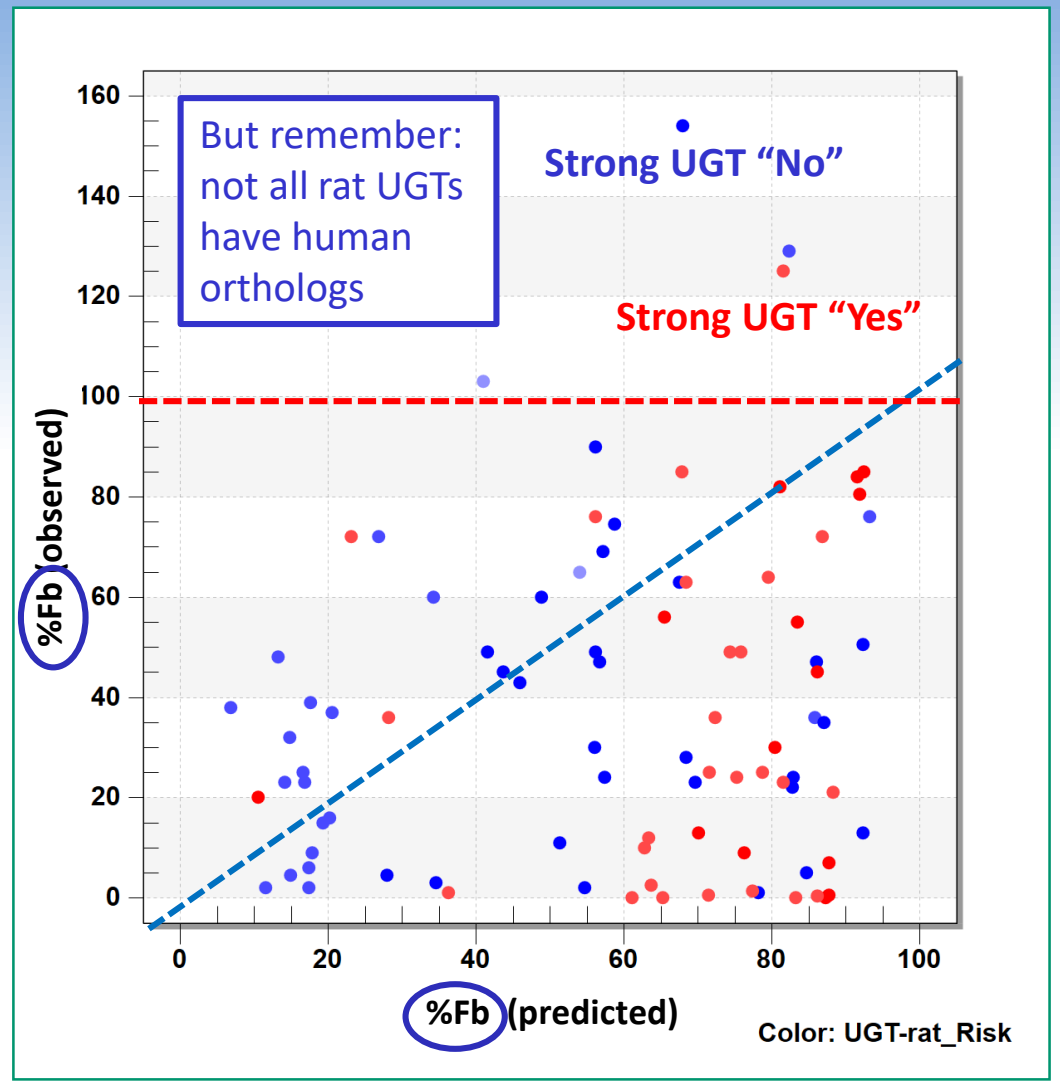
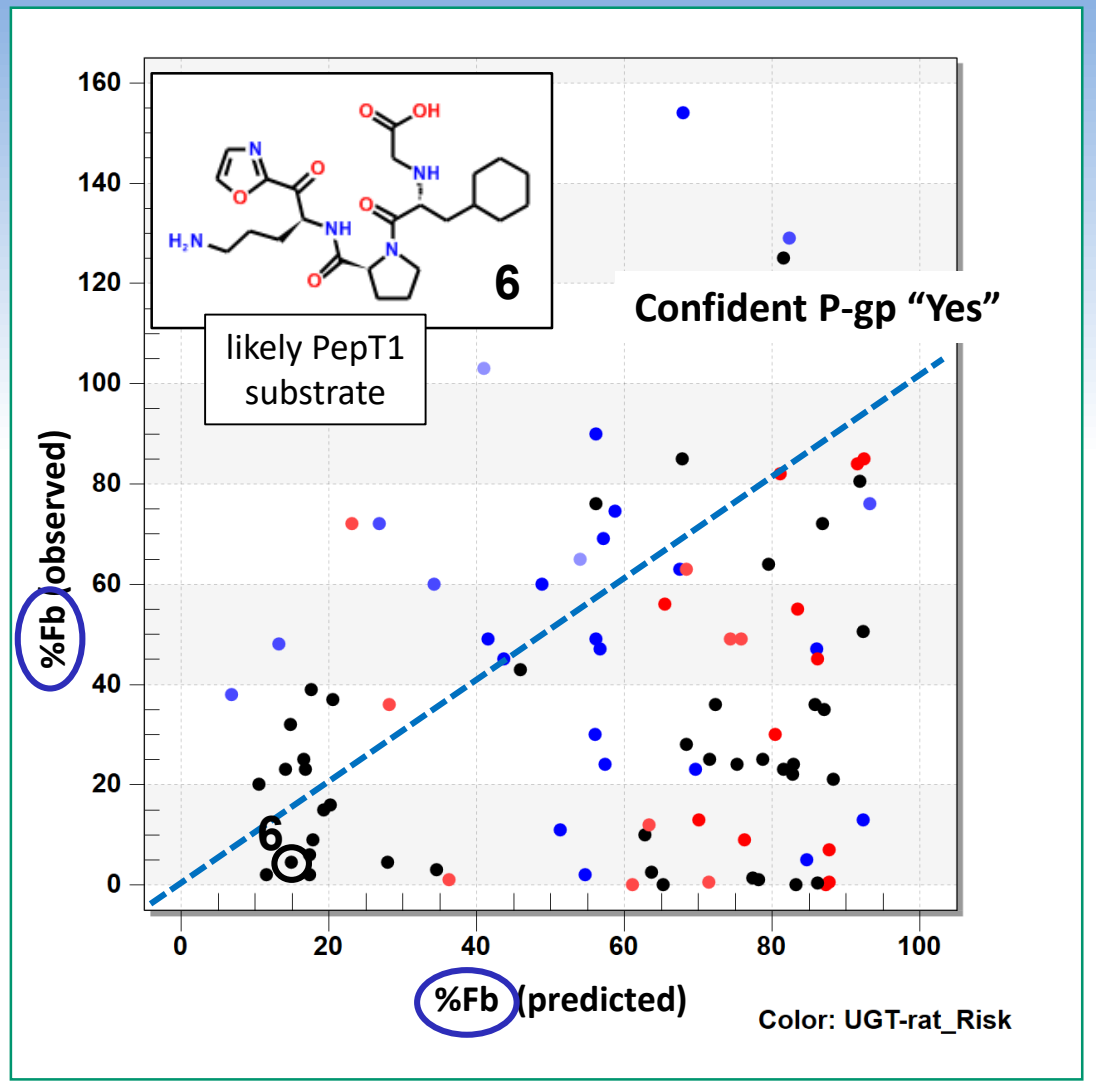
Why Are Some Bioavailabilities Underpredicted?





Expected Effects of UGT* and hP-gp Activity on Rat PK

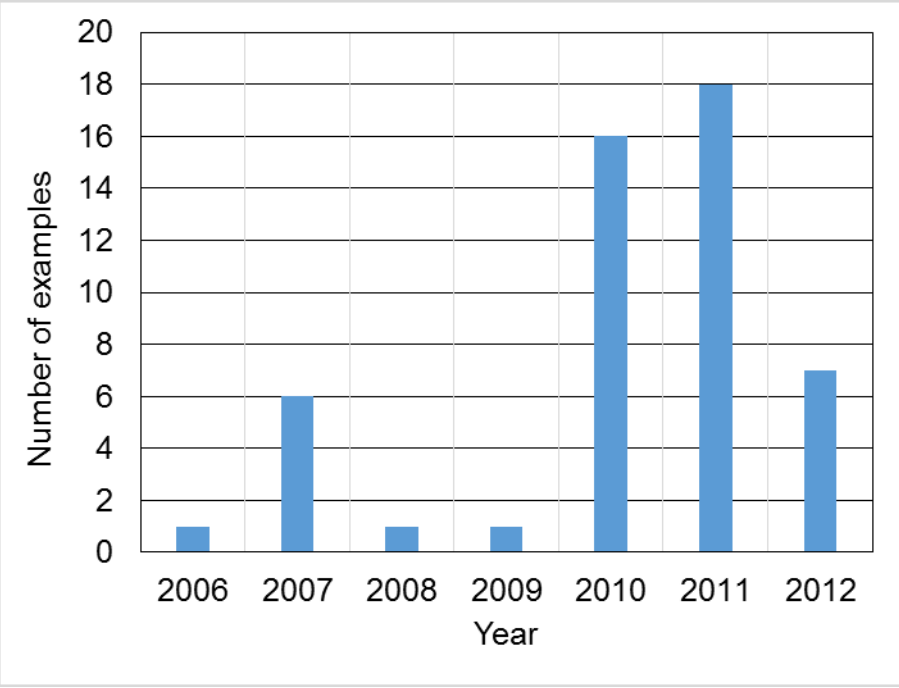


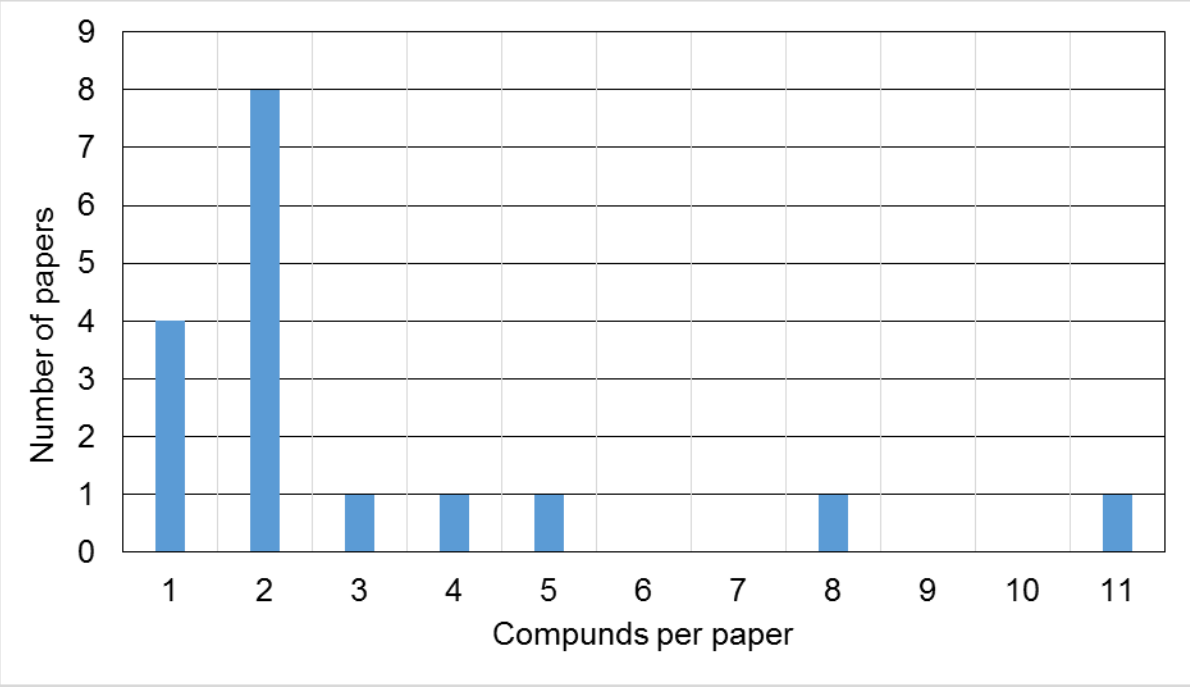


*Based on expression levels of rat orthologs of human UGTs and hUGT substrate classifications

Rat Bioavailability: Data Set 2

- Data taken from drug design and development papers published in the *Journal of Medicinal Chemistry* between 2006 and 2012 that report oral bioavailability in rats for one or more analogs
  - rat bioavailabilities for 51 compounds with many different targets
  - 1-11 examples from 17 papers





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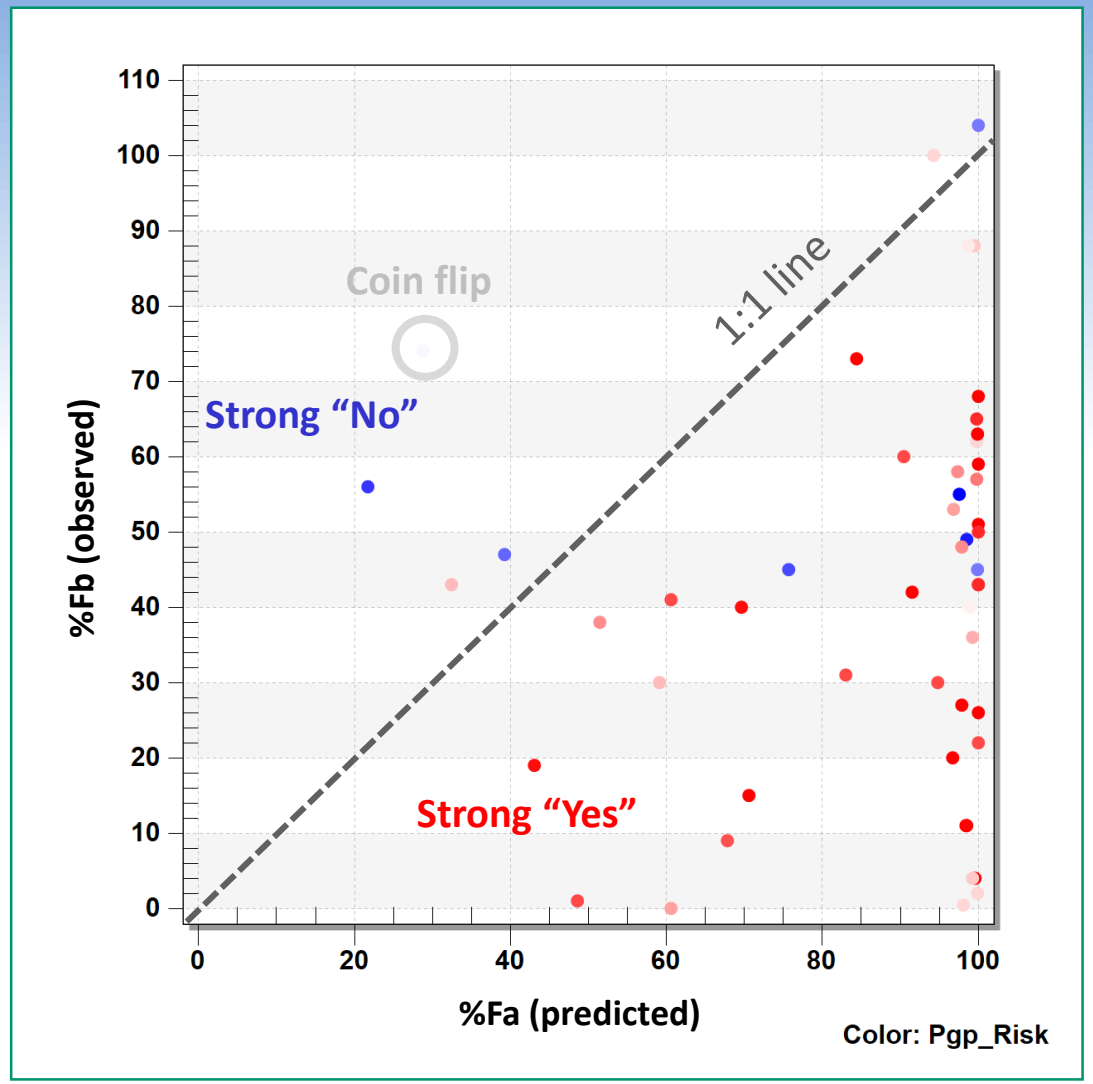
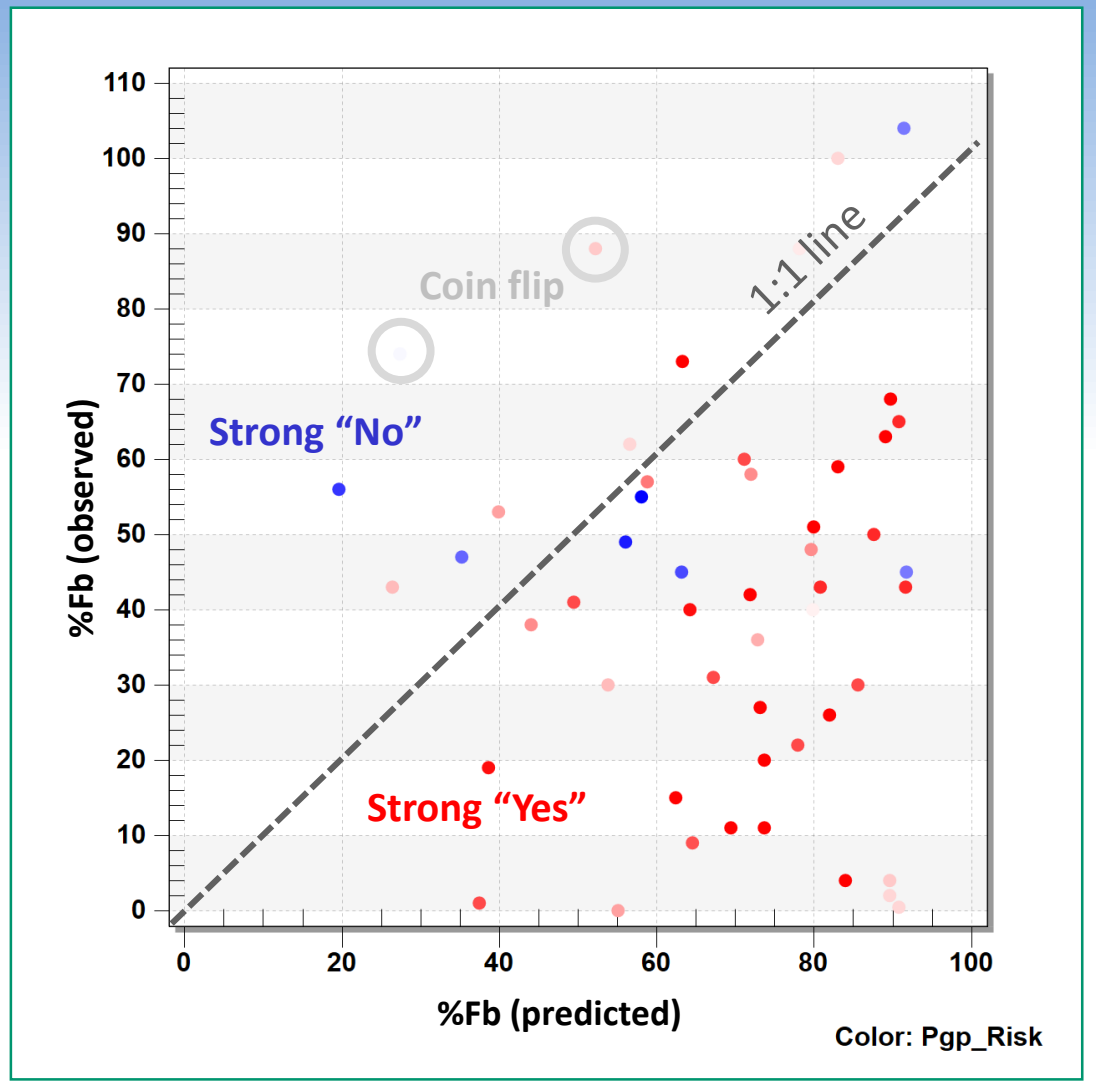
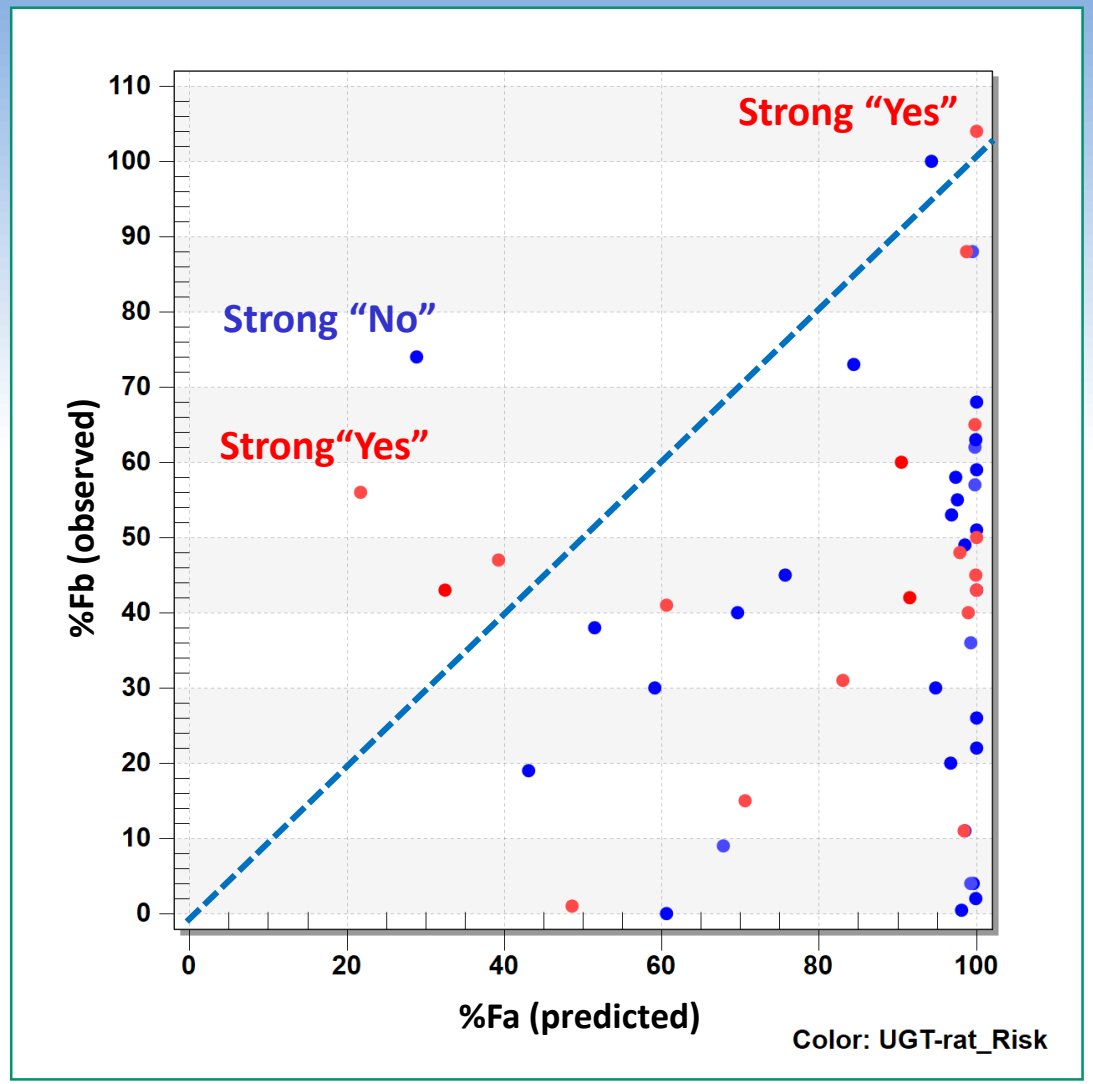
Effect of Being a Possible P-gp Substrate* on Predicted Rat PK

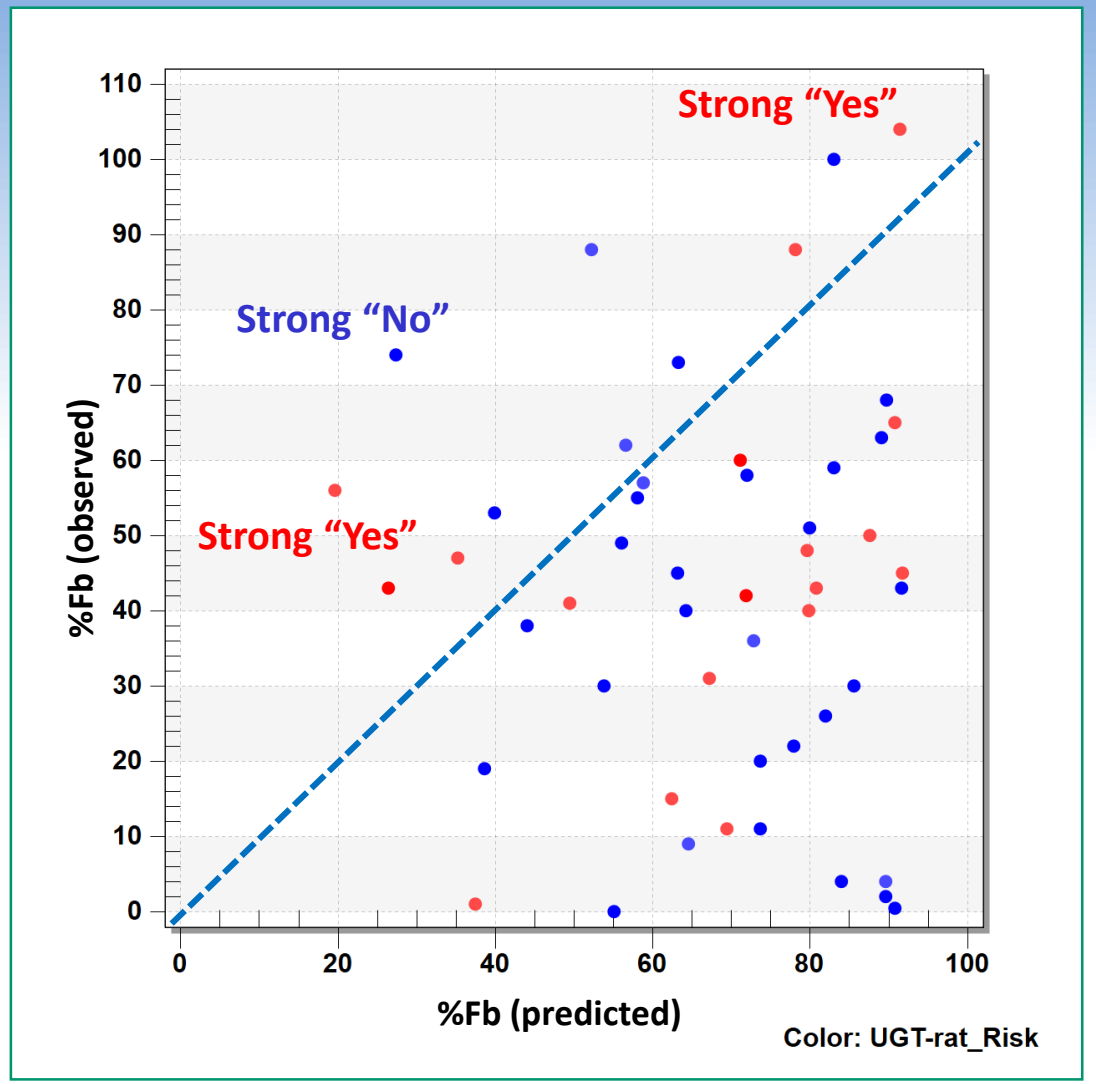




*Based on confidence in human P-gp substrate classification

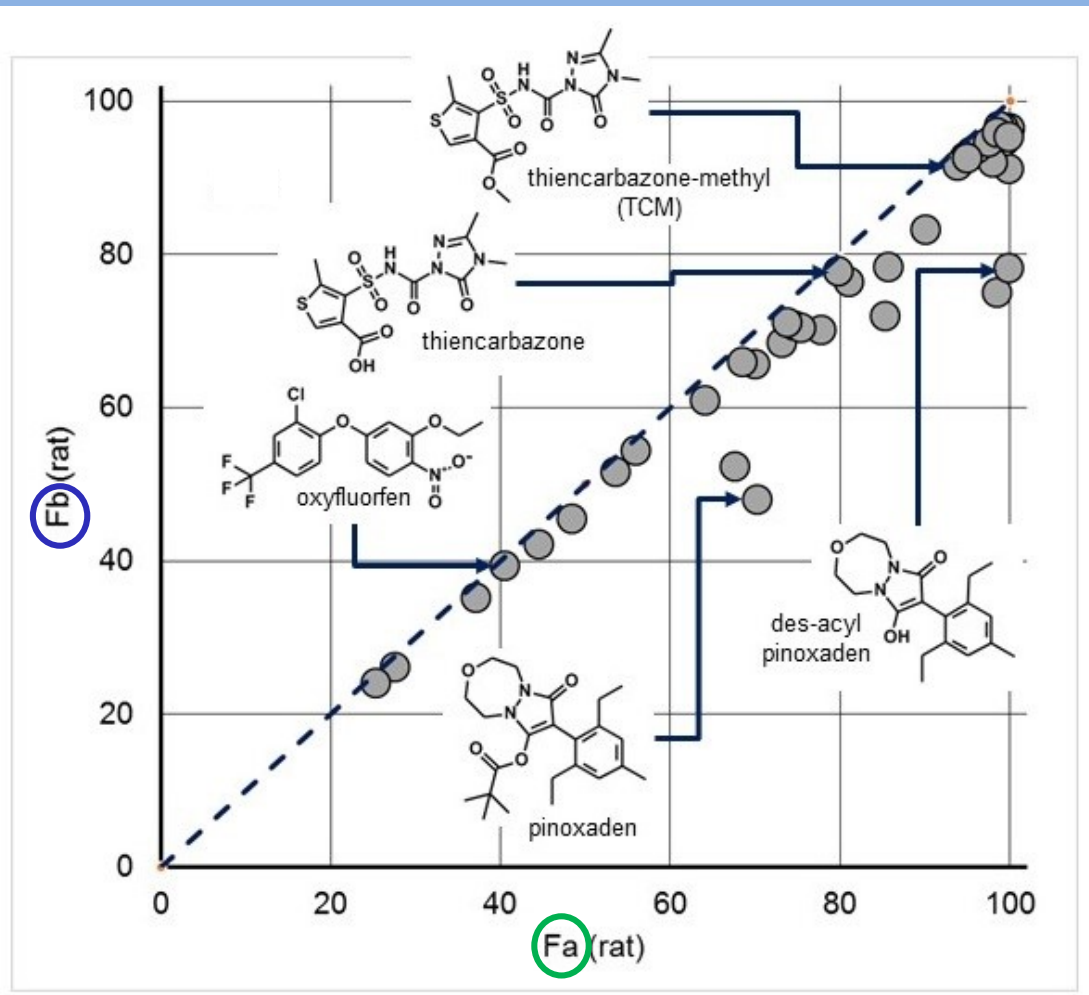
Effect of Being a Possible UGT Substrate* on Predicted Rat PK

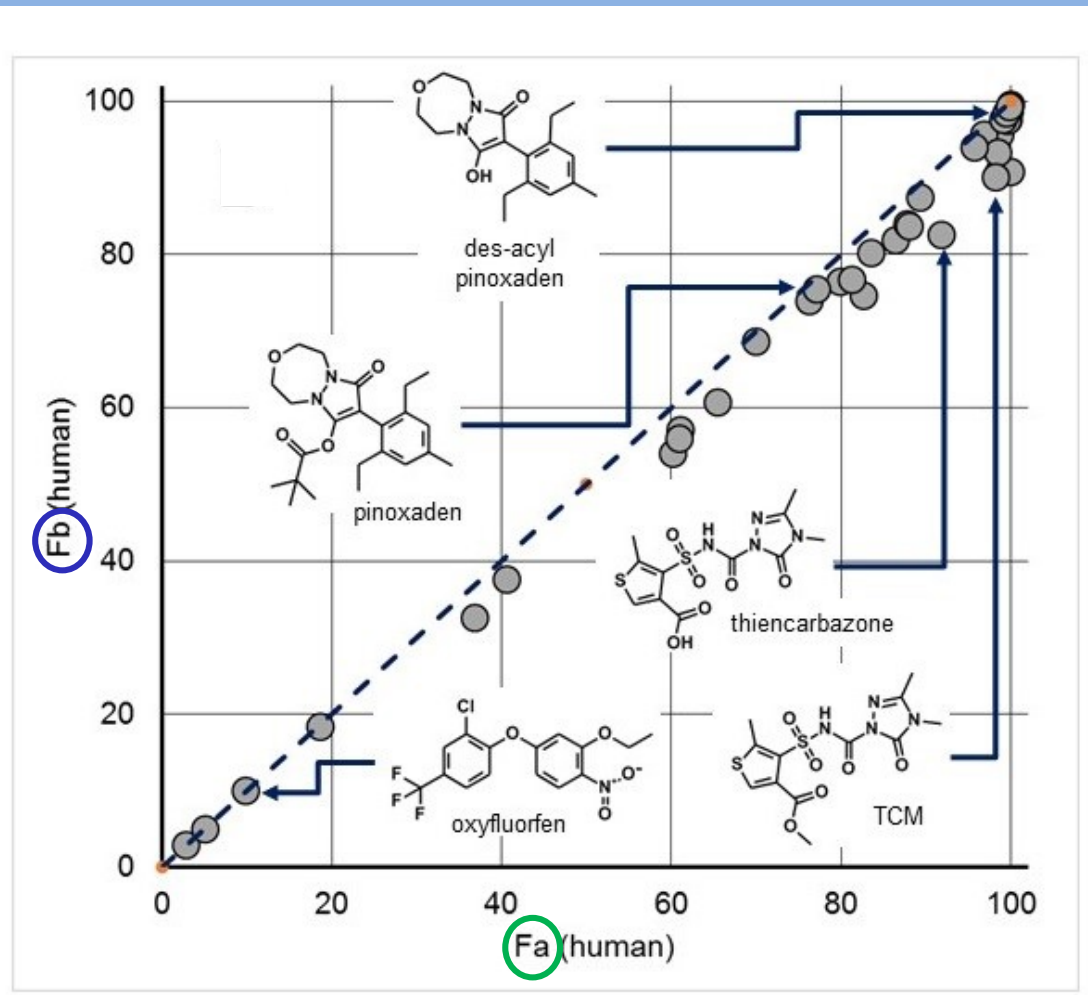




*Based on expression levels of rat orthologs of human UGTs and hUGT substrate classifications

Predicting Fa and Fb for Pesticides





RD Clark. Predicting mammalian metabolism and toxicity of pesticides *in silico*. *Pest Management Science*, published online 15 May 2018; DOI 10.1002/ps.4935.

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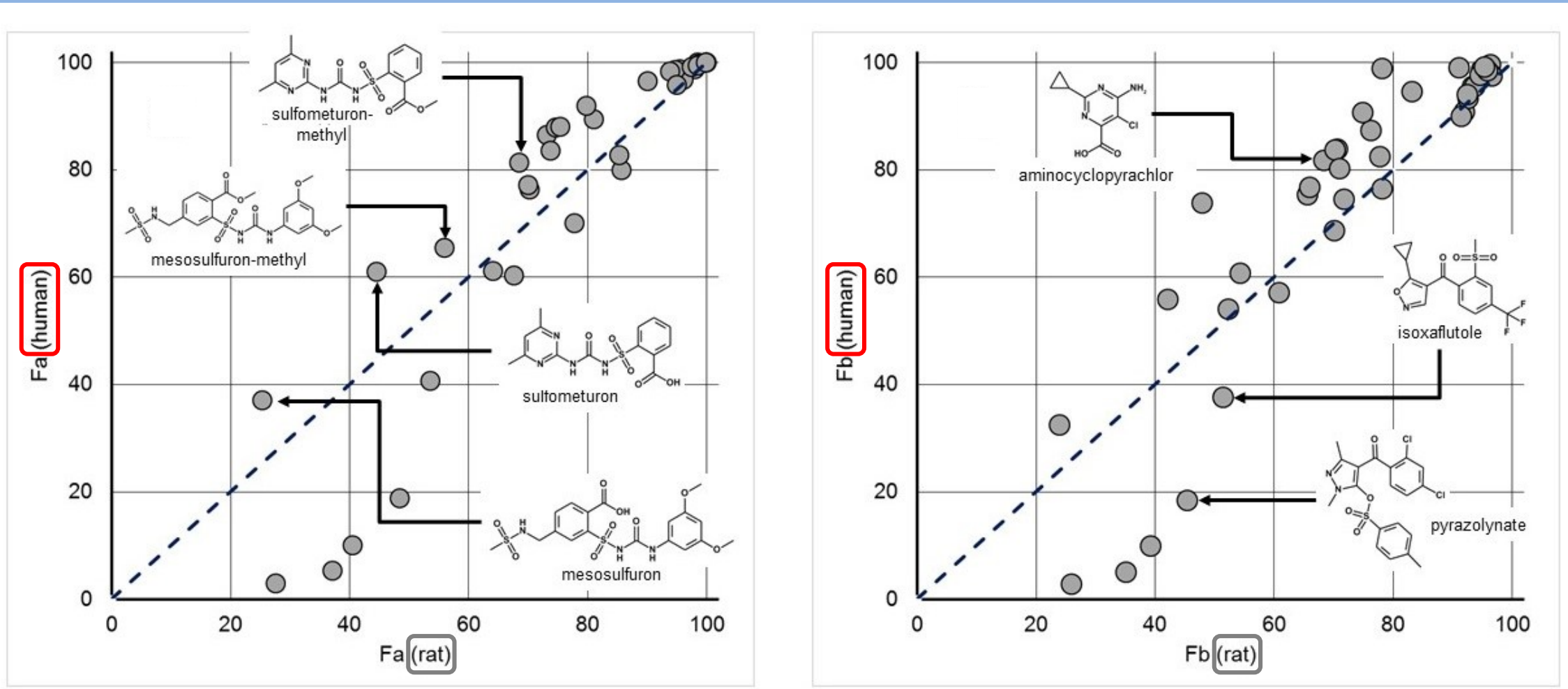
Comparing Predictions for Different Species



RD Clark. Predicting mammalian metabolism and toxicity of pesticides *in silico*. *Pest Management Science*, published online 15 May 2018; DOI 10.1002/ps.4935.

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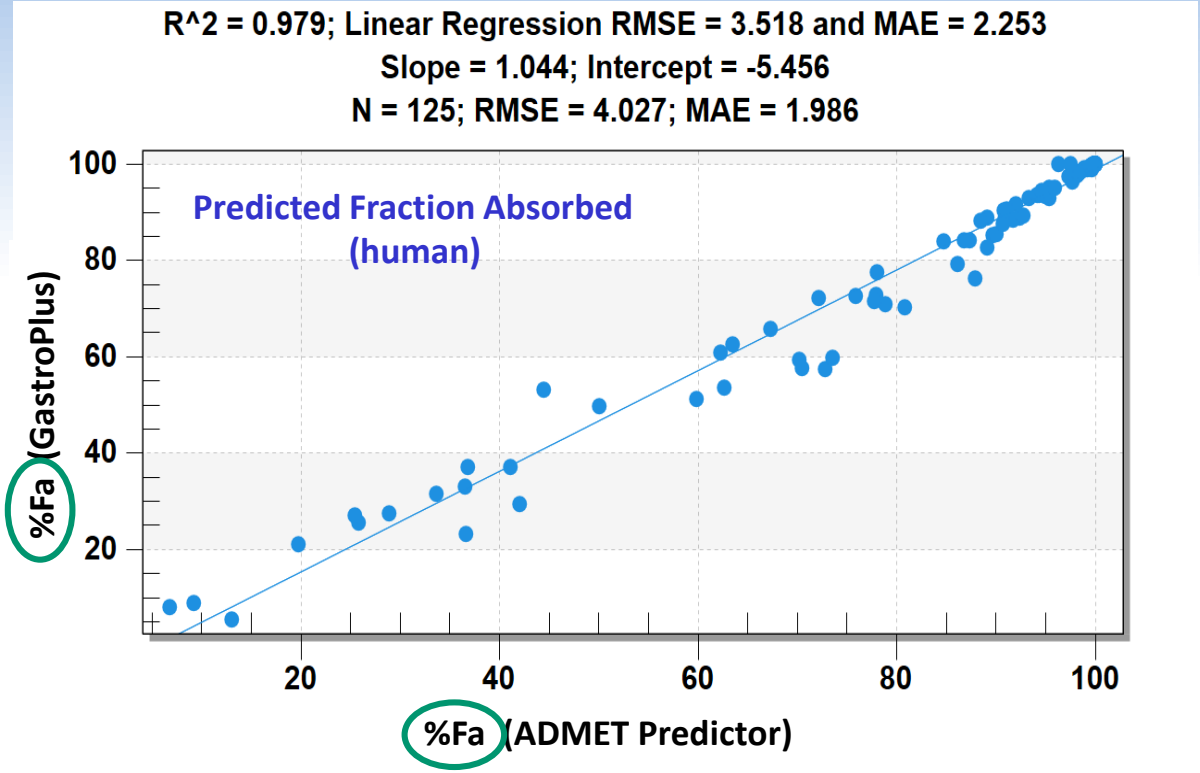
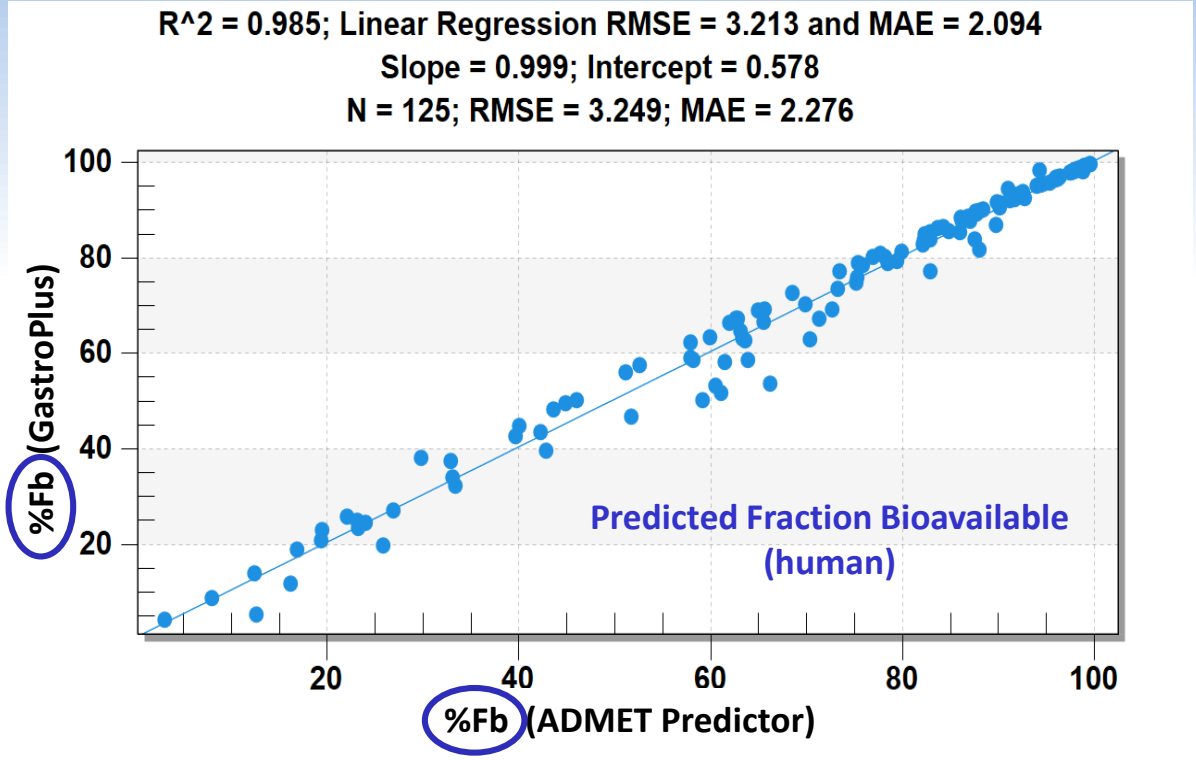
The Streamlined System Output is Similar to Full Simulation*

125 compounds from Zhao et al., *J. Pharm. Sci.* **2001**, 90:749





*GastroPlus run using a compartmental model with ACAT absorption vs HTPK in ADMET Predictor.

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Conclusions

- The high-throughput implementation of PBPK simulation in ADMET Predictor yields results in good agreement with analogous analyses in GastroPlus.
- HTPK simulations run using purely *in silico* property estimates are in reasonable but imperfect agreement with experimental results in humans and rats.
- Most experimental bioavailabilities for lead-type compounds in rat fall near or below the predicted fraction absorbed, which suggests that %Fa estimates are accurate.
- Increasing the accuracy of bioavailability estimation using *in silico* property estimates will require quantitative accounting for transporters and non-CYP metabolism.
- Measuring absorption and bioavailability is hard, as is modeling them. Validating the models designed to estimate them may be even harder.

My thanks to:

- Pankaj Daga & Robert Fraczkiewicz
- David Miller
- Eric Martin & Ben Madej (Novartis)
- Michael Lawless
- Mike Bolger
- Viera Lukacova
- John DiBella
- Karen Webster

…and to you: Hvala lepa!

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