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# SAWP DISCUSSION MEETING

## INITIAL QUALIFICATION PROCEDURE - SIMCYP SIMULATOR V19

## JANUARY 15, 2025

# Attendees

Dialling in from the UK

- Karen Rowland Yeo
- Masoud Jamei
- Iain Gardner
- Sibylle Neuhoff

Dialling in from France

- Frederic Bois

# Third list of issues

**Context of use 4**

- Please provide details on the selection of positive controls for in vitro system and how the range of inhibitory potency sensitivity analyses is defined based on positive control values.
- Please expand on how likely the different methods are to provide discordant results and how these should be weighted in a decision to waive a clinical DDI study. Are there cases in the DDI matrix where PBPK model predicts correctly in vivo data, i.e. no DDI, despite in vitro and/or mechanistic static modelling pointing to the opposite direction?
- Please provide additional analyses to support CoU4 as recommended in the scientific discussion.

**Model-based uncertainty quantification (UQ) *for COU1-3* based on the DDI QM**

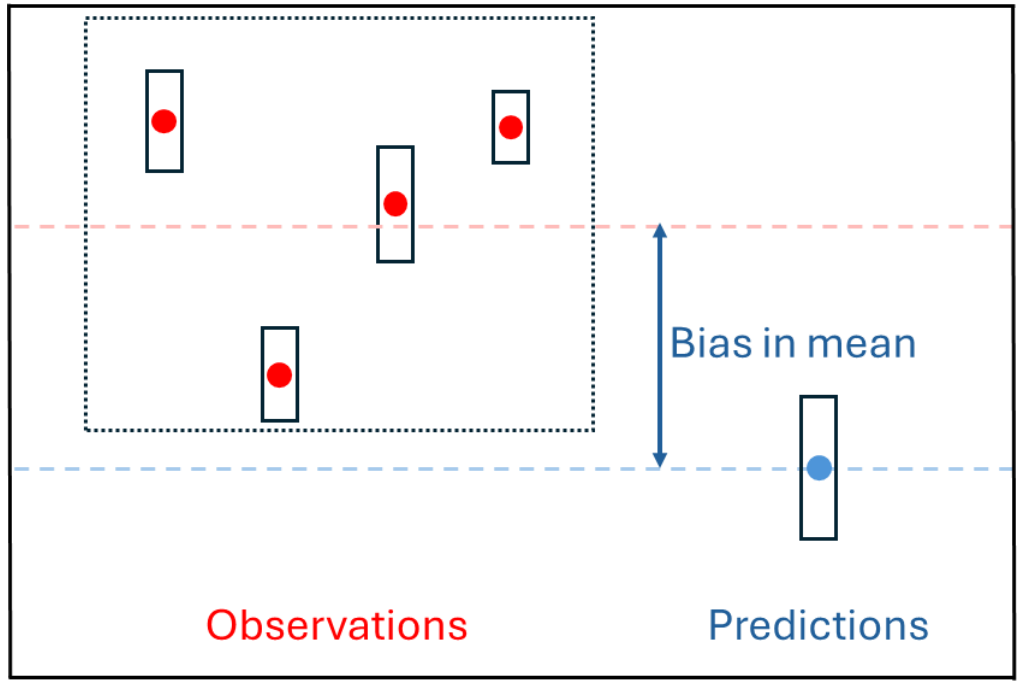
- Please replicate the analyses, metrics and visuals developed by the SAWP.
- Please discuss the SAWP recommendations on the Bayesian meta-regression model and visuals as expanded in the scientific discussion.
- For CoU1, please discuss the possibility of assessing the predictive performance of Simcyp in predicting the effect of weak and moderate inhibitors, respectively. For this discussion, the Applicant should present posterior predictive checks (see Figure 1) only including substrate-inhibitor pairs including weak and moderate inhibitors that have not been used to optimise compound files.

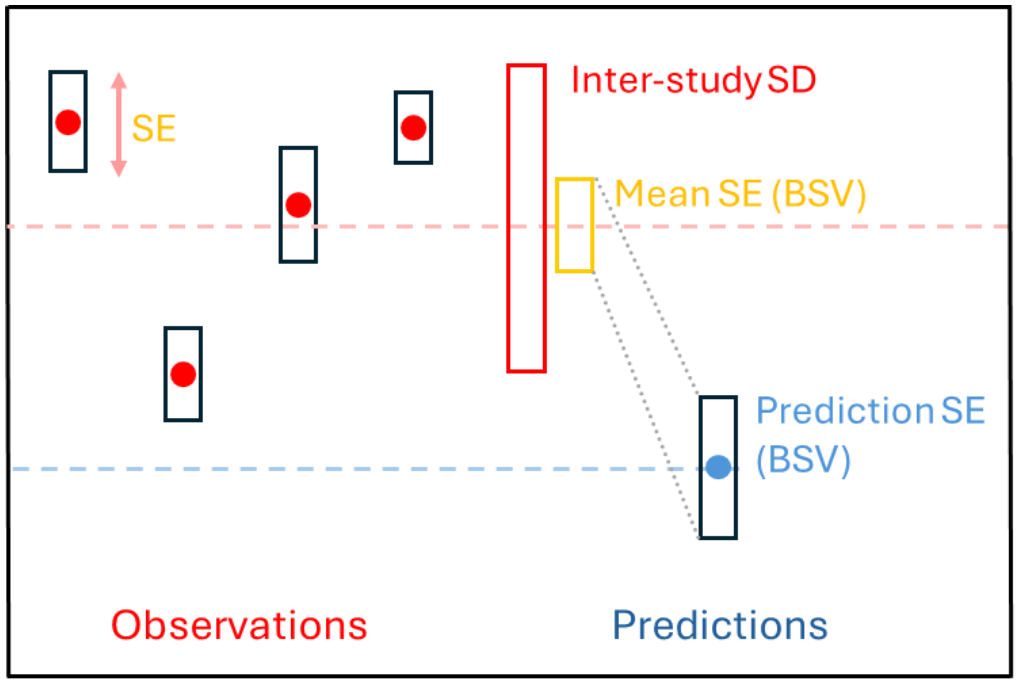
# Model-based uncertainty – key discussion points

1. Present alternative models to constant bias and between study variability across predicted GMRs.
2. Replicate the analyses developed by the SAWP.
3. Discuss Simcyp performance in predicting the effect of weak and moderate inhibitors. Present posterior predictive checks only including weak and moderate inhibitors.
4. Address concerns around goodness-of-fit of the Bayesian meta-regression model.
5. Discuss the SAWP recommendations on the model and visuals.

# 1. Alternative models to constant bias and between study variability

## Framework reminder: what we would like to estimate



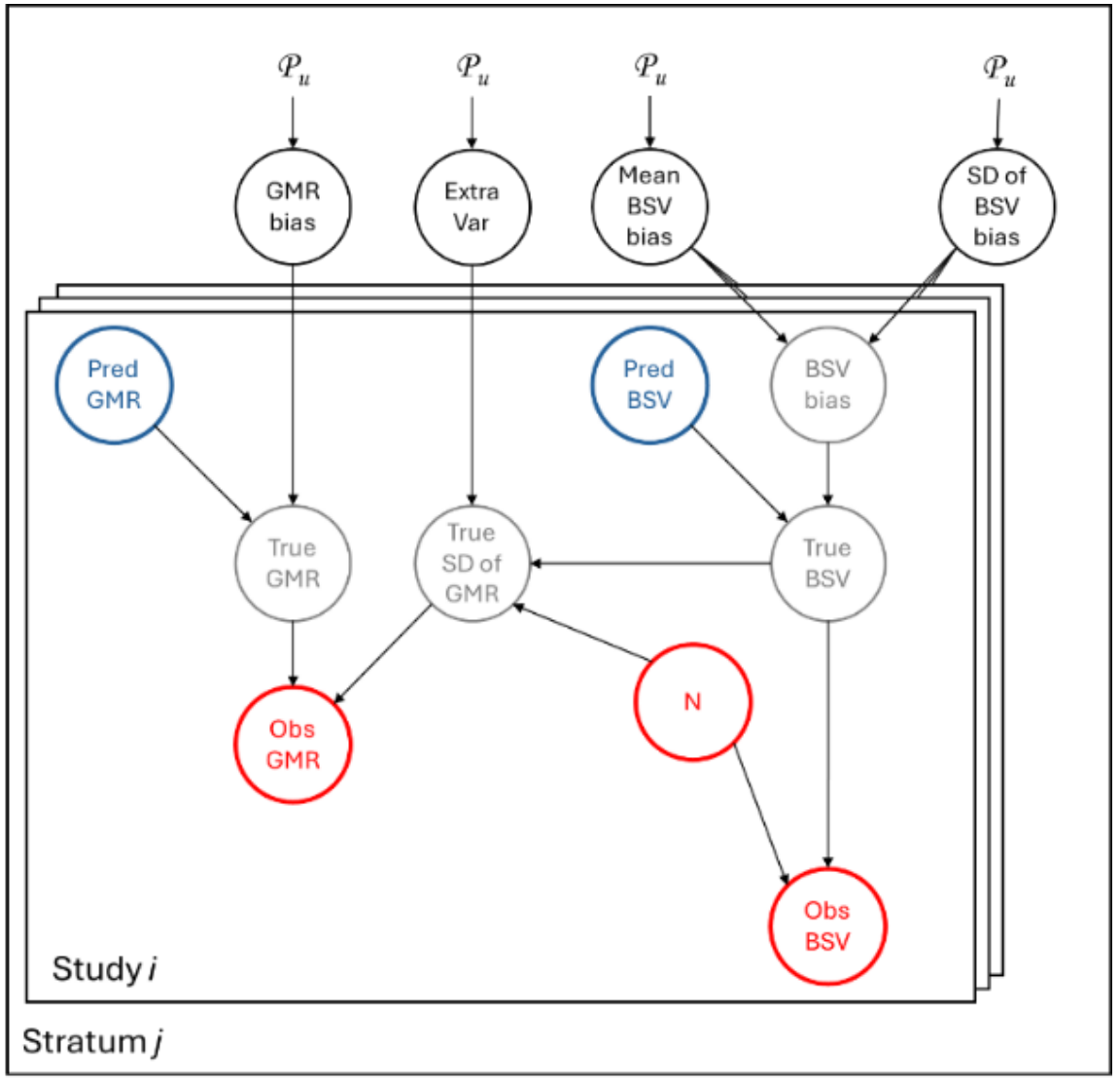




Bias in GMR

Inter-study variance = Between-subject variability (scaled) + [True between-study variance + Simcyp imprecision]

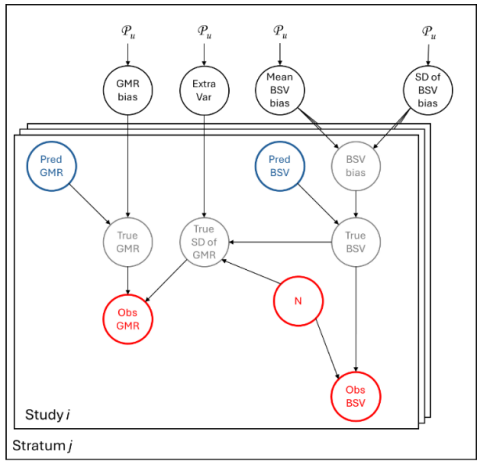
# 1. Alternative models to constant bias and between study variability

## Basic dependency model (model A, stratified)

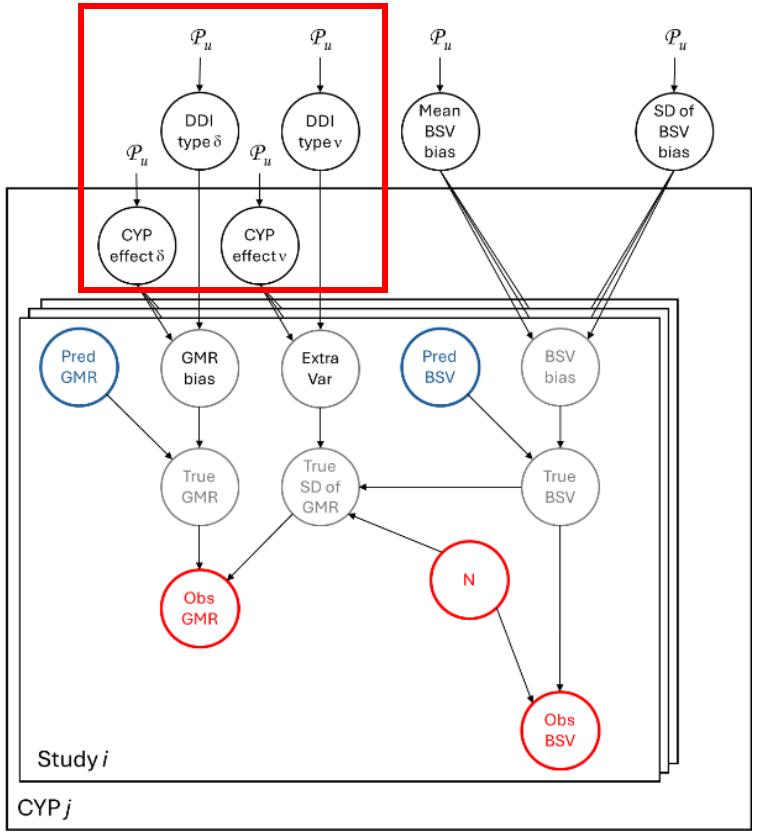


# 1. Alternative models to constant bias and between study variability

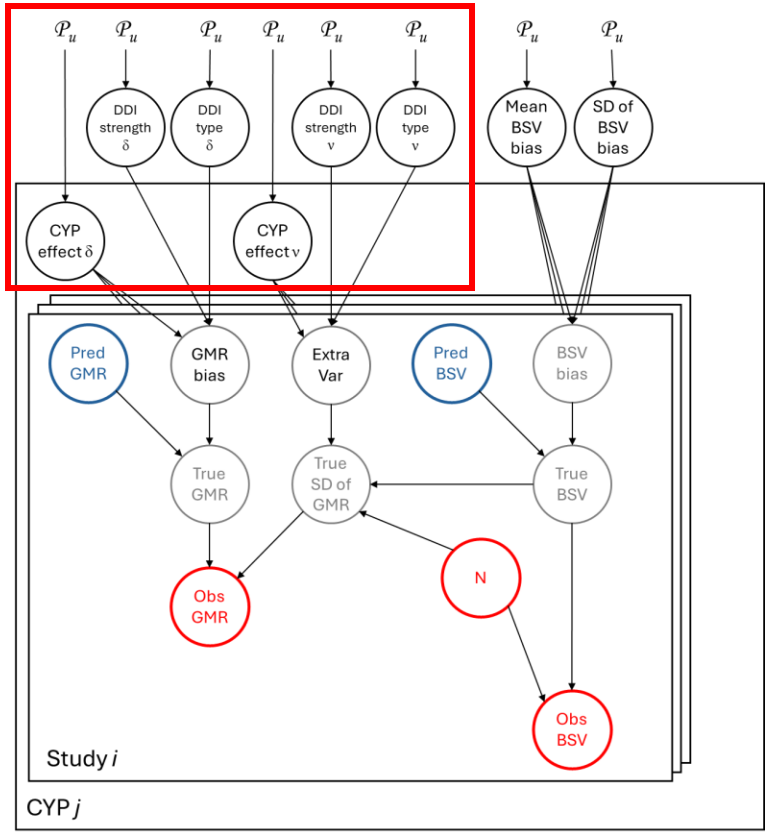
## From stratification to hierarchical models




Model A
(stratified)




Model B
(hierarchical)




Model C
(weak+moderate strength)

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4. Address concerns around goodness-of-fit of the Bayesian meta-regression model.
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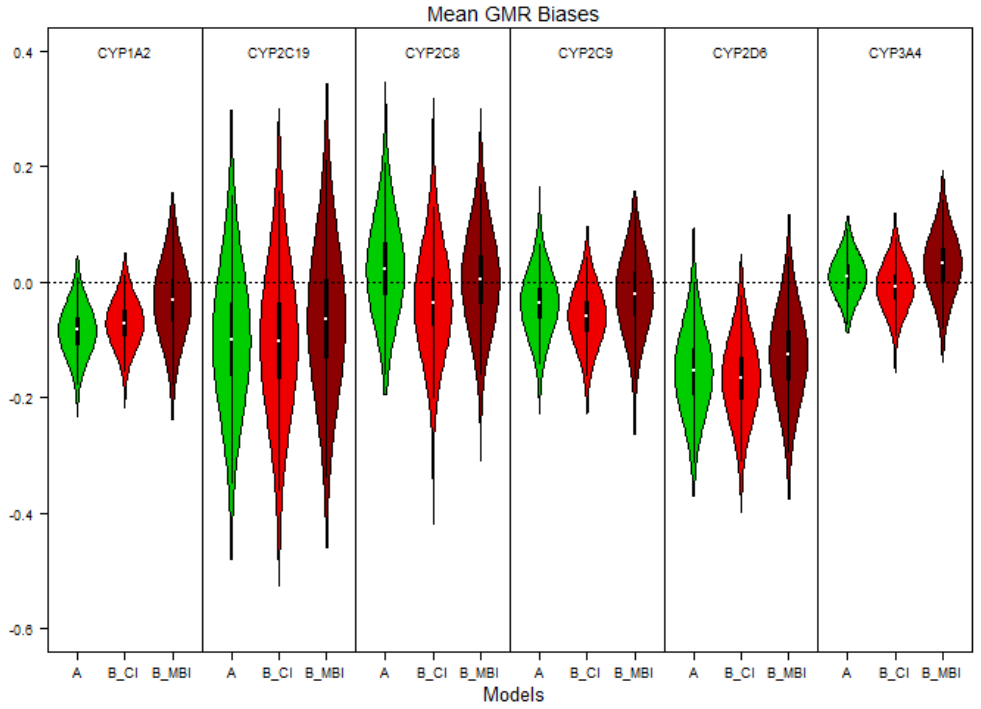
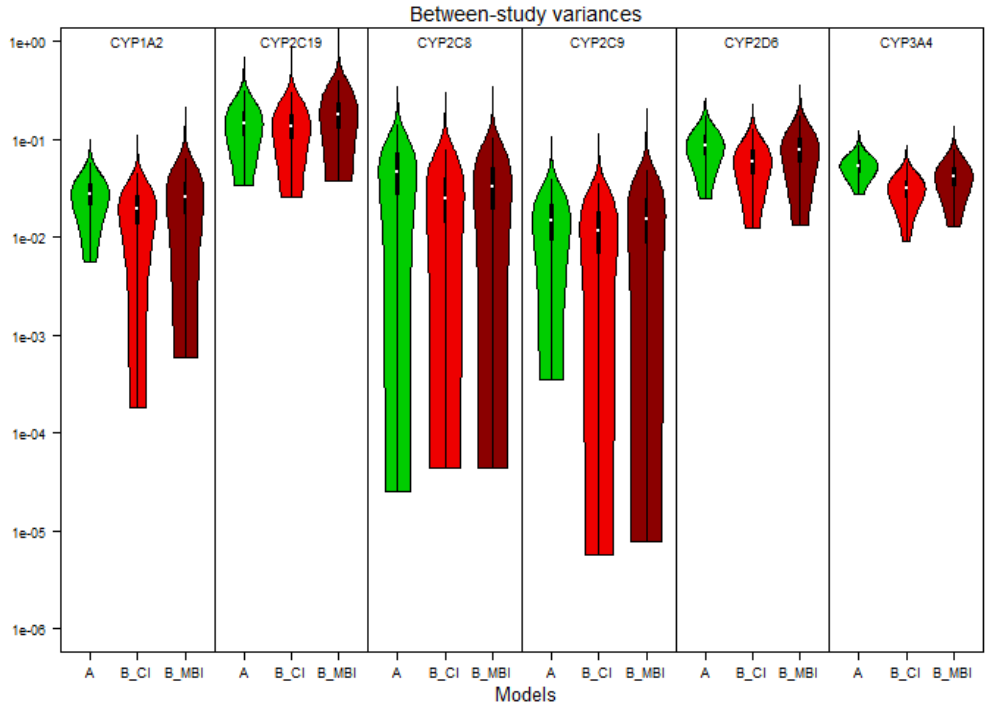
# 2. Replicate SAWP model B

## From stratification to hierarchical models (all in Stan), stable estimates




Minor differences for GMR bias




Slightly lower between-study variance estimates

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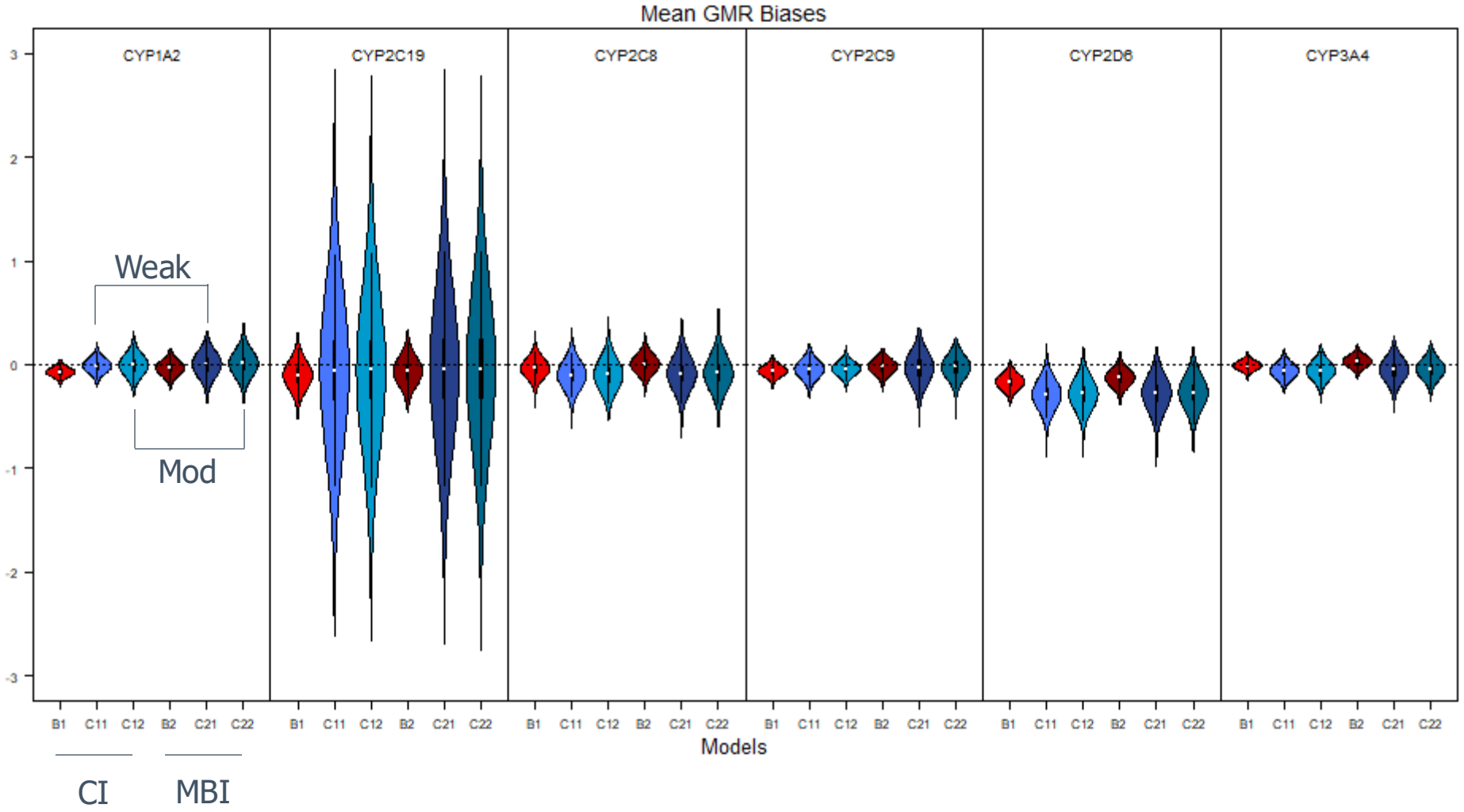
# 3. Model C, weak and moderate inhibitors

## Hierarchical models (in Stan), stable estimates but increased uncertainty in GMR bias




B1: model B, CI

C11: model C, CI + weak I

C12: model C, CI moderate I

B2: model B, MBI

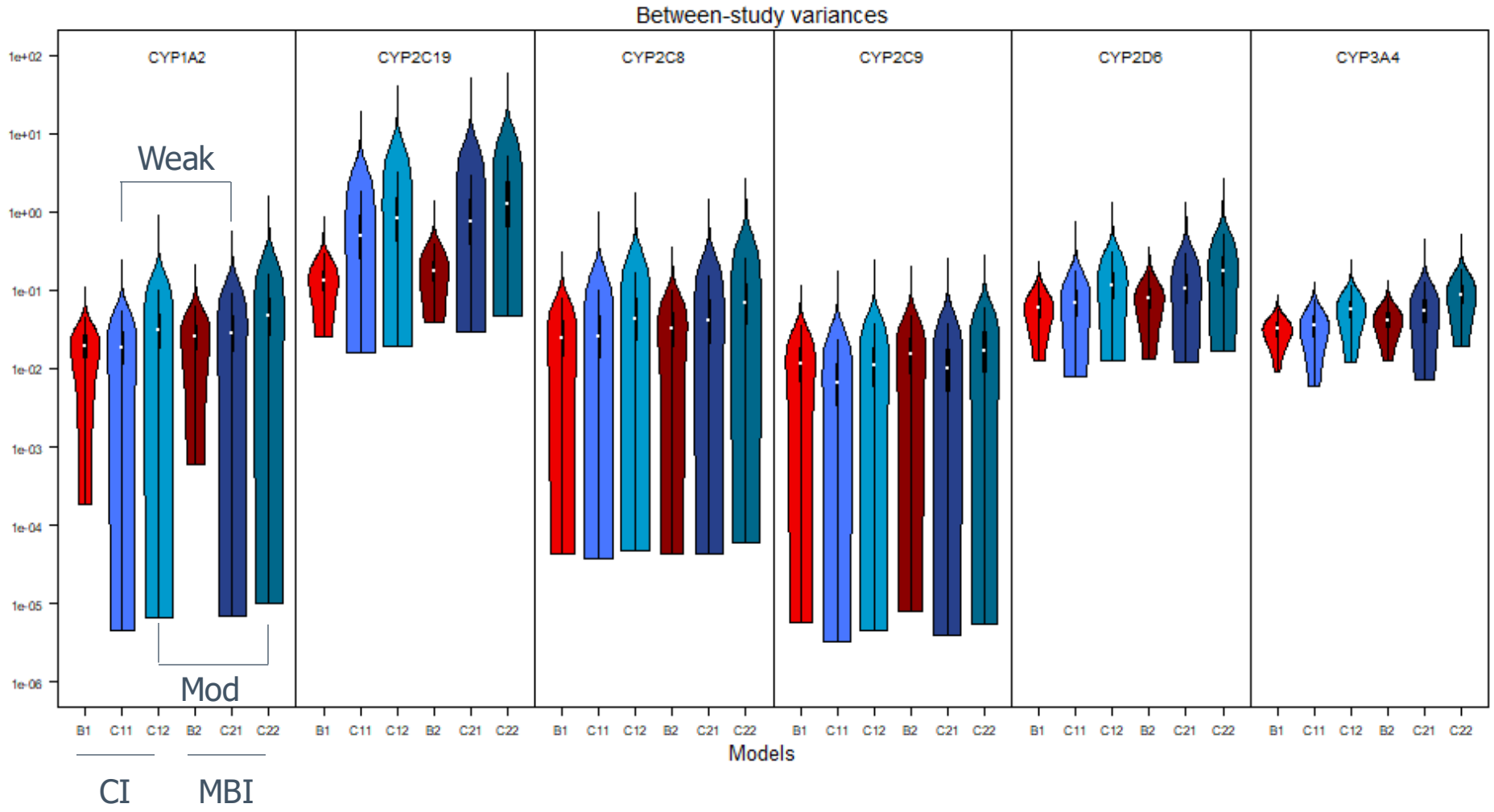
C21: model C, MBI weak I

C22: model C, MBI moderate I

| CYP | Number of studies | |
|---|---|---|
| | Models A and B | Model C |
| CYP1A2 | 39 | 16 |
| CYP2C19 | 23 | 3 |
| CYP2C8 | 17 | 9 |
| CYP2C9 | 19 | 17 |
| CYP2D6 | 40 | 18 |
| CYP3A4 | 82 | 45 |
| Total | **220** | **108** |

# 3. Model C, weak and moderate inhibitors

## Increased estimates and increased uncertainty in between-study variance




B1: model B, CI

C11: model C, CI + weak I

C12: model C, CI moderate I

B2: model B, MBI

C21: model C, MBI weak I

C22: model C, MBI moderate I

# Model-based uncertainty – key discussion points

1. Present alternative models to constant bias and between study variability across predicted GMRs.
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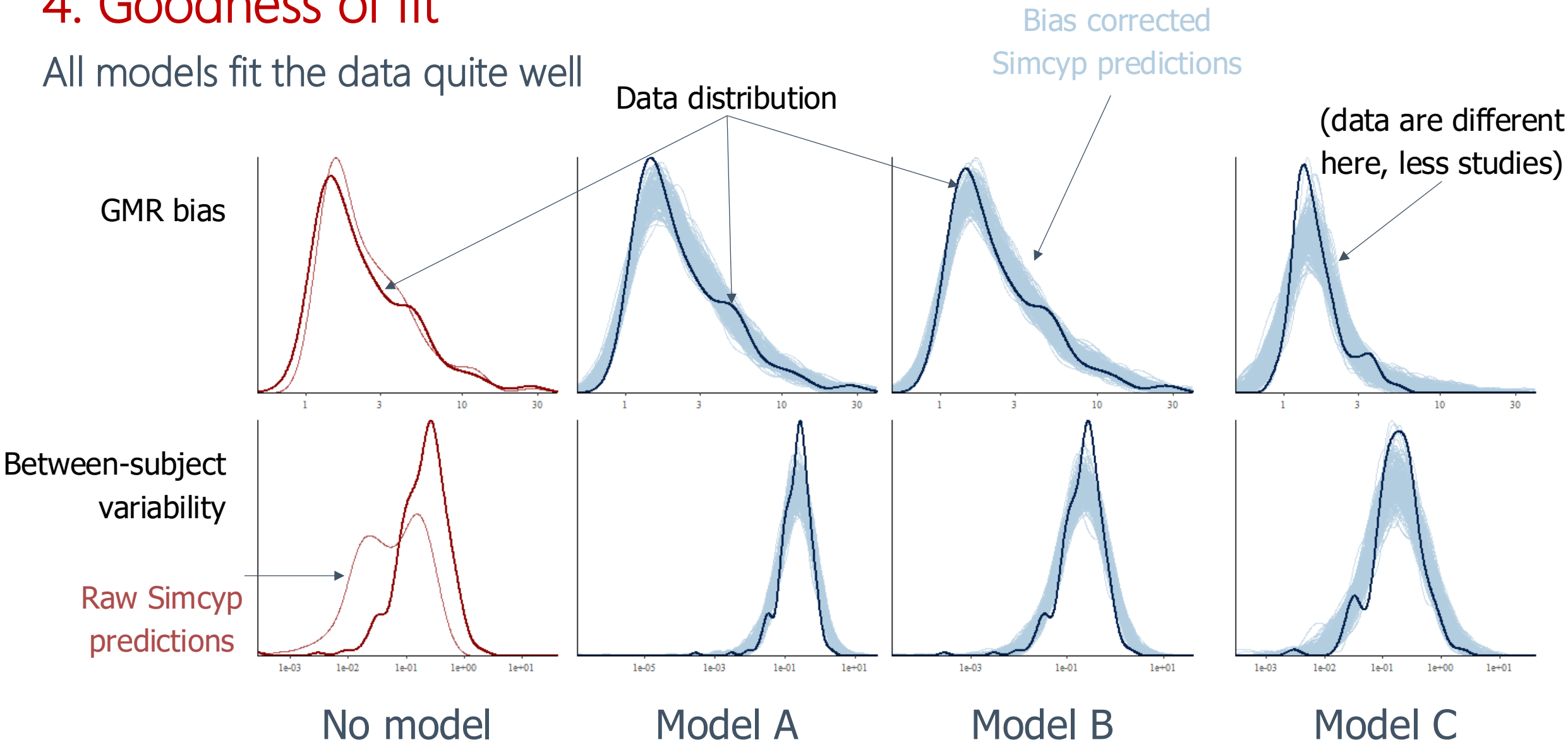
# 4. Goodness of fit

## All models fit the data quite well



# Model-based uncertainty – key discussion points

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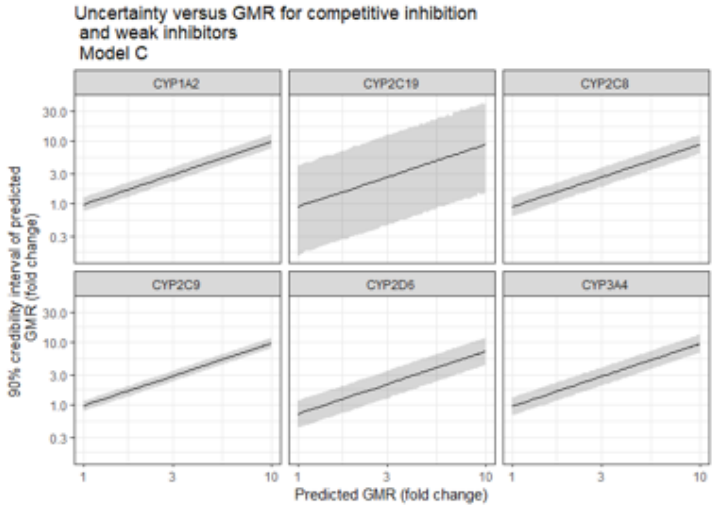
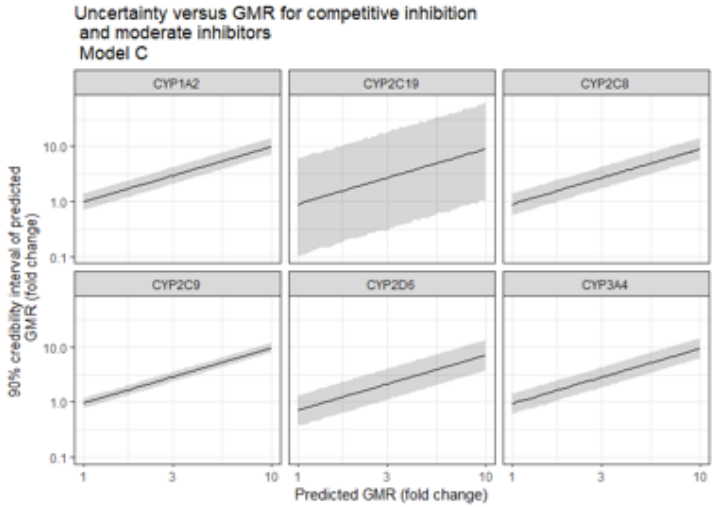
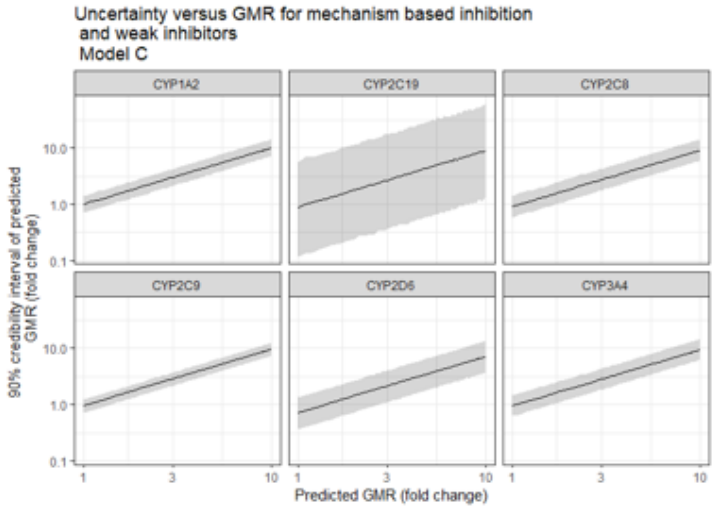
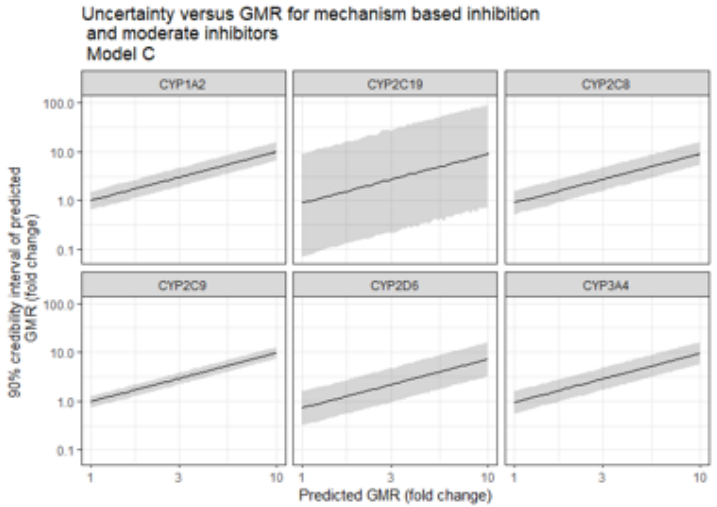
# 5. Posterior predictive visualizations

## Credibility interval at given predicted GMRs (model C)

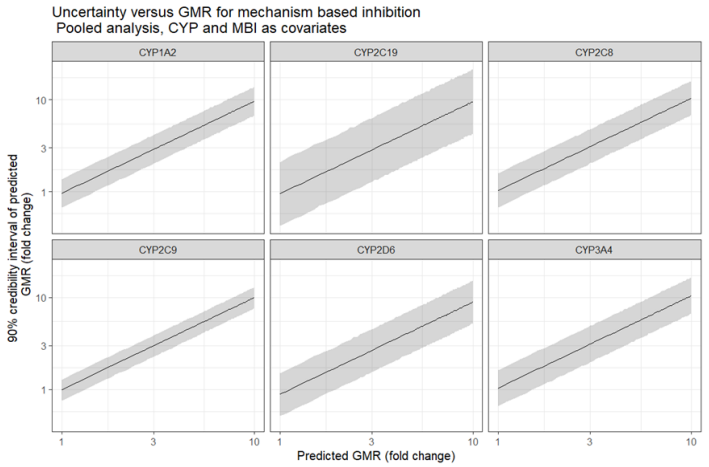



Conclusion: insufficient database for CYP2C19 in model C, not so dramatic in model B:



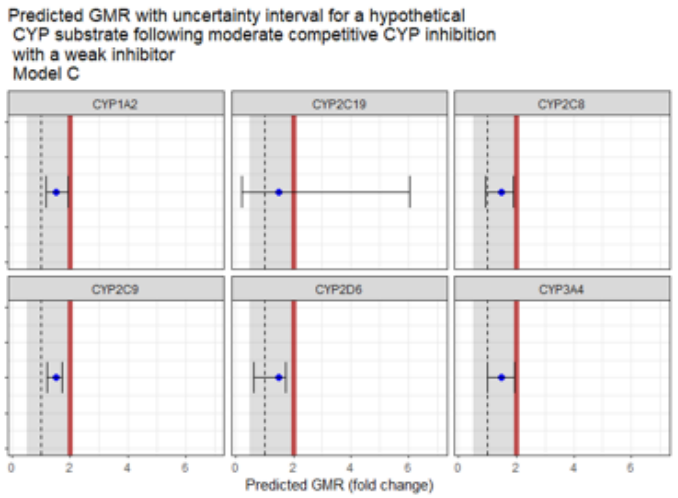
# 5. Posterior predictive visualizations

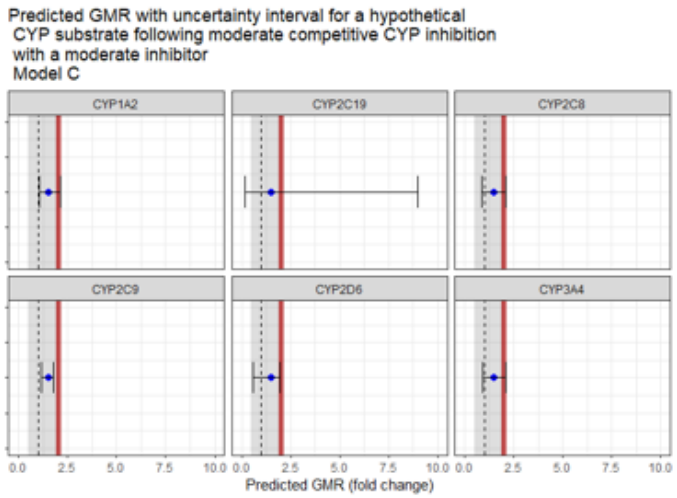
## Predicted GMR for hypothetical CYP substrates (model C)

Weak

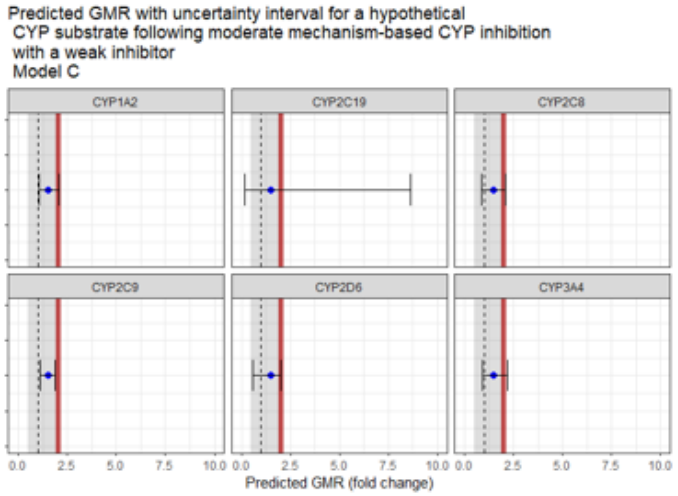
Moderate

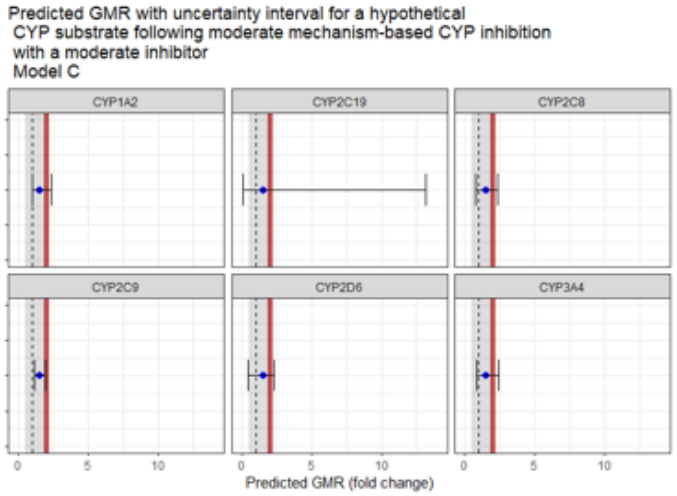
Competitive Inhibition




MBI





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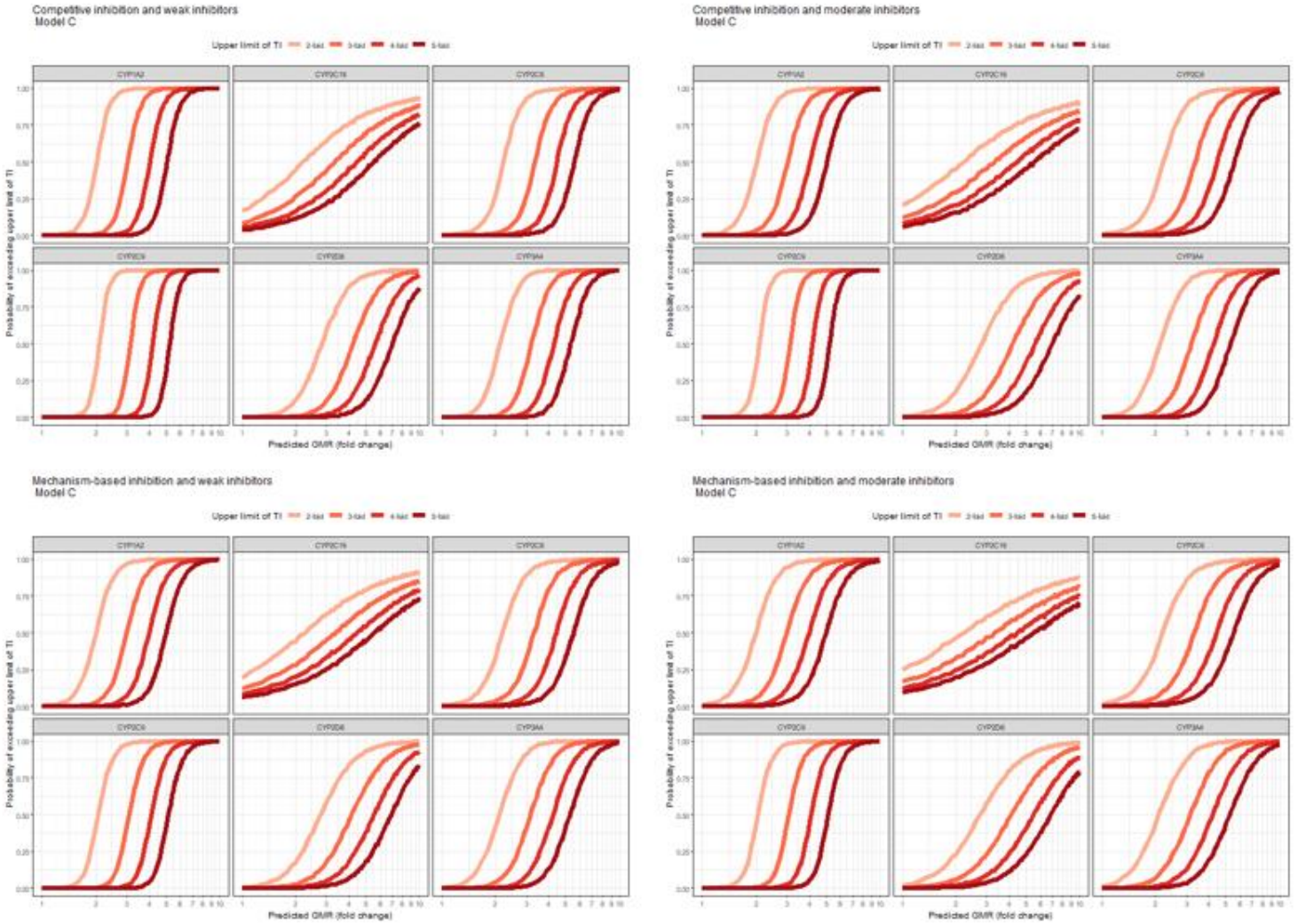
# 5. Posterior predictive visualizations

## Probability of exceeding a given therapeutic index at a predicted GMR (model C)





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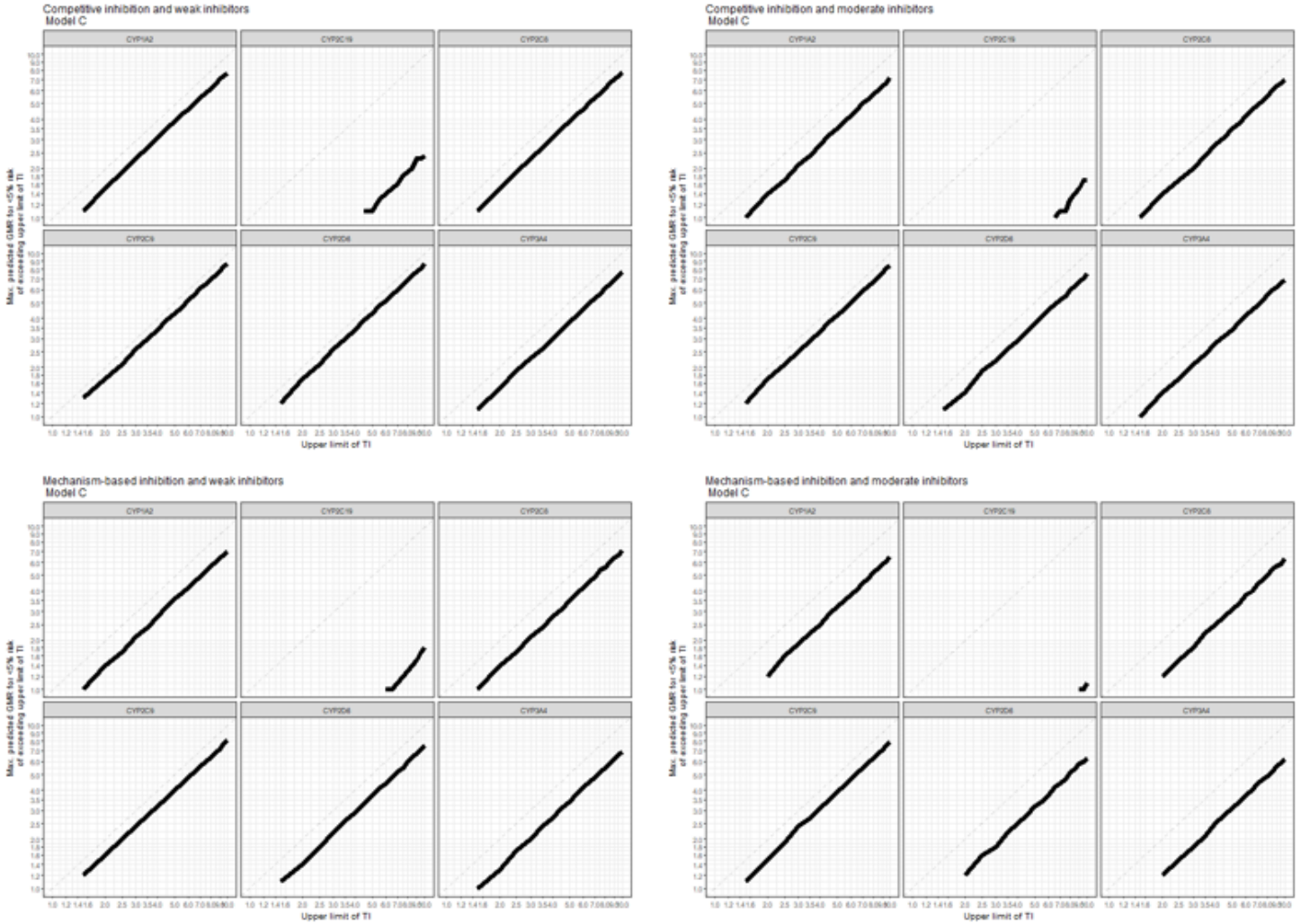
# 5. Posterior predictive visualizations

## Maximum predicted GMR for less than 5% risk of exceeding a given therapeutic index (model C)



# Summary: Performance of models A, B, and C

Table 1: Statistical summaries of the posterior distributions of the main parameters for models A, B, and C.

| Parameter | Model A | | Model B | | Model C | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| Mean GMR biases* | | | | | | |
| CYP1A2 | -0.0841 | 0.0347 | -0.0709 | 0.0314 | -0.0097 | 0.0485 |
| CYP2C19 | -0.0982 | 0.0939 | -0.1019 | 0.1011 | -0.0517 | 0.4725 |
| CYP2C8 | 0.0252 | 0.0687 | -0.0332 | 0.0628 | -0.0993 | 0.0864 |
| CYP2C9 | -0.0374 | 0.0406 | -0.0600 | 0.0393 | -0.0440 | 0.0658 |
| CYP2D6 | -0.1548 | 0.0575 | -0.1661 | 0.0539 | -0.2884 | 0.0863 |
| CYP3A4 | 0.0010 | 0.0306 | -0.0083 | 0.0309 | -0.0624 | 0.0533 |
| Between-study variances* | | | | | | |
| CYP1A2 | 0.0296 | 0.0119 | 0.0213 | 0.0102 | 0.0223 | 0.0161 |
| CYP2C19 | 0.1574 | 0.0679 | 0.1471 | 0.0657 | 0.7750 | 1.0515 |
| CYP2C8 | 0.0541 | 0.0380 | 0.0306 | 0.0245 | 0.0390 | 0.0450 |
| CYP2C9 | 0.0173 | 0.0114 | 0.0140 | 0.0104 | 0.0086 | 0.0079 |
| CYP2D6 | 0.0923 | 0.0328 | 0.0641 | 0.0266 | 0.0790 | 0.0469 |
| CYP3A4 | 0.0550 | 0.0121 | 0.0327 | 0.0093 | 0.0374 | 0.0162 |
| Effects of inhibition type | | | | | | |
| on bias | -† | -† | 0.0389 | 0.0448 | 0.0128 | 0.0765 |
| on between-study variance | -† | -† | 0.2798 | 0.2195 | 0.4403 | 0.3226 |
| Effects of inhibitor strength | | | | | | |
| on bias | -† | -† | -† | -† | 0.0048 | 0.0639 |
| on between-study variance | -† | -† | -† | -† | 0.5173 | 0.3563 |
| BSV‡ bias mean | 2.0244 | 0.0702 | 1.3994 | 0.0950 | 1.9114 | 0.1372 |
| BSV bias SD | 1.9396 | 0.0638 | 1.2853 | 0.0720 | 1.3307 | 0.1112 |

* For model B those estimates are for the competitive inhibition (CI) case; For model C, they are for the case of CI and weak inhibitors.
‡ BSV: Between-subject variance.
† Not computed by the model.

- Very similar results for models A and B
- Model B is more precise
- Model C – performance is affected by smaller number of studies

| CYP | Number of studies | |
|---|---|---|
| | Models A and B | Model C |
| CYP1A2 | 39 | 16 |
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# Conclusions

Model-based meta-analysis of PBPK performance gives useful insight and can help in decision-making

- The model extensions and refinements proposed by the EMA are appropriate and confirm that the Simcyp® Simulator DDI GMR prediction bias is globally acceptable and well-understood.
- Simcyp imprecision in GMR predictions is *at most* 12% to 40%.
- The mean bias in between-subject variability is ~ 2. This is an area where model-based assessment is strongly affected by data quality.
- The predictive visualization plots proposed by the EMA are informative.

# Context of Use 4

For scenarios where no clinical studies have been conducted, the Simcyp Simulator (V19 R1) can be used to predict the CYP-mediated inhibitory effect of a drug on the exposure of relevant CYP substrates (V19 files) to waive a clinical DDI study if a significant interaction is not predicted. Sensitivity analyses on relevant parameters including unbound fraction (fu) and inhibitory potency of the drug should be conducted to assess the risk of predicting a false negative.

For fu, the range should be determined by the variability associated with the in vitro determination of the parameter.

**For the inhibitory potency, the range can be determined by a comparison of the inhibitory potency of the positive control from the in vitro study versus that of the compound file used in the Simcyp Simulator (V19).**

# For example - optimisation of Ki values

- Industry-standard assays to determine Ki values have been refined over the years
- Non-specific microsomal binding (fumic) is often measured and used to correct Ki values to Ki,u
- In vitro Ki,u values may be optimized to Ki,u in vivo values using a clinical study (x-fold)
- Positive controls could be used to correct/calibrate the x-fold values across industry assays

# For example - optimisation of Ki values

- Ongoing discussions with Consortium Members
- Intend to use as many compounds as possible where clinical DDI studies have been conducted
- Determine x-fold values for each CYP enzyme

# Paroxetine – Ki values in UOW database

| System | Enzyme | $fu_{mic}$ | Ki,u [uM] | Ki [uM] |
|---|---|---|---|---|
| HLM | 2D6 | 0.25 | 0.0175 | 0.07 |
| HLM | 2D6 | 0.17 | 0.01105 | 0.065 |
| HLM | 2D6 | 0.17 | 0.0612 | 0.36 |
| HLM | 2D6 | 0.17 | 0.0255 | 0.15 |
| HLM | 2D6 | 0.51 | 0.2754 | 0.54 |
| HLM | 2D6 | 0.51 | 0.3111 | 0.61 |
| HLM | 2D6 | 0.51 | 0.2754 | 0.54 |
| HLM | 2D6 | 0.2 | 0.034 | 0.17 |
| HLM | 2D6 | 0.09 | 0.0405 | 0.45 |
| HLM | 2D6 | 0.09 | 0.0396 | 0.44 |
| HLM | 2D6 | 0.09 | 0.0252 | 0.28 |
| HLM | 2D6 | 0.09 | 0.0477 | 0.53 |
| HLM | 2D6 | 0.09 | 0.081 | 0.9 |
| HLM | 2D6 | 0.09 | 0.0396 | 0.44 |
| HLM | 2D6 | 0.09 | 0.117 | 1.3 |
| HLM | 2D6 | 0.09 | 0.09 | 1 |
| HLM | 2D6 | 0.09 | 0.117 | 1.3 |
| HLM | 2D6 | 0.09 | 0.0342 | 0.38 |
| HLM | 2D6 | 0.09 | 0.126 | 1.4 |
| HLM | 2D6 | 0.09 | 0.108 | 1.2 |
| | | | | |
| | mean= | 0.2 | 0.0876 | 0.46 |

## For basic compounds

$$fu_{mic} = 1 / [ ([P]_{mic} \times 10^{0.646 * logP - 2.236}) + 1 ]$$

$fu_{mic}$ varies because of different microsomal protein concentration [P]

| | Ki range before $fu_{mic}$ correction | Ki range after $fu_{mic}$ correction |
|---|---|---|
| Min [µM] | 0.065 | 0.01105 |
| Max [µM] | 1.4 | 0.126 |
| fold | 21.54 | 11.4 |

# THANK YOU


| | |
|---|---|
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