

## INTRODUCTION AND OBJECTIVES

Physiologically based pharmacokinetic (PBPK) models incorporate factors influencing oral drug absorption and may be used to predict **food effect of BCS class II/IV drugs** [1,2]. Nevertheless, model parameterization is often challenged by in vitro- in vivo disconnect and/or parameter non-identifiability [3,4]. These challenges may be overcome by simplifying PBPK models by recognizing that **solubility-limited absorption (SLA)** is the main driver of positive food effect [5,6] if the exposure of the drug is not significantly impacted by intestinal efflux or metabolism. The aim of this study is

- to propose a **novel approach for in silico prediction of food effect** based on determining a sensitive range of dose-adjusted solubility (FaSSIF/D) and solubility-limited absorption (SLA) for BCS class II/IV compounds.

## MATERIALS AND METHODS

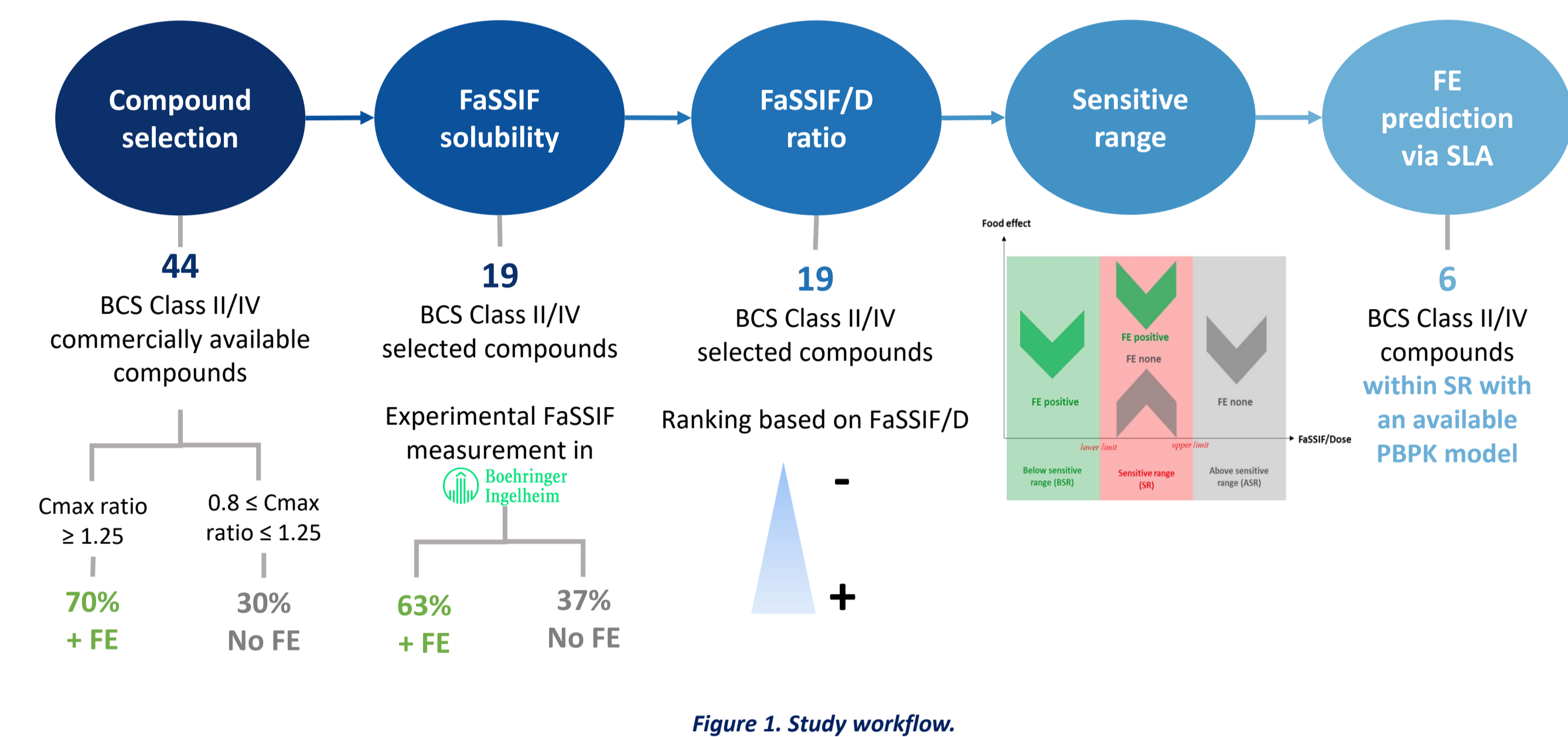


Figure 1. Study workflow.

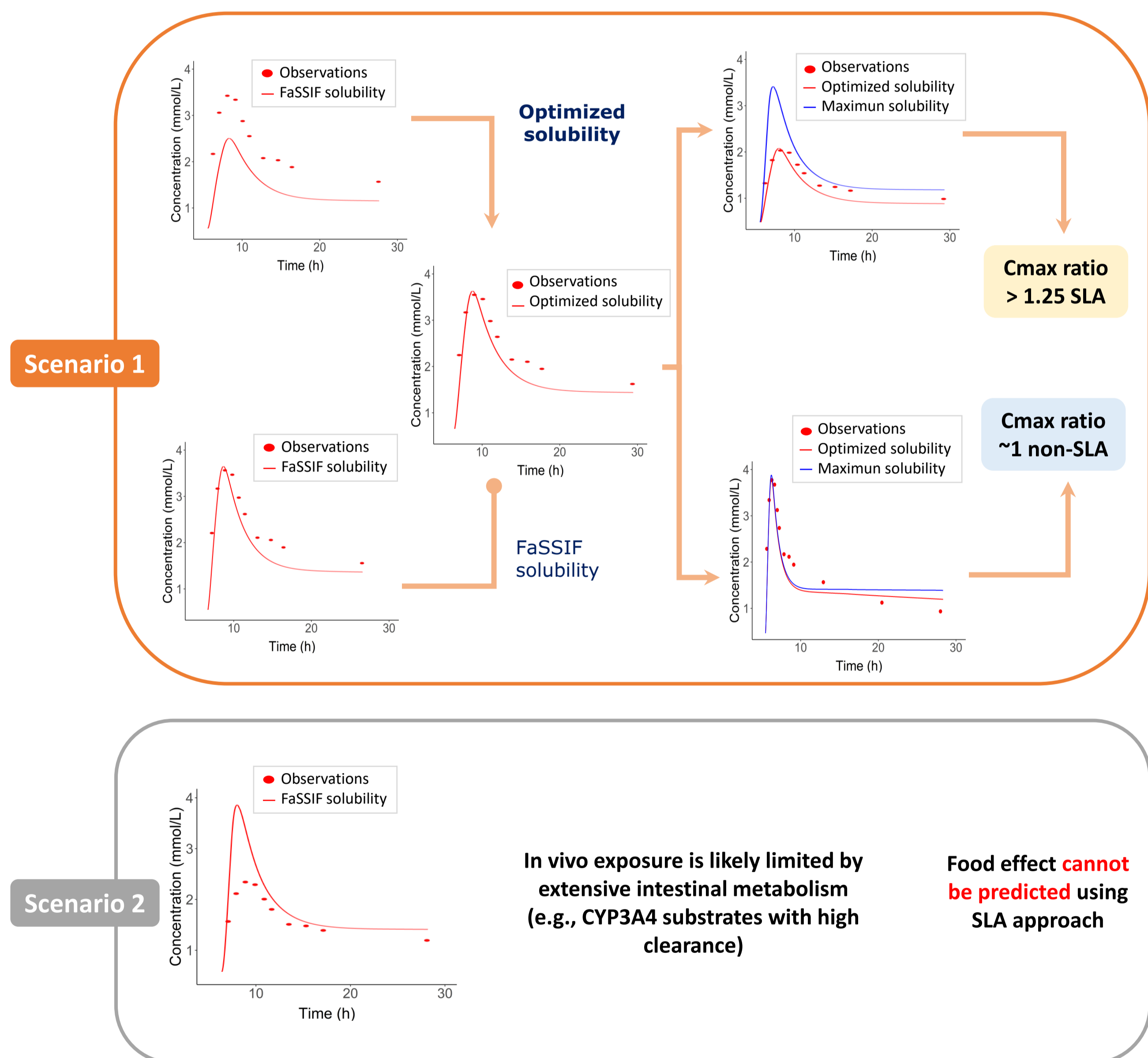


Figure 2. Solubility limited absorption (SLA) determination for food effect (FE) prediction.

## RESULTS

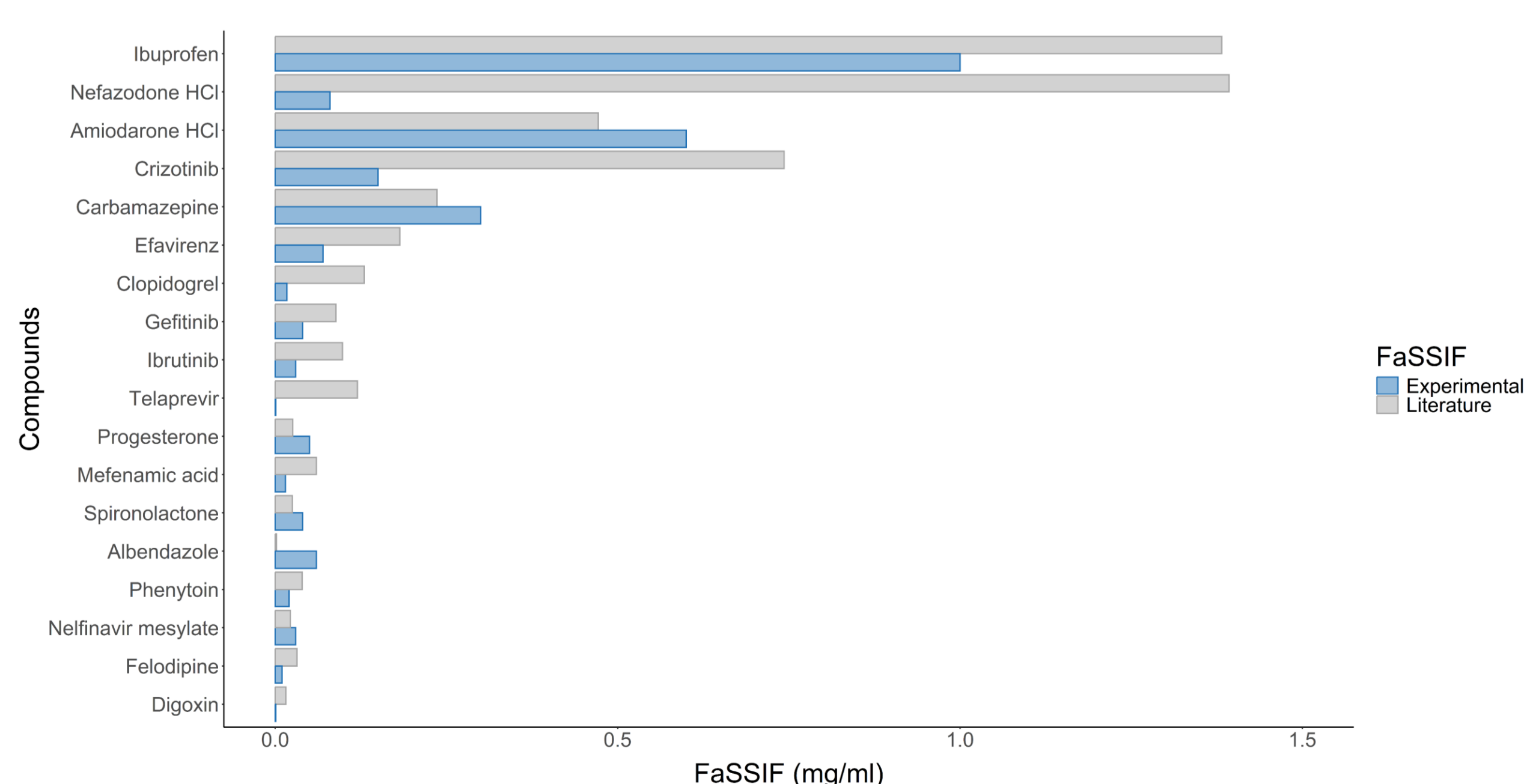


Figure 3. Comparison of experimentally determined and literature-reported FaSSIF values; FaSSIF: fasted state simulated intestinal fluid solubility.

### FaSSIF solubility

Compound	BCS	C <sub>max</sub> ratio		FE	Dose (mg)	FaSSIF (mg/ml)	FaSSIF/D (1/ml)
		in vivo	in vitro				
Telaprevir	II	5.96	positive	750	0.001	1.33x10 <sup>-06</sup>	
Nelfinavir mesylate	II/IV	4.37	positive	1250	0.03	2.40x10 <sup>-05</sup>	
Mefenamic acid	II	1.05	none	250	0.015	6.60x10 <sup>-05</sup>	
Phenytoin	II	1.41	positive	300	0.02	6.67x10 <sup>-05</sup>	
Ibrutinib	II	2.83	positive	420	0.03	7.14x10 <sup>-05</sup>	
Efavirenz	II	1.79	positive	600	0.07	1.17x10 <sup>-04</sup>	
Albendazole	II/IV	5.93	positive	400	0.06	1.50x10 <sup>-04</sup>	
Gefitinib	II	1.32	positive	250	0.04	1.60x10 <sup>-04</sup>	
Spiroonolactone	II	2.1	positive	200	0.04	2.00x10 <sup>-04</sup>	
Clopidogrel	II	6.5	positive	75	0.017	2.27x10 <sup>-04</sup>	
Progesterone	II	5.19	positive	200	0.05	2.50x10 <sup>-04</sup>	
Nefazodone HCl	II	0.93	none	200	0.08	4.00x10 <sup>-04</sup>	
Crizotinib	IV	0.86	none	250	0.15	6.00x10 <sup>-04</sup>	
Carbamazepine	II	1.35	positive	400	0.3	7.50x10 <sup>-04</sup>	
Amiodarone HCl	II	3.68	positive	600	0.6	1.00x10 <sup>-03</sup>	
Digoxin	IV	0.8	none	1	0.001	1.00x10 <sup>-03</sup>	
Felodipine	II	1.04	none	10	0.01	1.00x10 <sup>-03</sup>	
Ibuprofen	II	1.1	none	800	1	1.25x10 <sup>-03</sup>	
Tizanidine	II	1.24	none	8	1	1.25x10 <sup>-01</sup>	

Table 1. Selected compounds for determination of FaSSIF solubility and the conservative SR. The shadow FaSSIF/D area represents the conservative SR, and the red FaSSIF/D values represent the upper and lower limits of the conservative SR. FaSSIF/D: dose-adjusted FaSSIF.

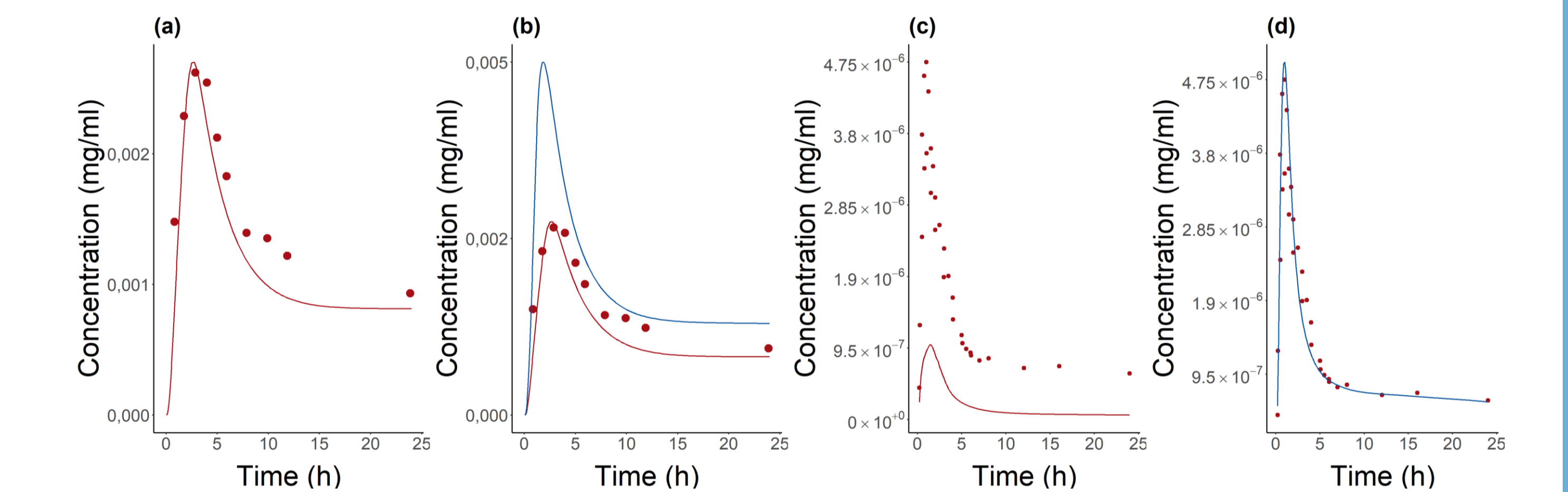
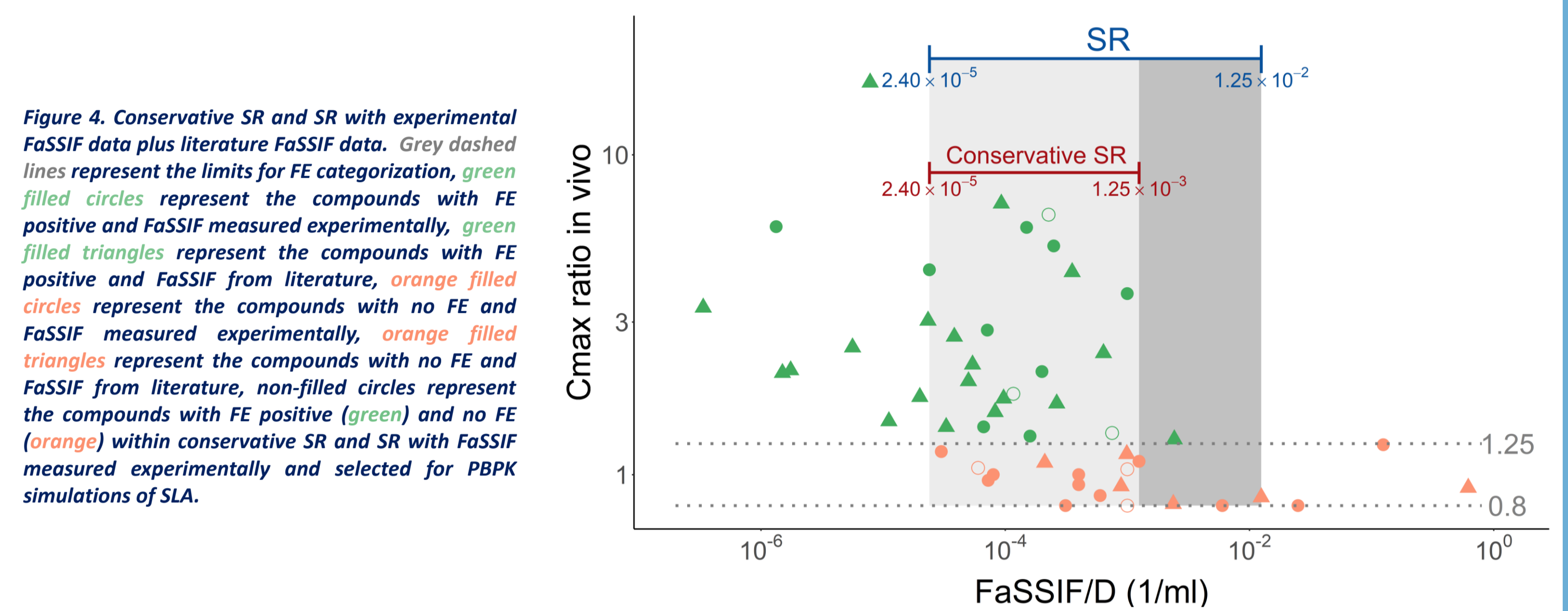


Figure 5. PBPK simulations of PK profiles of efavirenz (a, b) and digoxin (c, d). (a) Efavirenz 600 mg oral administration simulated with measured FaSSIF solubility. (b) Efavirenz 600 mg oral administration simulated with optimized (red line) and maximum solubility (blue line). (c) Digoxin 1 mg oral administration simulated with measured FaSSIF solubility. (d) Digoxin 1 mg oral administration simulated with optimized (red line) and maximum solubility (blue line), in this case, overlapped. FaSSIF: fasted state simulated intestinal fluid solubility.

Table 2. Solubility limited absorption (SLA) for the prediction of food effect (FE) using the PBPK modeling approach.

Compound	Solubility			C <sub>max</sub> ratio			Positive FE in vivo	Positive FE predicted by SLA	Agreement	
	FaSSIF (mg/ml)	Optimized (mg/ml)	Maximum (mg/ml)	In vivo	Predicted	In vivo / Predicted				
Scenario 1	Carbamazepine	0.3	0.85	1.8	1.35	1.21	1.12	yes	yes	
	Efavirenz	0.07	0.068	0.22	1.79	1.87	0.95	yes	yes	
	Digoxin	0.001	0.055	0.055	0.8	1	0.8	no	no	
Scenario 2	Mefenamic acid	0.015	0.5	0.5	1.05	1	1.05	no	no	
	Felodipine	0.01	0.012	*	1.04	*	*	no	*	
	Clopidogrel	0.017	0.06	*	6.5	*	*	yes	*	

Table 3. SLA for the prediction of FE using the PBPK modeling approach.

	FE in vivo positive	FE in vivo none	Total
Predicted FE positive (SLA)	2	0	2
Predicted FE none (no SLA)	0	2	2
Unpredictable FE (not determined SLA)	1	1	2
Total	3	3	6

### FE prediction

## DISCUSSION AND CONCLUSION

- FaSSIF/D can be used to classify drugs with positive FE from those with no FE outside SR. Within SR, drugs with SLA identified by PBPK are likely to have FE.
- The SR limits are not too sensitive to inter-laboratory differences in the FaSSIF values, therefore the established SR in this work can be applied to drugs with FaSSIF solubility measured elsewhere.
- This approach cannot be applied to drugs with extensive gut metabolism or transport.
- The selection of SR based on conservative, in-house FaSSIF measurements, and identification of SLA by PBPK allows for reliable prediction of FE to enable decisions on the need for pilot FE study and timing of pivotal FE study.
- Extension of this work to cover all compounds within SR will serve to further enhance confidence in the use of SLA to identify drugs that are likely to exhibit positive FE.

### References

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