V22 comparison

Population name	Healthy volunteer (Caucasian)
Prefix	Sim
Species	Human

Simcyp Version this document relates to: V22 (Release 1)

Prepared: December 2022

The Sim-Healthy Volunteer population within the Simcyp Simulator database has been used for these simulations with the following settings: age range 20-50; 50% of subjects were female. At least 10 trials were simulated for each compound file with 50 subjects per trial. Simulations were run for all compounds (substrates, metabolites and inhibitors) within the Simcyp database.

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Model Performance

Diagnostic plots - Dynamic simulations

The solid line represents the line of unity and the dashed lines a 2-fold difference in the following plots.

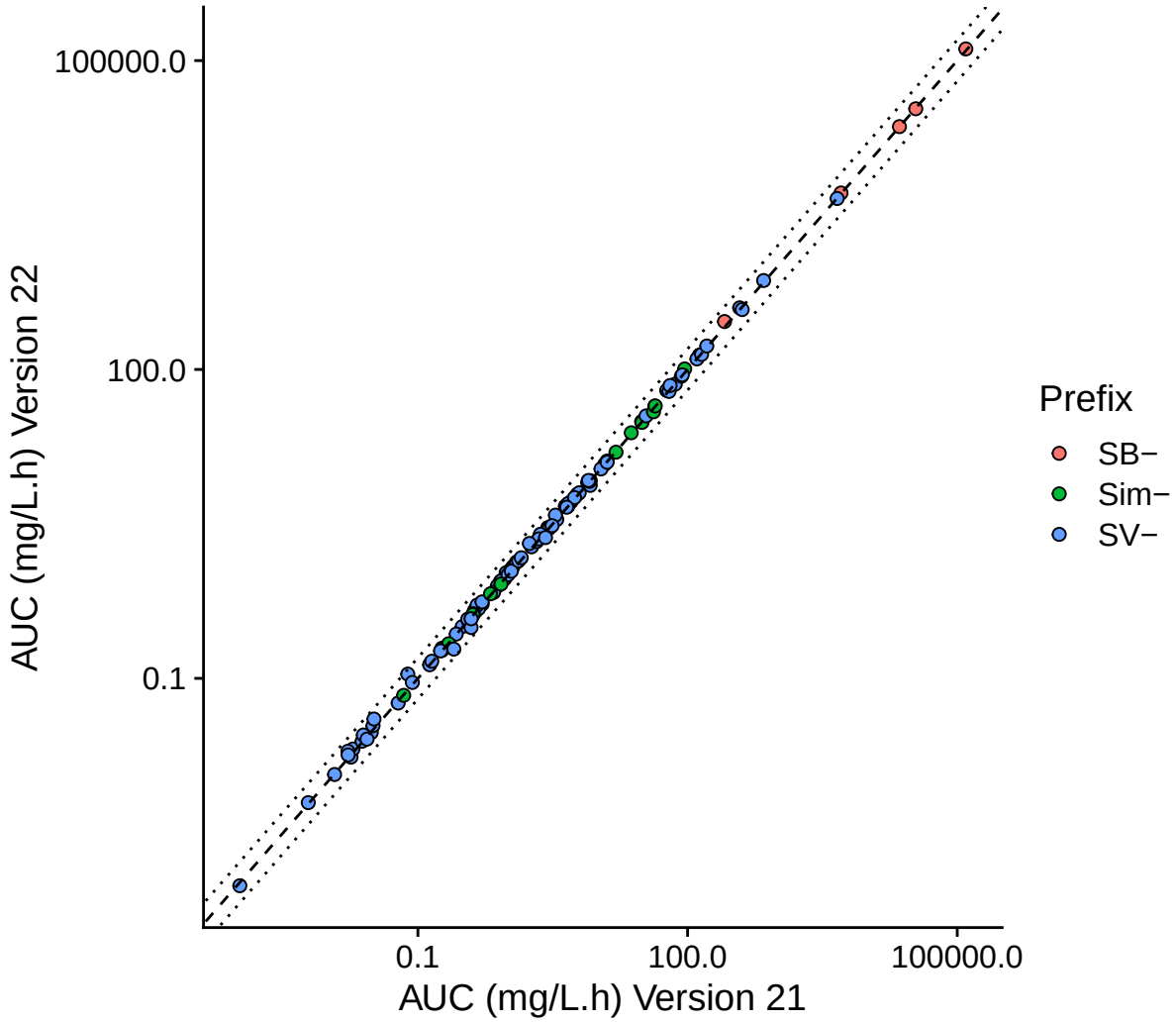

Figure 1. Mean simulated AUC (mg/L*h) for the Sim- (green), SV-(blue) and SB-(red) compound files using the Simcyp Simulator Version 22 release 1 or Version 21 release 1.

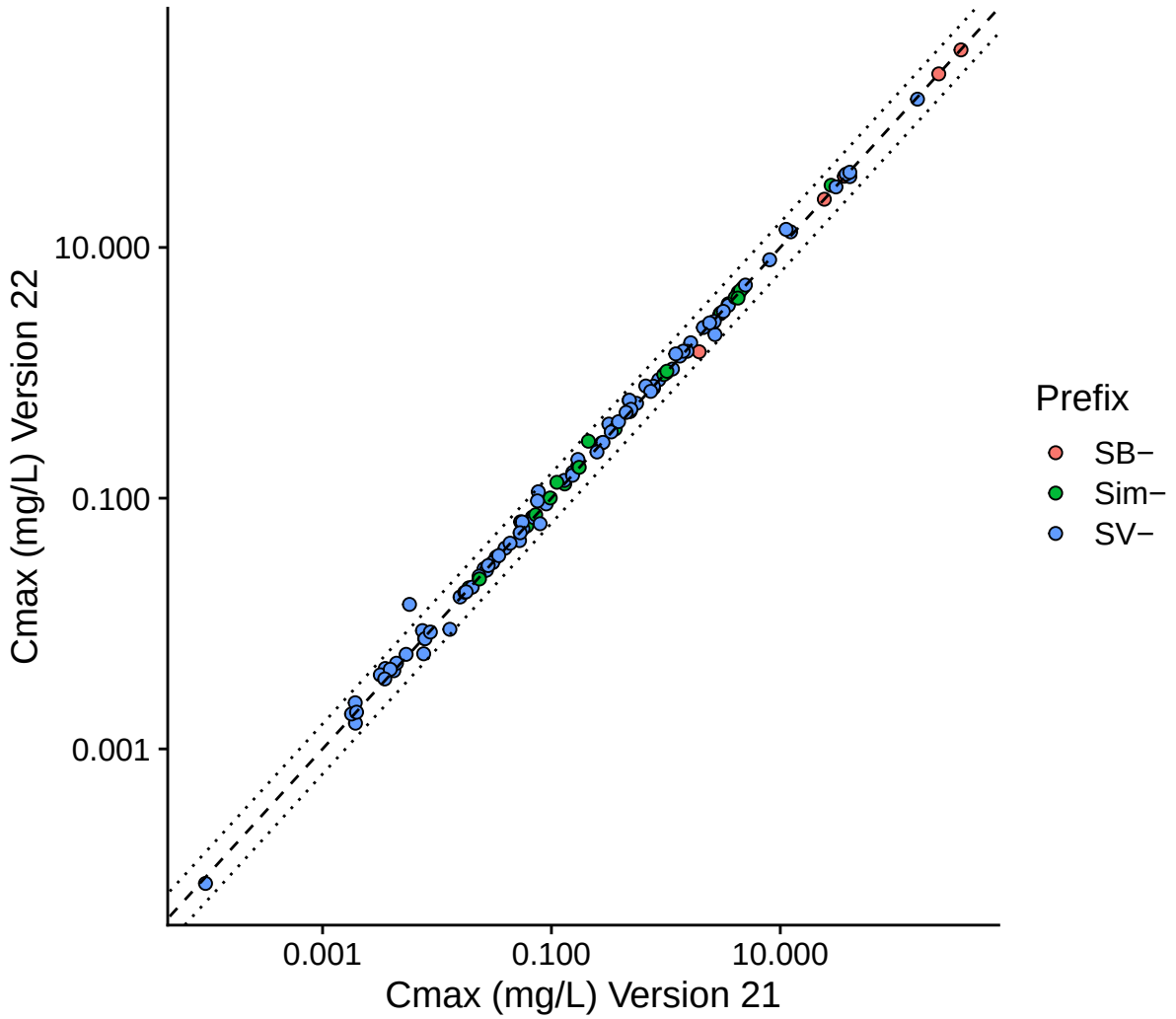

Figure 2. Mean simulated Cmax (mg/L) for the Sim- (green), SV-(blue) and SB-(red) compound files using the Simcyp Simulator Version 22 release 1 or Version 21 release 1.

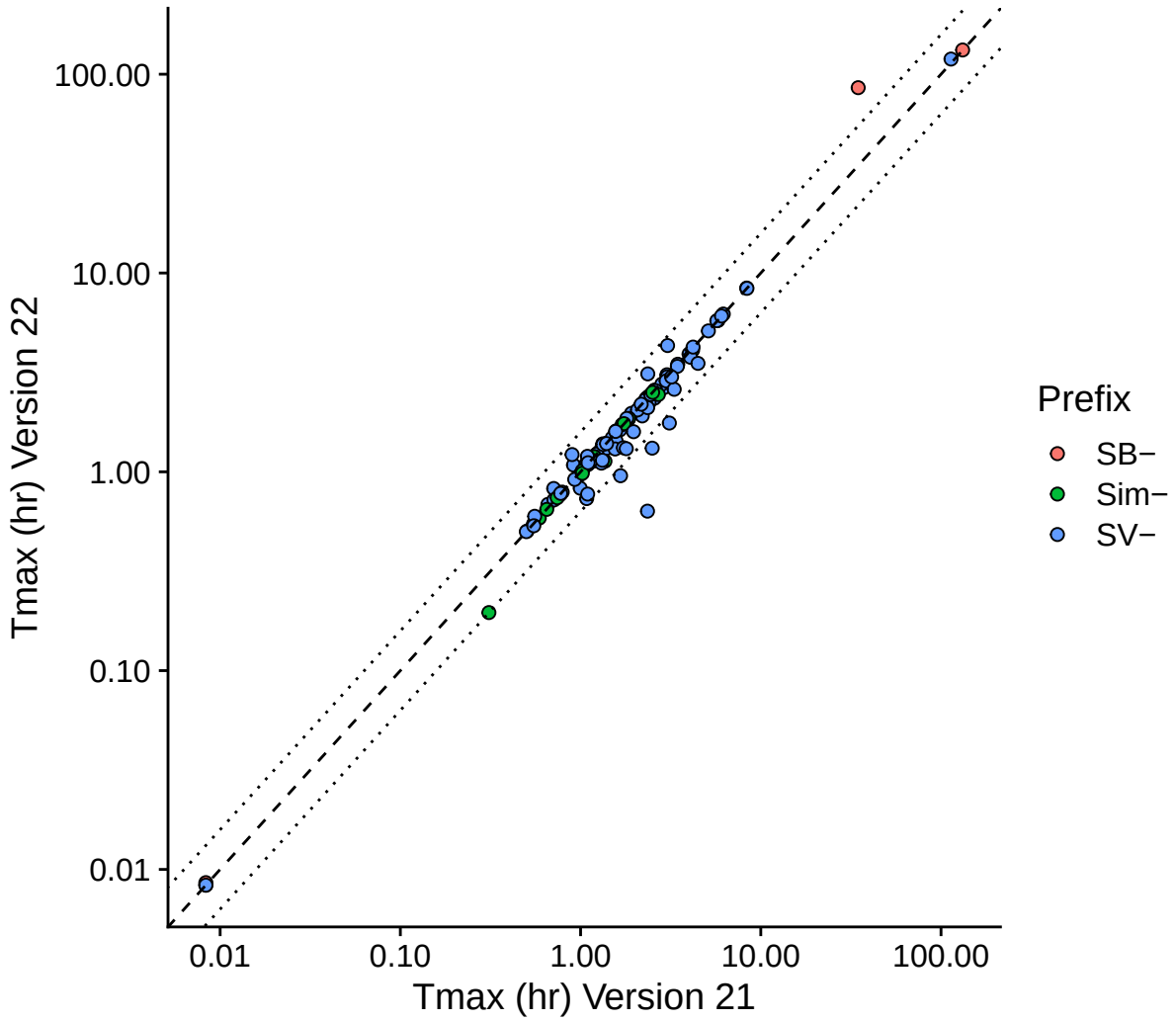

Figure 3. Mean simulated Tmax (hr) for the Sim- (green), SV-(blue) and SB-(red) compound files using the Simcyp Simulator Version 22 release 1 or Version 21 release 1.

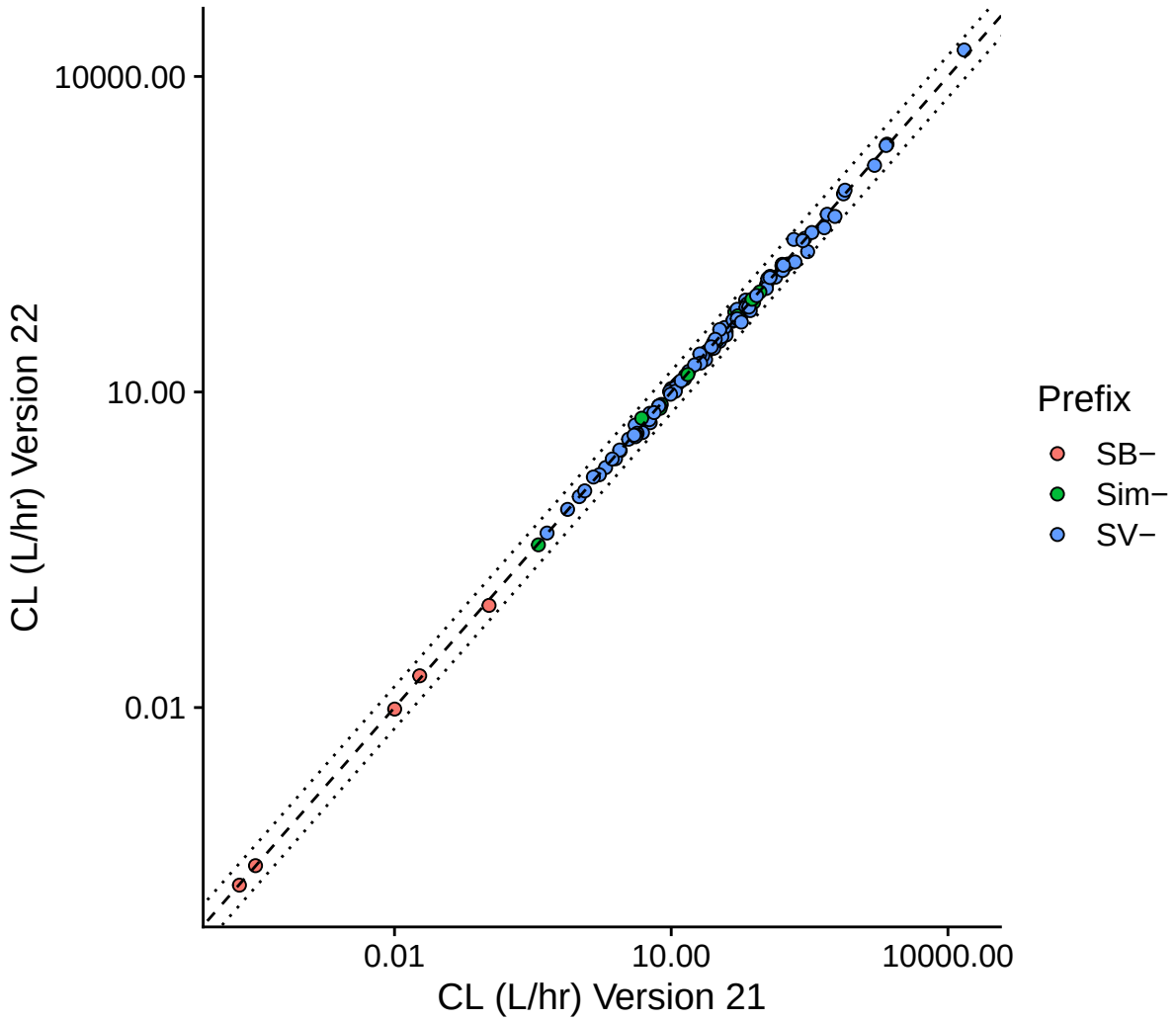

Figure 4. Mean simulated CL (L/hr) for the Sim- (green), SV-(blue) and SB-(red) compound files using the Simcyp Simulator Version 20 release 1 or Version 21 release 1.

Diagnostic plots - Static simulations

The solid line represents the line of unity and the dashed lines a 2-fold difference in the following plots.

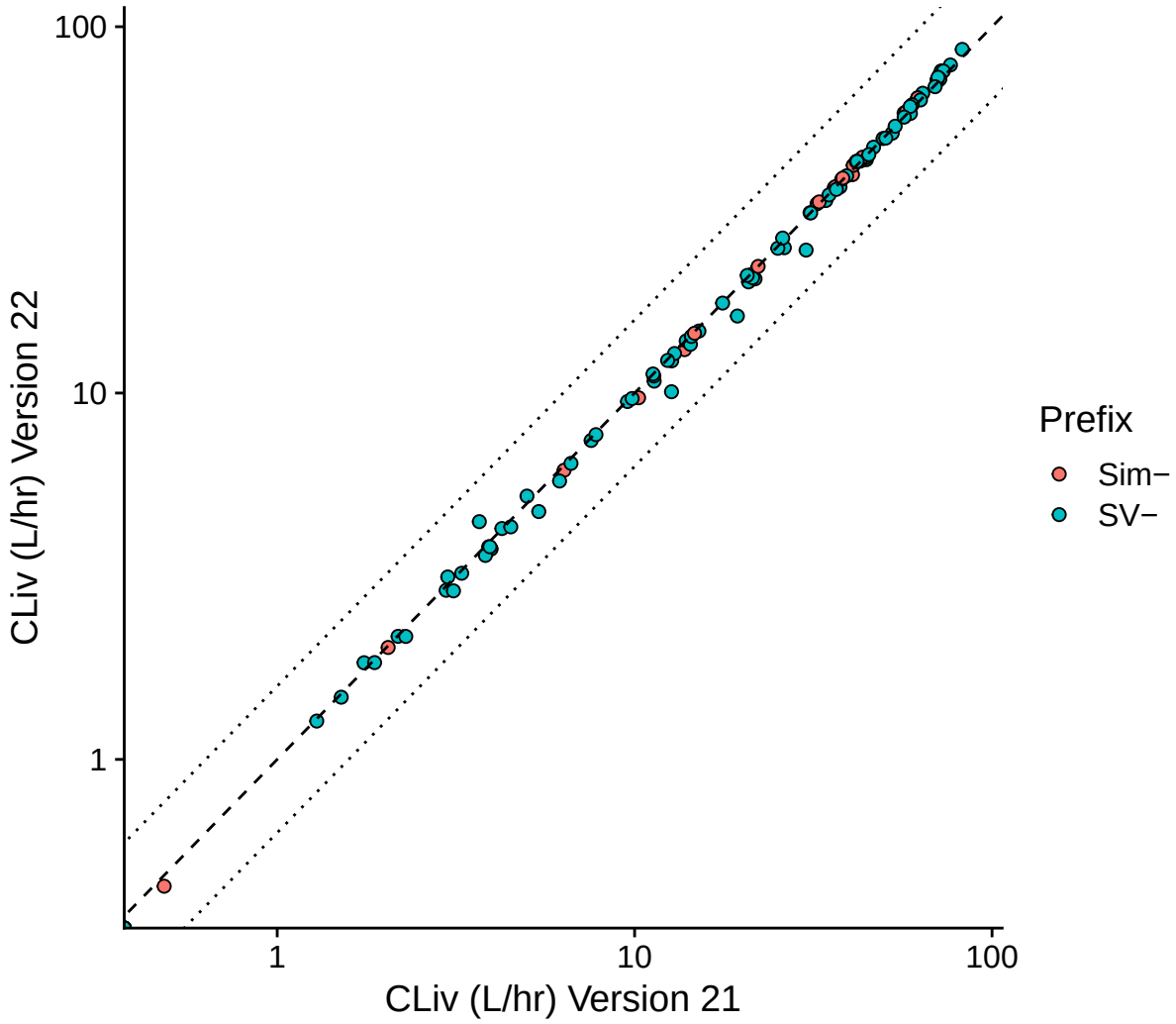

Figure 5. Mean simulated CLiv (L/hr) for the Sim- (red) and SV-(blue) compound files using the Simcyp Simulator Version 22 release 1 or Version 21 release 1.

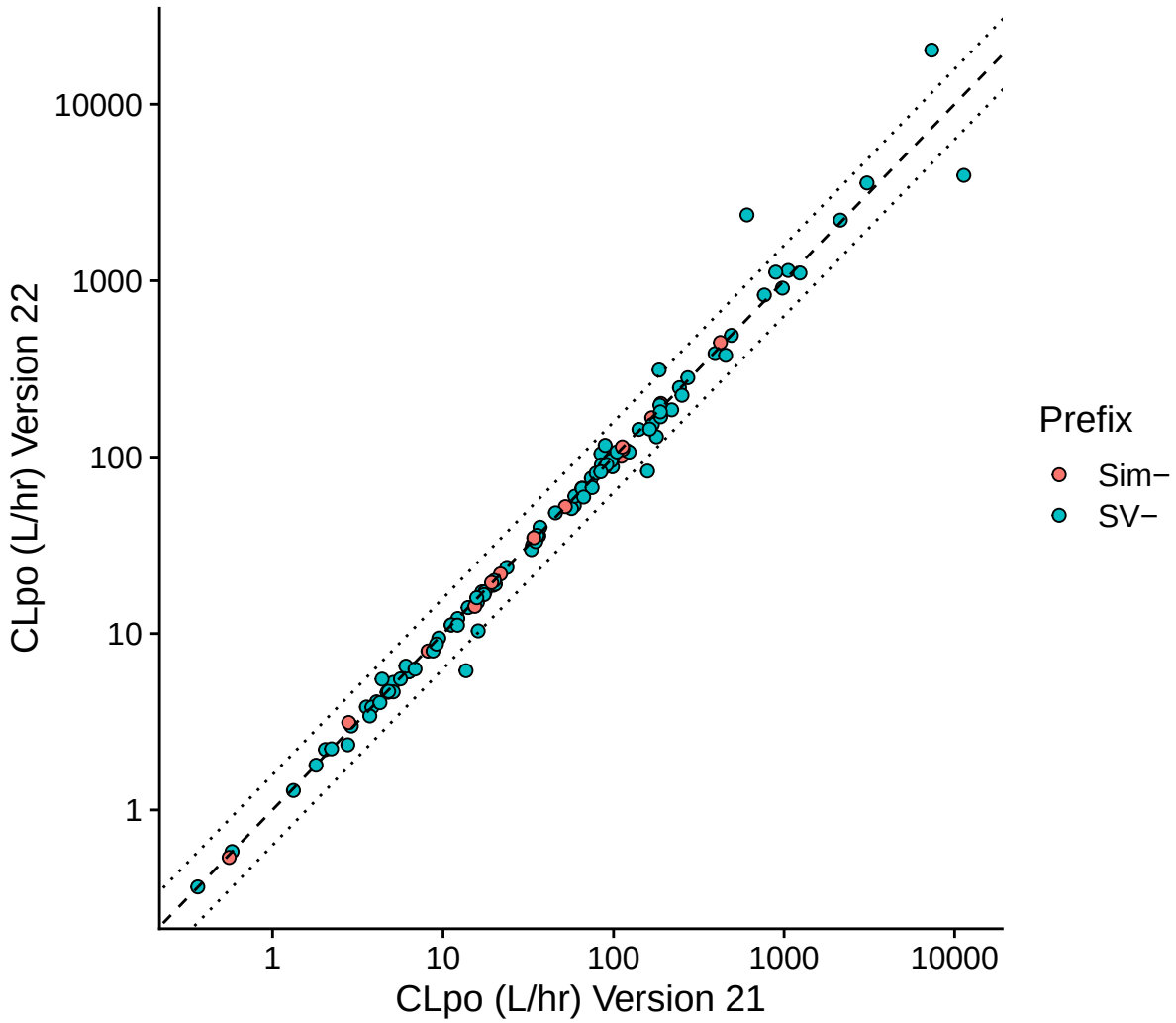

Figure 6. Mean simulated CLpo (L/hr) for the Sim- (red) and SV-(blue) compound files using the Simcyp Simulator Version 22 release 1 or Version 21 release 1.

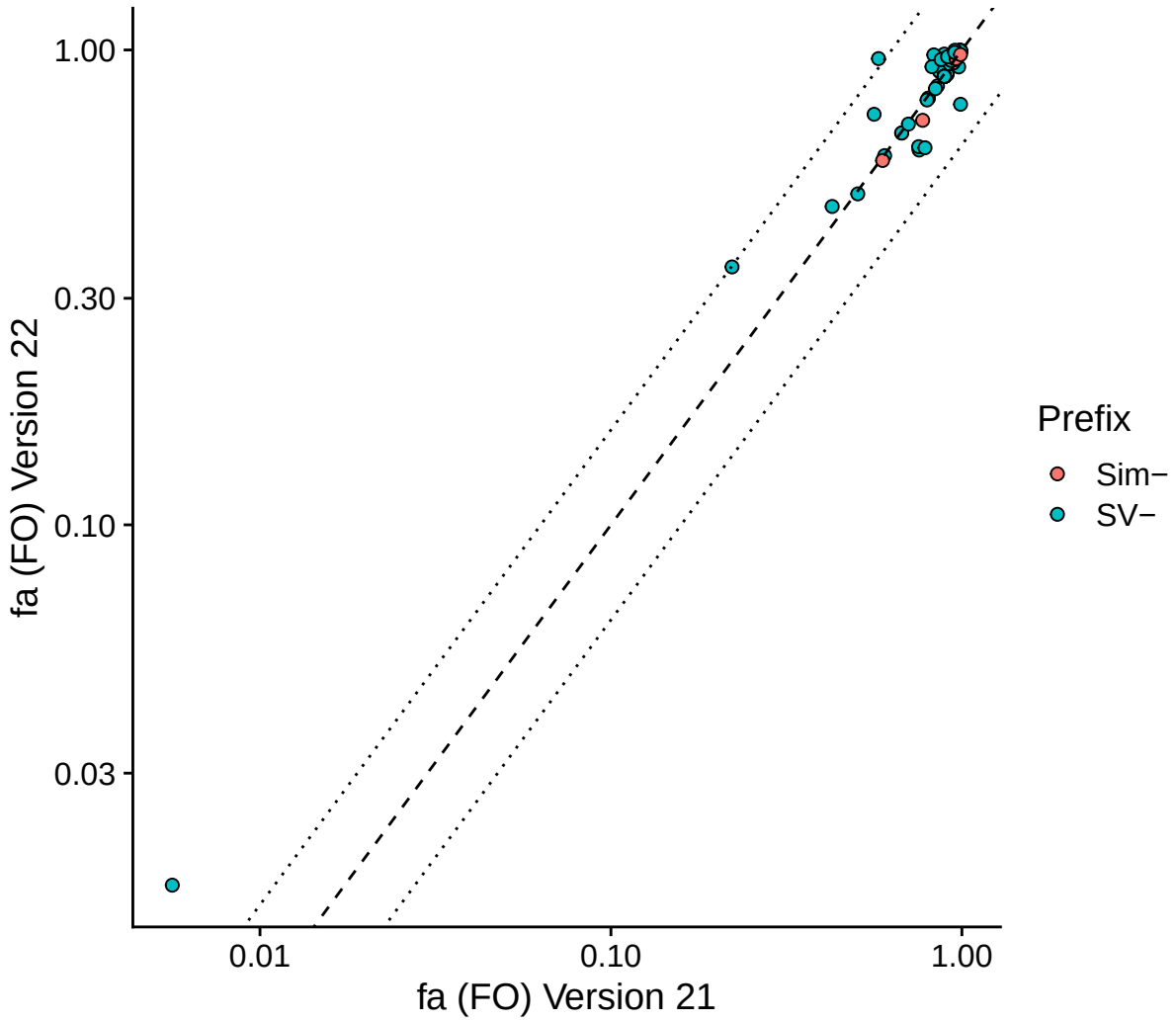

Figure 7. Mean simulated fa for the Sim- (red) and SV-(green) compound files using the Simcyp Simulator Version 22 release 1 or Version 21 release 1.

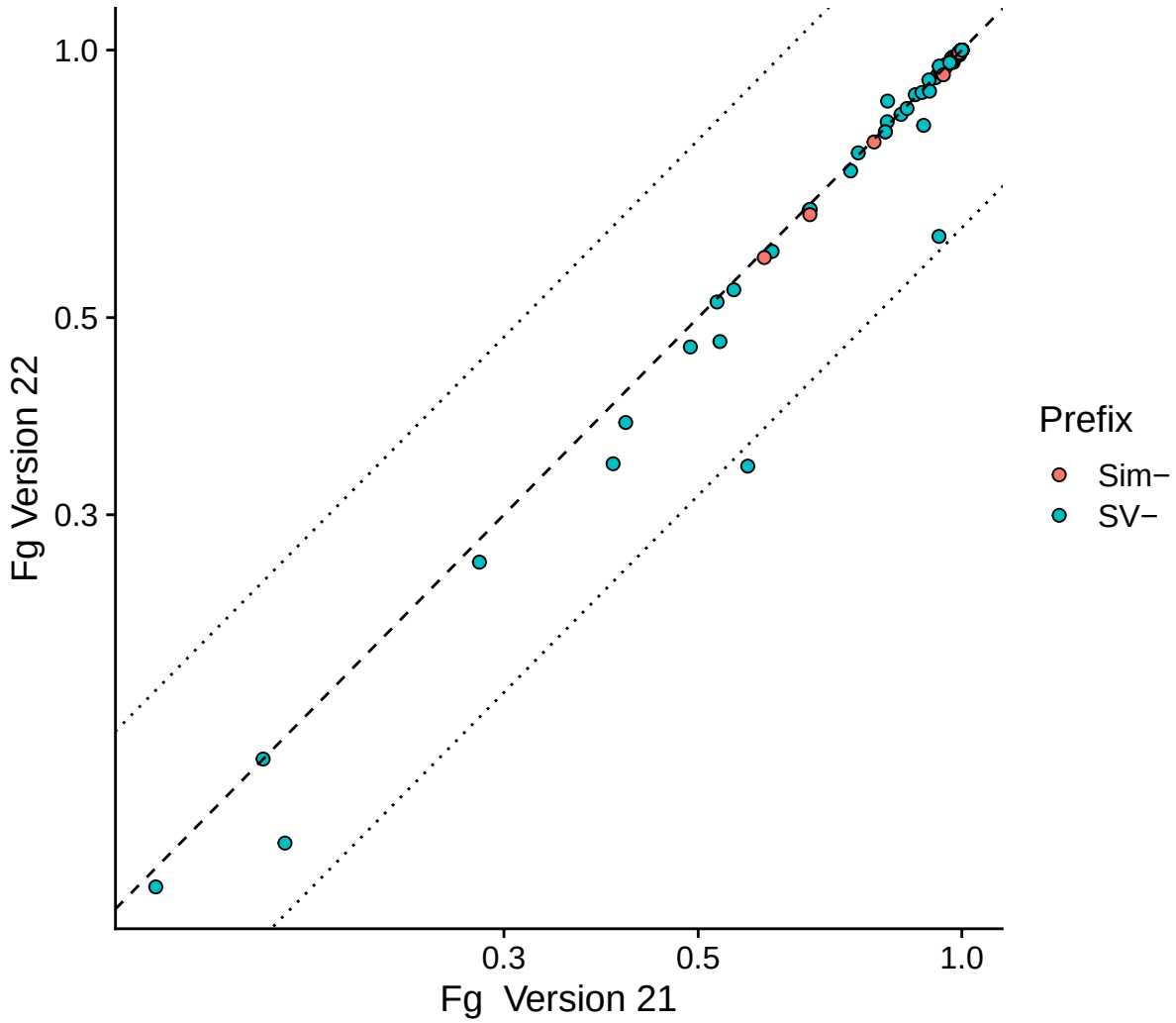

Figure 8. Mean simulated F_g for the Sim- (red) and SV-(green) compound files using the Simcyp Simulator Version 22 release 1 or Version 21 release 1.

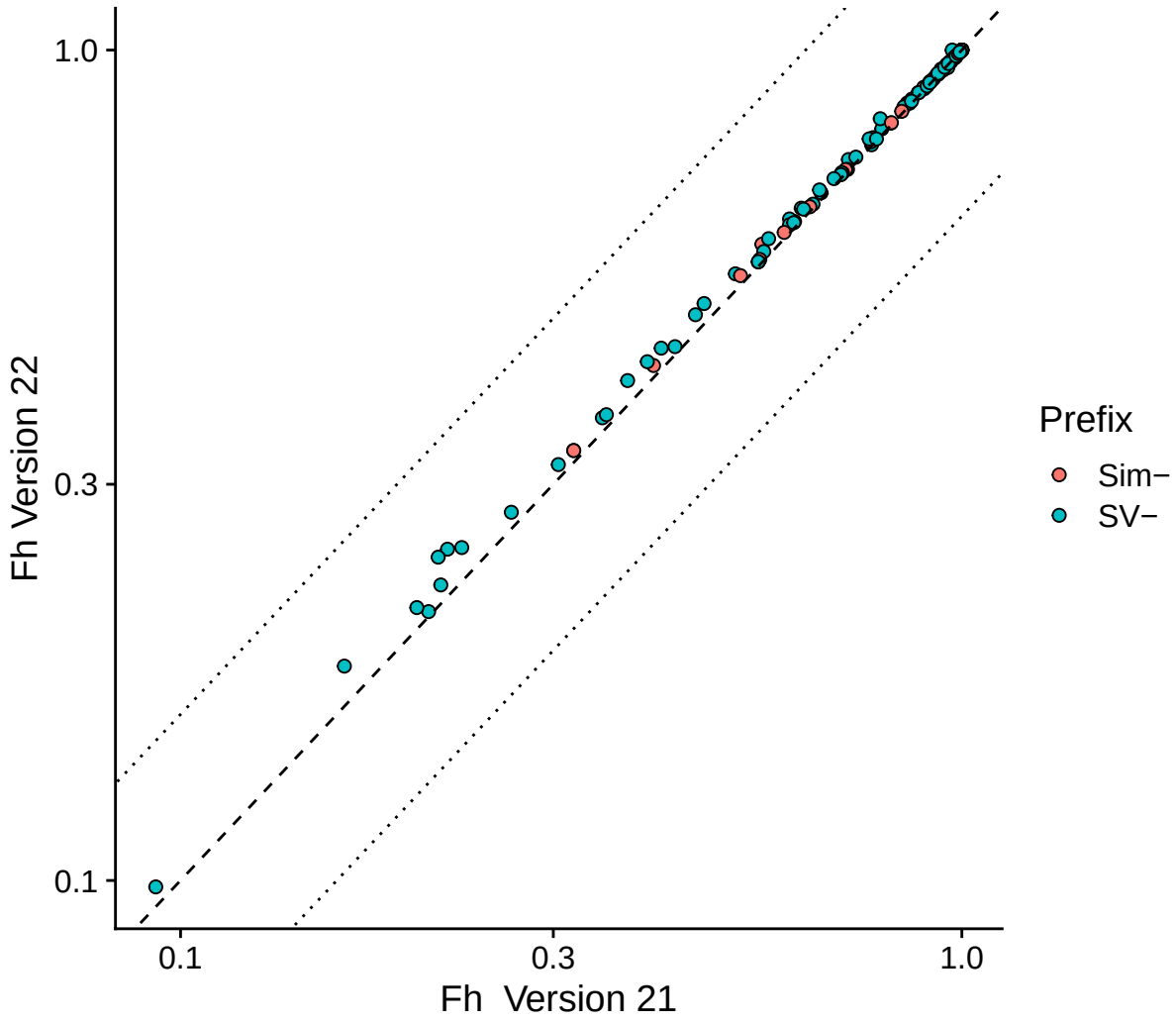

Figure 9. Mean simulated F_h for the Sim- (red) and SV-(blue) compound files using the Simcyp Simulator Version 22 release 1 or Version 21 release 1.

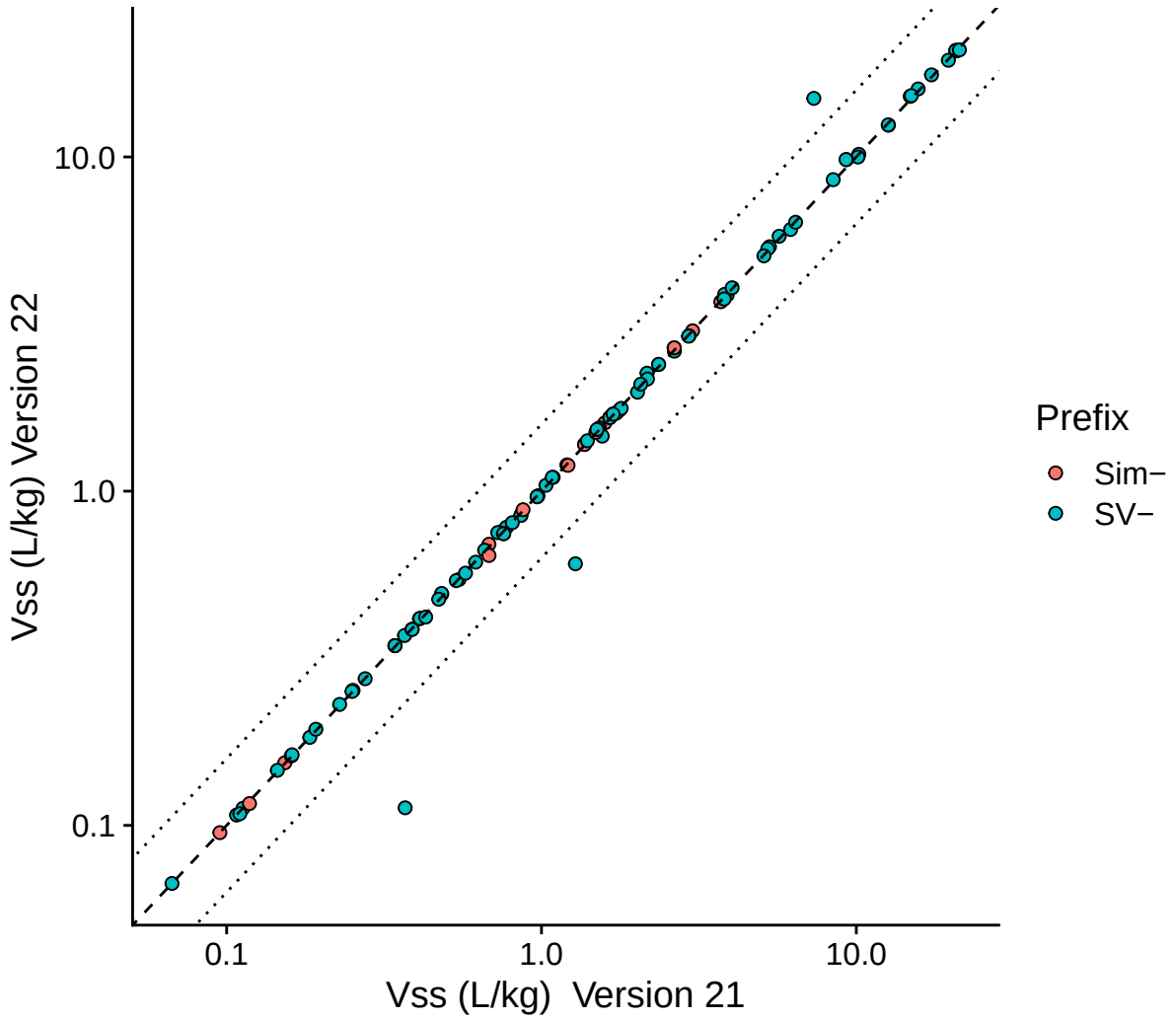

Figure 10. Mean simulated V_{ss} (L/kg) for the Sim- (red) and SV-(blue) compound files using the Simcyp Simulator Version 22 release 1 or Version 21 release 1.

Deviations

The table below shows the relative difference in pharmacokinetic parameters for the SV and Sim Compound files when they are run in V22 and V21. Results are presented as a percentage with 100% meaning no difference in the results for that compound between V22 and V21.

	PKPD Parameters						PKPD Profiles			
Name	**CLiv**	**CLpo**	**Fa**	**Fg**	**Fh**	**Vss**	**Cmax**	**Tmax**	**AUC**	**Dose/AUC**
Alfentanil	101	98	101	98	101	101	102	116	96	100
Alprazolam	100	103	99	100	100	101	97	99	101	103
Atazanavir	102	169	98	66	102	47	105	87	100	101
Atomoxetine	95	90	99	101	103	98	104	101	106	91
Atomoxetine-PM	97	99	99	100	100	98	100	100	101	99
Atorvastatin	101	102	105	92	102	102	124	68	95	104

(continued)

Name	CLiv	CLpo	Fa	Fg	Fh	Vss	Cmax	Tmax	AUC	Dose/AUC
Bufuralol	97	91	99	100	105	101	104	102	107	91
Bufuralol-PM	95	95	99	100	101	101	99	101	104	95
Buprenorphine	103	108	99	94	104	104	100	100	98	103
Bupropion-SR	101	85	110	99	107	204	101	93	111	90
Caffeine	97	98	99	100	100	99	101	100	101	98
Carbamazepine	99	103	99	100	100	100	101	100	102	103
Carbamazepine epoxide	NaN	101	99	100	100	101	99	101	99	100
Celecoxib	99	90	104	101	102	101	97	91	105	95
Cimetidine	99	101	99	100	101	99	108	100	104	103
Cinacalcet	104	98	100	101	105	98	106	98	102	98
Ciprofloxacin	97	124	94	100	100	100	75	118	99	117
Clarithromycin	100	103	99	99	101	99	101	99	101	103
Clozapine	99	98	99	100	101	101	99	100	102	98
Crizotinib	101	73	130	99	103	100	107	92	104	98
Cyclosporine-Neoral	102	107	99	98	101	101	100	99	99	108
Cyclosporine-M1	105	108	99	100	100	101	99	99	103	108
Cyclosporine-M17	105	108	99	100	100	101	100	99	103	107
Dabigatran Etexilate	105	276	110	76	101	102	122	83	109	119
Dabigatran	100	102	99	100	100	100	100	100	100	102
Desipramine	97	90	99	100	104	101	102	101	106	90
Desipramine-PM	98	100	99	100	100	101	98	100	100	102
Desmethyl diltiazem	100	102	99	100	101	99	102	100	101	102
Dexamethasone	100	100	100	100	101	101	101	98	100	100
Dextromethorphan	103	89	99	101	112	102	109	104	110	89
Dextromethorphan-PM	96	98	99	100	101	102	102	103	105	99
Dextrorphan	104	100	99	100	106	99	106	100	102	100
Digoxin	80	64	117	100	103	98	121	71	114	86
Diltiazem	102	100	99	100	103	100	103	99	102	100
Drospirenone	99	100	100	100	100	102	87	102	101	100
Efavirenz-MD	95	96	99	100	100	102	102	105	105	98
Efavirenz-SD	95	96	99	100	100	102	98	100	103	101
Erythromicin	100	101	99	99	101	98	103	100	100	101
Erythromycin-EC	100	101	99	99	101	103	99	99	102	102
Esomeprazole	98	90	102	100	104	101	123	95	105	88
Esomeprazole-PM	99	95	103	100	101	101	118	91	105	95
Ethinylestradiol	98	108	101	89	101	101	89	94	93	108
Fluconazole	99	97	101	100	100	98	98	132	100	98
Fluoxetine	95	94	99	100	101	100	101	100	102	101
Flurbiprofen	94	96	99	100	100	100	108	84	107	93
Fluvoxamine	97	95	99	100	102	98	102	100	103	96
Gemfibrozil-glucuronide	98	100	99	100	100	100	102	101	101	100
Gemfibrozil	95	93	101	99	101	101	113	83	109	92
3-HydroxyMorphinan	101	108	99	100	114	99	118	102	124	108
Ibrutinib	105	117	100	86	106	99	121	76	99	104
Imipramine	100	91	100	100	106	102	103	102	105	91
Itraconazole-fasted solution	103	103	99	100	103	102	96	98	99	113
Itraconazole-fed capsule	103	105	98	100	103	102	99	98	103	118
Ketoconazole 200mg BD	NaN	100	99	100	100	101	99	100	98	100

(continued)

Name	CLiv	CLpo	Fa	Fg	Fh	Vss	Cmax	Tmax	AUC	Dose/AUC
Ketoconazole 200mg QD	NaN	100	99	100	100	101	99	100	98	100
Ketoconazole 400mg QD	NaN	100	99	100	100	101	99	100	98	100
Lansoprazole	94	91	100	100	103	101	99	104	109	90
Lorazepam	97	91	104	100	101	101	96	103	113	86
S-Mephenytoin	100	90	99	101	105	101	103	100	102	90
S-Mephenytoin-PM	98	100	99	100	100	101	97	100	101	102
Metformin	100	102	99	100	101	99	94	93	91	118
3-Methoxymorphinan	97	95	99	100	102	99	102	100	102	95
Metoprolol	97	91	99	101	105	99	106	102	108	91
Metoprolol-PM	99	101	99	100	100	99	101	100	102	101
Midazolam	102	106	99	98	101	101	97	100	99	107
Mirabegron	103	89	112	99	102	99	116	93	98	103
Montelukast	88	45	166	107	101	101	106	98	114	84
Nebivolol	101	125	81	91	115	105	83	85	118	78
Nebivolol-PM	84	101	83	99	105	106	75	89	106	90
Nifedipine	101	99	101	99	101	102	135	63	102	97
Norfluoxetine	105	108	99	100	100	99	100	98	100	105
Norverapamil	100	100	99	99	102	99	100	100	99	103
Hydroxybupropion	121	126	99	100	99	94	147	27	89	119
Hydroxyitraconazole	101	103	99	100	102	102	100	100	101	103
3-Hydroxyquinidine	NaN	100	99	100	100	99	101	100	99	100
Ompeprazole	99	86	103	100	105	101	120	57	107	83
Omeprazole-PM	99	95	103	100	100	101	126	53	107	94
Ondansetron	99	89	107	100	103	98	104	103	104	96
Paroxetine	102	93	102	95	104	99	69	142	80	72
Phenacetin	101	98	99	100	103	101	101	100	103	98
Phenobarbital	NaN	100	100	100	100	101	97	99	98	102
Phenytoin	97	100	99	100	100	99	101	100	103	101
Pioglitazone	93	95	99	100	100	101	101	102	103	95
Pravastatin	98	131	79	100	101	100	79	97	77	133
Probenecid	95	85	109	100	100	100	91	96	94	109
Quinidine	100	102	99	100	101	99	101	100	101	102
Raltegravir	98	99	100	99	103	99	105	101	106	99
Repaglinide	95	94	100	98	101	101	111	107	103	93
Rifabutin	100	102	99	100	100	101	99	98	98	104
Rifampicin-MD	98	92	106	100	100	98	124	73	109	92
Rifampicin-SD	98	92	106	100	100	99	99	100	101	97
Ritonavir-ADAM	102	99	101	100	101	102	126	79	106	80
Ritonavir-FO	102	105	99	100	101	103	103	94	103	117
Rosiglitazone	93	92	100	100	101	100	93	136	105	92
Rosuvastatin	81	53	158	100	100	31	247	57	143	80
Sildenafil	101	102	100	97	102	98	101	99	98	101
Simvastatin	103	103	99	95	104	102	96	100	95	103
Siponimod	96	92	103	100	100	99	106	78	105	92
Sulphaphenazole	NaN	100	99	100	100	101	96	100	99	101
Theophylline	97	98	99	100	100	101	97	100	102	98
Ticlopidine	102	83	105	102	110	101	107	81	117	79

(continued)

Name	CLiv	CLpo	Fa	Fg	Fh	Vss	Cmax	Tmax	AUC	Dose/AUC
Tolbutamide	98	100	99	100	100	98	102	101	104	99
Tolterodine	100	89	99	100	106	101	103	101	108	89
Tolterodine-PM	99	100	99	100	101	101	98	100	100	100
Triazolam	101	106	99	98	101	101	99	99	99	106
Trimethoprim	NaN	98	104	100	100	99	104	110	103	98
Valsartan	99	112	92	100	100	100	93	91	93	118
Verapamil	103	390	78	60	105	102	126	87	97	103
S-Warfarin	93	97	99	100	100	98	101	100	102	97
Zidovudine-glucuronide	98	35	310	100	100	100	98	100	102	99
Zidovudine	99	96	99	100	106	99	116	97	105	97
Zolpidem	99	101	99	98	101	94	120	96	103	97
5-Hydroxymethyltolerodine	99	98	99	100	102	101	101	101	103	98

NaN = no value is calculated for this compound and parameter pair.

Discussion

In V22 a number of compounds were updated to make them compatible with the switch to the new GI tract anatomy. In the majority of cases the performance of the V22 files are in line with those of the V21 file. Individual compound summaries will be prepared to describe the changes to these files. For some compounds additional updates were made that change the performance of the V22 file compared to previous versions. A summary of the changes made for these compounds are summarised below.

Alfentanil
Model updated to use ADAM with solution option. Permeability was predicted using the mechanistic permeability model with P_{trans0} predicted using method 2. The basolateral scalar was adjusted to recover an F_g of 0.52.

Atazanavir
Model was updated to use ADAM with solution option. Permeability was predicted using the mechanistic permeability model with P_{trans0} set to give a value of effective permeability in the Jejunum 1 section that was equivalent to the value predicted previoulsy using Caco-2 cells. The basolateral scalar was adjusted to recover the observed F_g and the K_p scalar was also adjusted.

Atorvastatin
Permeability prediction updated to use the mechanistic permeability model with P_{trans0} predicted using method 1. Predicted C_{max} and T_{max} following this change were in line with observed clinical data.

Bupropion-SR and Hydroxybupropion
The file was updated to new GI anatomy and the SV-Bupropion-SR file was switched to ADAM and full PBPK. The absorption within the file was specified using the CR option with dissolution data taken from the publication by Hsieh et al. (2021). The profiles were optimised using the data from Connarn et al. (2017) and the performance of the file was checked for performance. The default model is with CR/MR for the SV-Bupropion-SR file. But this can also be switched to solution to simulate IR. The SV-hydroxybupropion file was updated in V22 to use a full PBPK model with a Kp scalar used to keep the Vss consistent with previous versions of the file. The elimination clearance used in the file was updated following a meta-analysis of available data. A summary of the performance of the V22 Bupropion and Hydroxybupropion files has been prepared and will be made available via the members area.

Ciprofloxacin
The permeability input was switched from a user input value to a value predicted from Caco-2 pH 7.4:7.4

(passive and active). The SV-ciprofloxacin model was also updated to use segregated transit times in the intestine.

Crizotinib
The absorption model was updated to use the particle population balance model. The P_{gp} J_{max} value was re-fitted within the context of the revised GI anatomy with a value of 200 pmol/min being used in the final file.

Dabigatran Etexilate
Changing to the new GI anatomy resulted in an increased C_{max} and a shorter T_{max}. To compensate for this change the passive permeation in the intestine was corrected by adjusting the intrinsic transcellular permeability and using an absorption scalar in the colon. In addition the J_{max} for intestinal P-gp was re-optimised. The resultant changes in file performance in V22 produce results within the observed data range, although there are limited measurements available for parent compound. The metabolite file Dabigatran required no modification.

Dextromethorphan
Some small differences in performance between V21 and 22 were noted. This can be attributed to differences in the number of UM and IM subjects generated in a population of 500 individuals in V21 (14, 162) and V22 (12, 168), respectively.

Digoxin
In V22 of the simulator absolute abundance scaling was used for intestinal and hepatic P-gp activity. Previously hepatic metabolism was used as a surrogate for metabolism occurring in the gut lumen. In V22 this was removed from the file and gut lumenal metabolism of digoxin added directly into the file. The distribution model was also updated. After these modifications the V22 file shows slightly higher C_{max} and a shorter T_{max} compared to V21. The increased C_{max} better recovers observed clinical data and the earlier T_{max} is also within the range of observed data.

Drospirenone
Small differences in C_{max} (13%) were noted between V21 and 22 in a population of 500 subjects. In population representative simulations the Drospirenone file behaves comparably between V21 and 22.

Esomeprazole
A first order absorption model is retained with permeability predicted using the mechanistic permeability model. Small increases in C_{max} and decreases in clearance were noted when compared to V21 although these values are still in line with reported clinical data.

Ethinylestradiol
Some physicochemical parameters were updated. The absorption model uses a first order model with the permeability predicted from Caco-2 data.

Fluconazole
The absorption model was updated to use the ADAM model with permeability predicted using the mechanistic permeability model (P_{trans0} was predicted using method 1). Whilst longer than in V21 the T_{max} is in line with values reported in clinical studies.

Flurbiprofen
The C_{max} is increased in V22 compared to V21. This improves the recovery of the observed fasted C_{max} with a predicted fed state C_{max} that is still within the range of observed data.

Gemfibrozil
Inhibition (K_i) values were added for BCRP and UGT1A3.

3-Hydroxymorphinan
No changes to the file were made in V22. The differences observed between V21 and 22 are due to population updates made in V22.

Ibrutinib
The mechanistic permeability model used to predict $Peff_{man}$ and fu_{gut} was re-optimised to recover the observed

F_g with the new GI anatomy. The resultant file has a slightly earlier T_{max} than the V21 file but is still within the range of observed clinical data.

Itraconazole
Metabolism was assigned to CYP1A1 instead of using CYP1A2 as a surrogate enzyme. Overall the performance of the model in V21 and V22 was similar. The simulated and observed drug interaction with midazolam reported in the study by Olkkola et al. (1994) is described in the table below as an example

Drug interaction between midazolam and itraconazole as reported by Olkkola et al. (1994).
Simulations were performed using the default files in V21 and V22. For both C_{max} and $AUC_{0\text{-}inf}$ ratio the mean value and trial range (in parentheses are reported). The predicted/observed mean ratio was 0.82 and 1.06 for C_{max} and $AUC_{0\text{-}inf}$ ratio respectively. In V22 the predicted/observed mean ratio was 0.81 and 0.92 for C_{max} and $AUC_{0\text{-}inf}$ ratio respectively

Study	**C_{max} ratio**	**$AUC_{0\text{-}inf}$ ratio**
Observed	3.41	10.77
V21	2.8 (2.3-3.2)	11.4 (5.9 - 14.24)
V22	2.8 (2.5-3.0)	9.95 (7.5 - 11.9)

Lansoprazole
A first order absorption model was retained in the SV-Lansoprazole file but the permeability input was switched to use MDCK-II data. The predicted exposure and DDI were in line with those reported in clinical studies.

Lorazepam
The SV-lorazepam model was updated to use the ADAM absorption model in V22. The mechanistic permeability model was used to define intestinal permeability with the P_{trans0} adjusted to give the same jejunal P_{eff} as was predicted using physicochemical data (PSA/HBD).

Metformin
No changes were made to the SV-metformin model. The clearance value was a bit higher than in V21 but is still consistent with observed clinical data.

Mirabegron
The K_{app} was updated to include new published values. Although showing small differences to V21 the simulated C_{max} and T_{max} are consistent with published clinical data.

Montelukast
Absorption was switched from ADAM to use a first order model with a user input fa, ka and T_{lag}. The V_{sac} and UGT1A3 CL_{int} were refined to better recover the exposure in UGT1A3 PM and UM subjects. The revised fm was verified using DDI data with Gemfibrozil (CYP2C8 inhibitor) incorporating a K_i for Gemfibrozil inhibiton of UGT1A3.

Nebivolol
The absorption model in the SV-nebivolol file was updated to use ADAM. Permeability was described using the mechanistic permeability model with the P_{trans0} fitted to give the same jejunal P_{eff} as the V21 file (predicted from PSA/HBD). The distribution model was updated.

Nifedipine
The Sim-Nifedipine file was not updated for V22. The simulated C_{max} and T_{max} for the file in V22 are within the range of reported clinical data. Although the C_{max} is towards the higher end of the range and the T_{max}towards the lower end of the reported range.

Omeprazole
The mechanistic absorption model within the SV-omeprazole file was extended to use the ADAM model together with dissolution data for the enteric coated granule formulation. USPII dissolution data was modelled in SIVA to derive the DLM scalar used within the V22 omeprazole compound file. The distribution model was changed from minimal to full PBPK.

Ondansetron
The Log P was updated with new data and small adjustments were made to the K_p and absorption rate scalar. As in V21 the SV-Ondansetron file uses the ADAM model for absorption and the exposure in the PK profiles mode of the simulator is similar to the performance in V21. Some differences are noted in the PK parameter calculations between V21 and 22 but these are not relevant for the performance of the file.

Paroxetine
The model was updated from a first-order absorption model to use the ADAM solution option. The K_{app} was adjusted to better recover the multiple dose exposure at the lower (20 mg) dose level. The simulated DDI with the SV-paroxetine file are similar to V21 and in line with clinical observations.

Pravastatin
The P_{trans0} value was optimised in the V22 file. Renal transporter clearance values were updated to account for the increase in proximal tubule cells per gram of kidney (results updated following a meta-analysis of newly available literature data). The predicted C_{max} is decreased compared to V21 but within the range of clinically reported values.

Probenecid
The SV-Probenecid file was switched from ADAM solution in V21 to use an immediate release setting with solubility described using a diffusion layer model. Intrinsic solubility, P_{trans0} and $Log_{km:w}$ values were taken from *in vitro* experiments. The SV-Probenecid model was also updated to use the particle population balance model. Although some differences are noted in the PK parameter results compared to V21 these are not relevant for the performance of the file. The SV-probenecid model in V22 compares well to both the clinical data and the PK profile results from V21.

Repaglinide
The SV-repaglinide model in V22 still uses a first order absorption model with the same value of effective permeability although the prediction method was switched from Caco-2 data to use the mechanistic permeability model with a calibrated P_{trans0}.

Rifampicin-MD
The SV-Rifampicin-MD model was not updated in V22. The model has an increased C_{max} and shorter T_{max} in V22 compared with V21 although the values are in line with the clinical data and the DDI prediction performance is similar to V21.

Ritonavir-ADAM
An experimental value of P_{Trans0} is used in the V22 SV-Ritonavir-ADAM file. The model now uses segregated transit times with only the ascending colon transit time utilised. Absorption rate and basolateral permeability scalars were used in the updated model.

Rosiglitazone
The Sim-Rosiglitazone model was updated to use an ADAM (solution) absorption model in V22 with permeability predicted using the mechanistic permeability model (Log P prediction; method 2). The bile:micelle partition coefficient ($Log_{km:w}$) was calibrated using the compound pKa, intrinsic solubility and FASSIF and FESSIF data. The distribution model was switched from minimal to full PBPK.

Rosuvastatin
The SV-Rosuvastatin was significantly updated in V22 to better recover intestinal BCRP and hepatic OATP1B drug-drug interactions. The previous model had a tendency to underpredict oral C_{max}. This was resolved by removing the distribution K_p scalar in V22. The renal clearance was updated using data reported by Martin et al. (2003), this in turn increases the fraction transported in the liver and increases the impact of transporter DDI. In the V22 model the sinusoidal MRP4 efflux was set to be equal to the BCRP mediated

clearance reported in sandwich cultured human hepatocytes Pfeifer et al. (2013). In the intestine absolute scaling was used for the transporter CL_{int} and the absorption rate scalar in the colon was re-calculated to account for the updated intestinal anatomy. The global hepatic uptake was re-optimised in V22 and as previously apportioned to transport by OATP1B1, 1B3, 2B1 and NTCP. The V22 model predicts well the observed C_{max} and AUC ratios in DDI studies although there is a tendency to overestimate the C_{max}

Siponimod
The SV-Siponimod file was not updated for V22 and the performance of the file is in line with reported clinical data.

Ticlopidine
Changing to the new GI anatomy resulted in an increased C_{max} and a shortened T_{max} for the ticlopidine file. In V21 absorption was described by a first-order model with a lag-time. In V22 retaining the first order model would have required a much longer lag-time. In the V22 file the model was switched to ADAM and a mechanistic absorption model accounting for formulation disintegration and describing absorption with a diffusion layer model was implemented. The salt model within ADAM was used to account for the chloride counterion in the formulation. The effects of endogenous chloride, surface pH and precipitation models were also included. Absorption was described using the segregated transit time model. This mechanistic description of absorption allows the observed C_{max} and T_{max} to be recovered with reasonable accuracy.

Valsartan
In V22 the P_{trans0}, MRP2 REF value and the percentage of biliary excreted drug available for re-absorption were updated.

Verapamil and Norverapamil
Permeability for the SV-Verapamil model was predicted using the mechanistic permeability model and within ADAM the solution with precipitation option was utilised. In the intestine transport by MRP2 was deactivated and uptake transport by OCTN1 utilised. In addition the K_{app} value used within the Norverapamil file was reduced.

Zidovudine
Renal clearance was updated due to changes in the number of proximal tubules per gram of kidney. The small increase in C_{max} compared to V21 is within the range of reported clinical values.

Zidovudine glucuronide
The changes observed for Zidovudine glucuronide in the compound summary between V21 and V22 are expected based on the changes in the intestinal anatomy. There is no oral data with dosing of the metabolite for performance verification. Performance of the file after IV dosing or when used as a metabolite of zidovudine are comparable with V21 and are consistent with observed clinical data.

Zolpidem
The SV-Zolpidem model was updated to use the ADAM model in solution mode. The permeability was described using the mechanistic permeability model with P_{trans0} predicted using Log P and method 2. The bile:micelle partition coefficient (LogK:mw) was calibrated using pKa, intrinsic solubility and FASSIF and FESSIF data. The distribution was switched to a full PBPK model.

New compounds for V22

The new compounds introduced into Simcyp V22 are: fedratinib (SV); ruxolitinib (SV); modafinil (SV); cobcistat (SV); oxycodone (SV); glyburide micronized (SV) and two metabolites (3-cis and 4-trans hydroxy, both SV); voriconazole (SV) and the N-oxide voriconazole metabolite (SV); posaconazole-DR tablet (SV), enzalutamide (SV), duloxetine (SV), letermovir (SV), tenofovir (SV), rivaroxaban (SV), and trastuzumab (SB). Additionally, the following research compounds were developed in the V22 cycle and will be made available in the Simcyp Members' Area: isavuconazole; morphine; dronedarone and N-desbutyl dronedarone metabolite; and trastuzumab emtansine (T-DM1) antibody drug conjugate.

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