V21 comparison

Population name	Healthy volunteer (Caucasian)
Prefix	Sim
Species	Human

Simcyp Version this document relates to: V21 (release 1)

Prepared: November 2021

The Sim-Healthy Volunteer popuation 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/inducers) within the Simcyp database.

Certara UK (Simcyp Division),
Level 2 - Acero, 1 Concourse Way,
Sheffield, S1 2BJ, United Kingdom

Please contact support@simcyp.com for more information

Model Performance

Diagnostic plots - Dynamic simulations

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

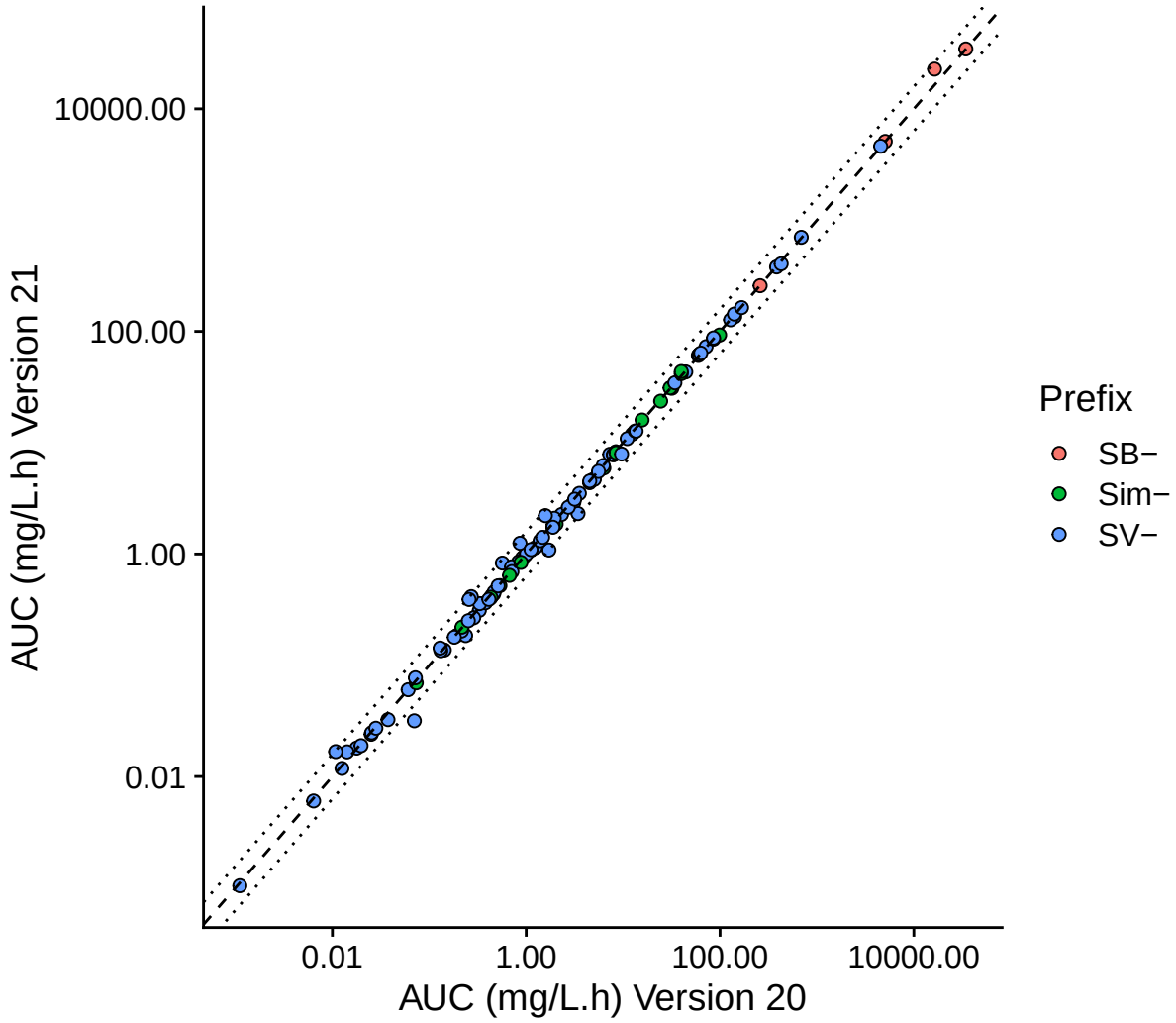

Figure 1. Mean simulated AUC (mg/L*h) for the Sim- (green), SV-(blue) and SB-(red) compound files using the Simcyp Simulator Version 20 release 1 or Version 21 release 1.

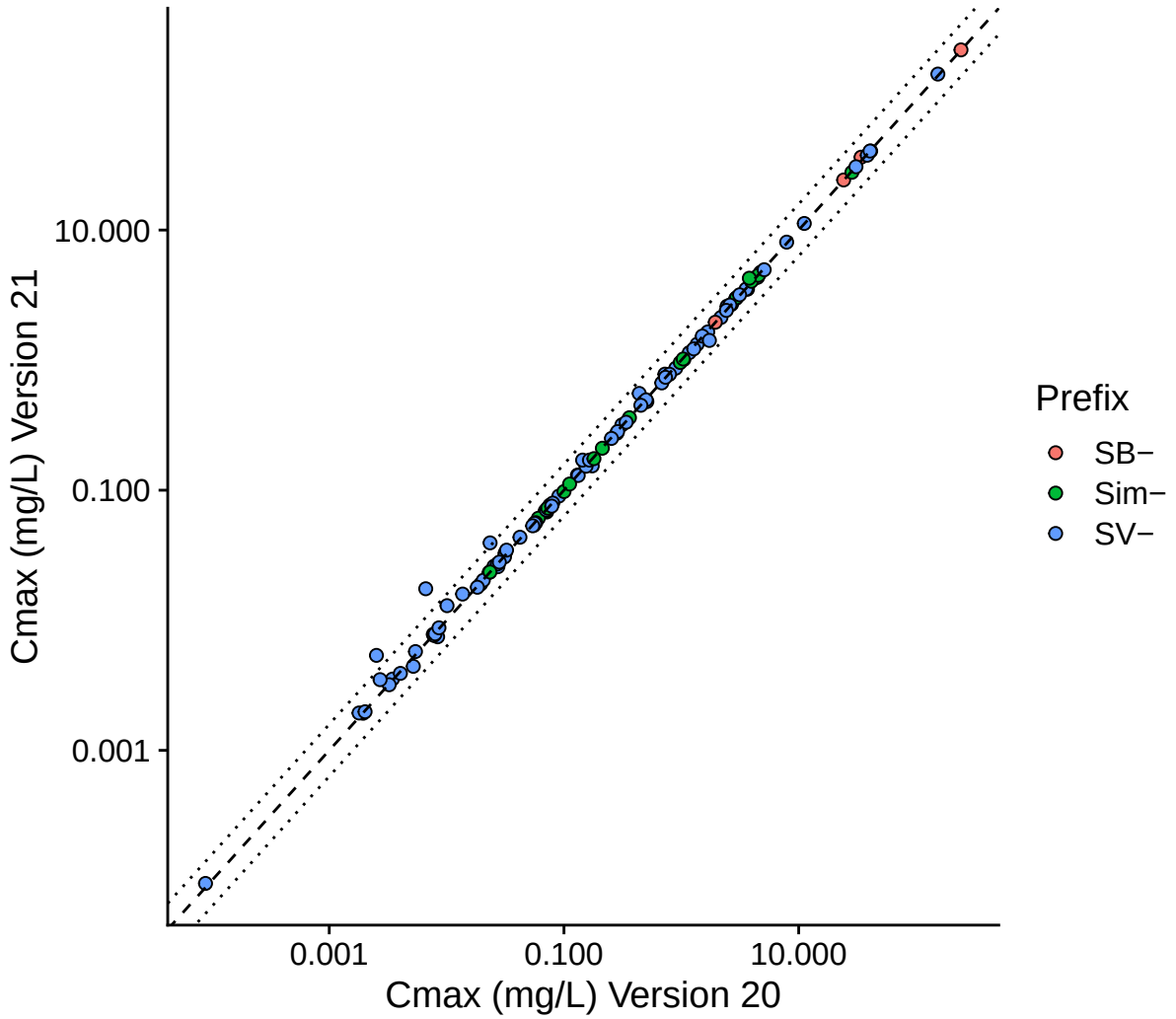

Figure 2. Mean simulated Cmax (mg/L) for the Sim- (green), SV-(blue) and SB-(red) compound files using the Simcyp Simulator Version 20 release 1 or Version 21 release 1.

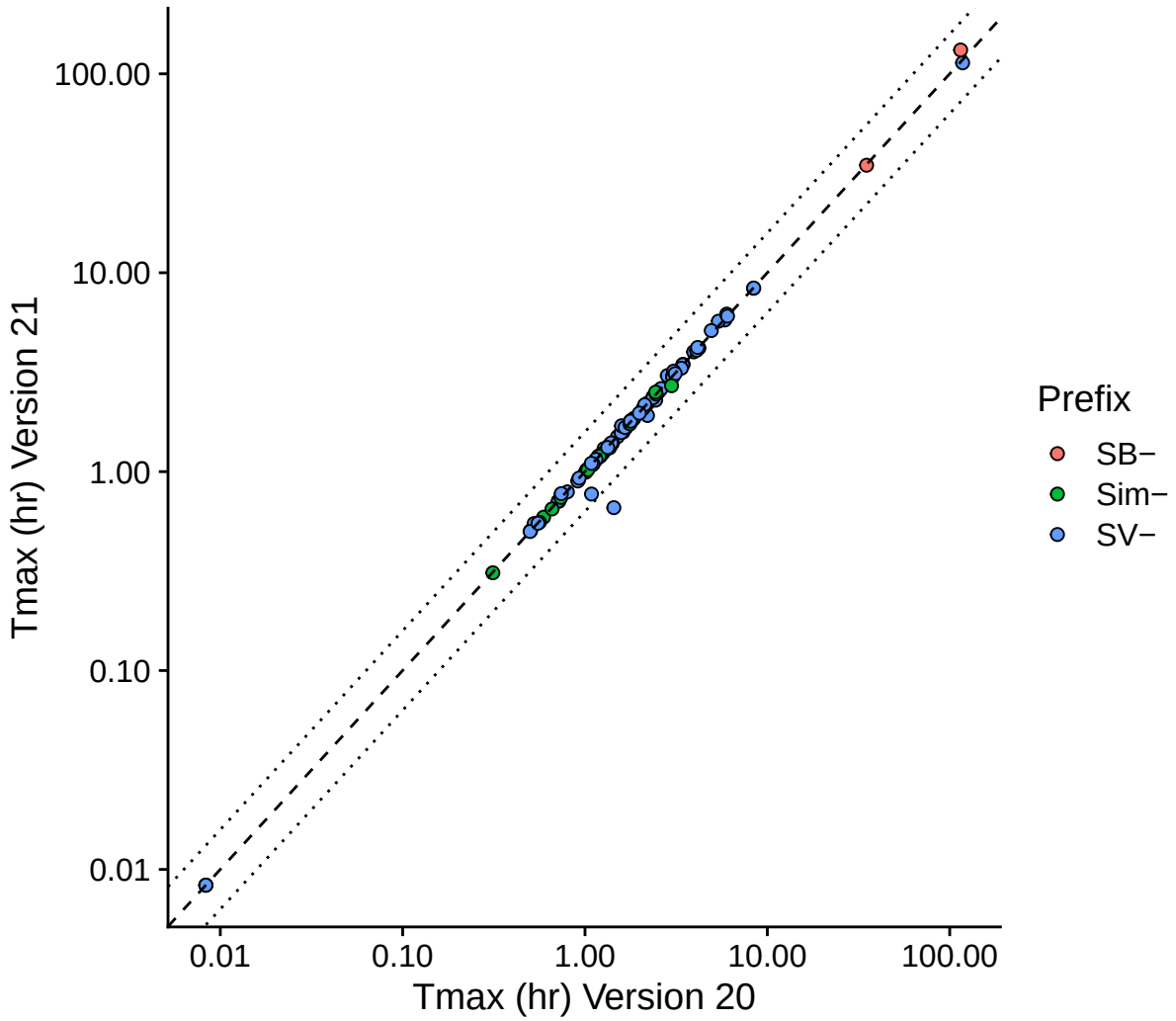

Figure 3. Mean simulated Tmax (hr) for the Sim- (green), SV-(blue) and SB-(red) compound files using the Simcyp Simulator Version 20 release 1 or Version 21 release 1.

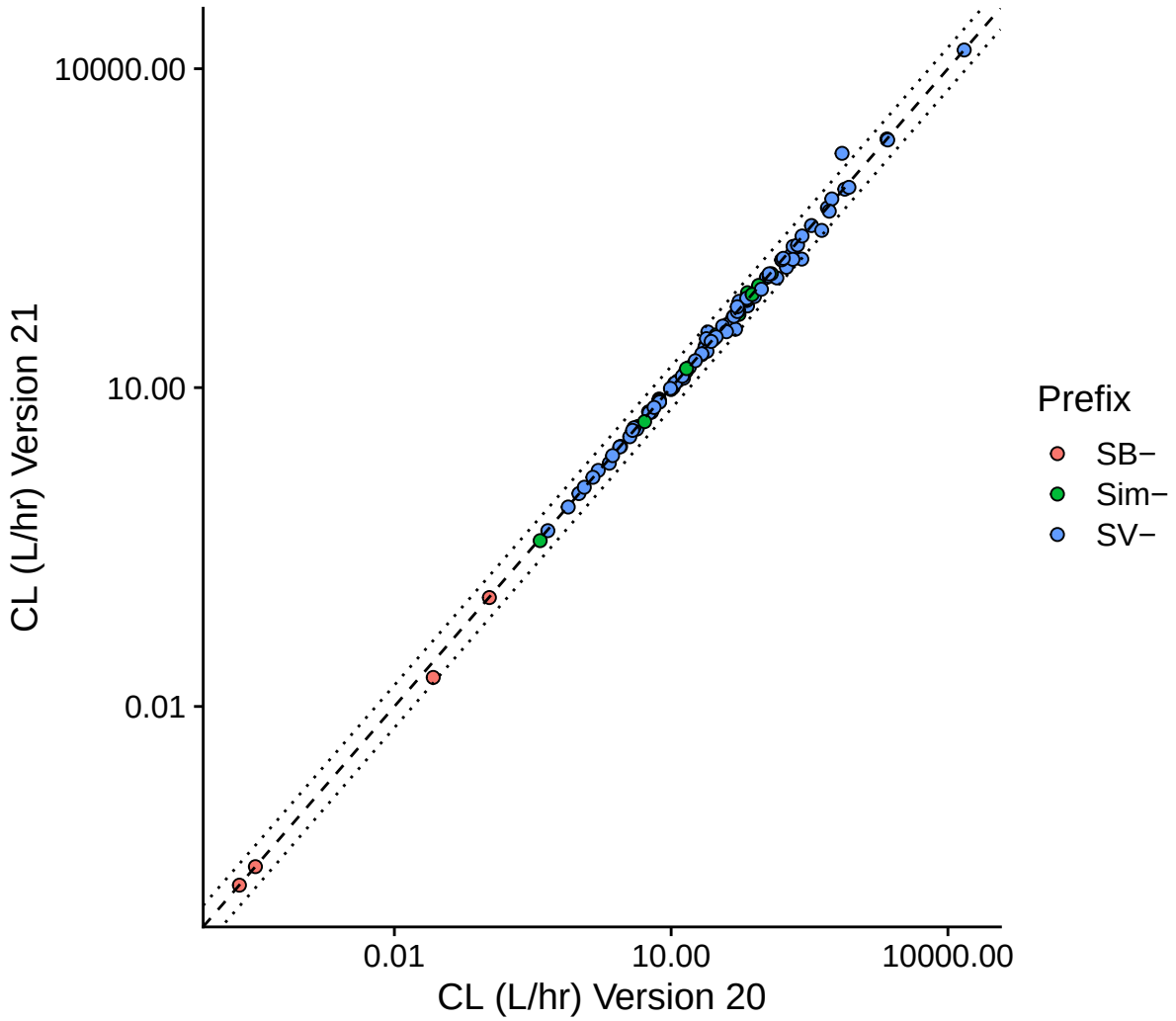

Figure 4. Mean simulated CL (L/hr) for the Sim- (green), SV-(blue) and SB-(red) compound files using the Simcyp Simulator Version 20 release 1 or Version 21 release 1.

Diagnostic plots - Static simulations

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

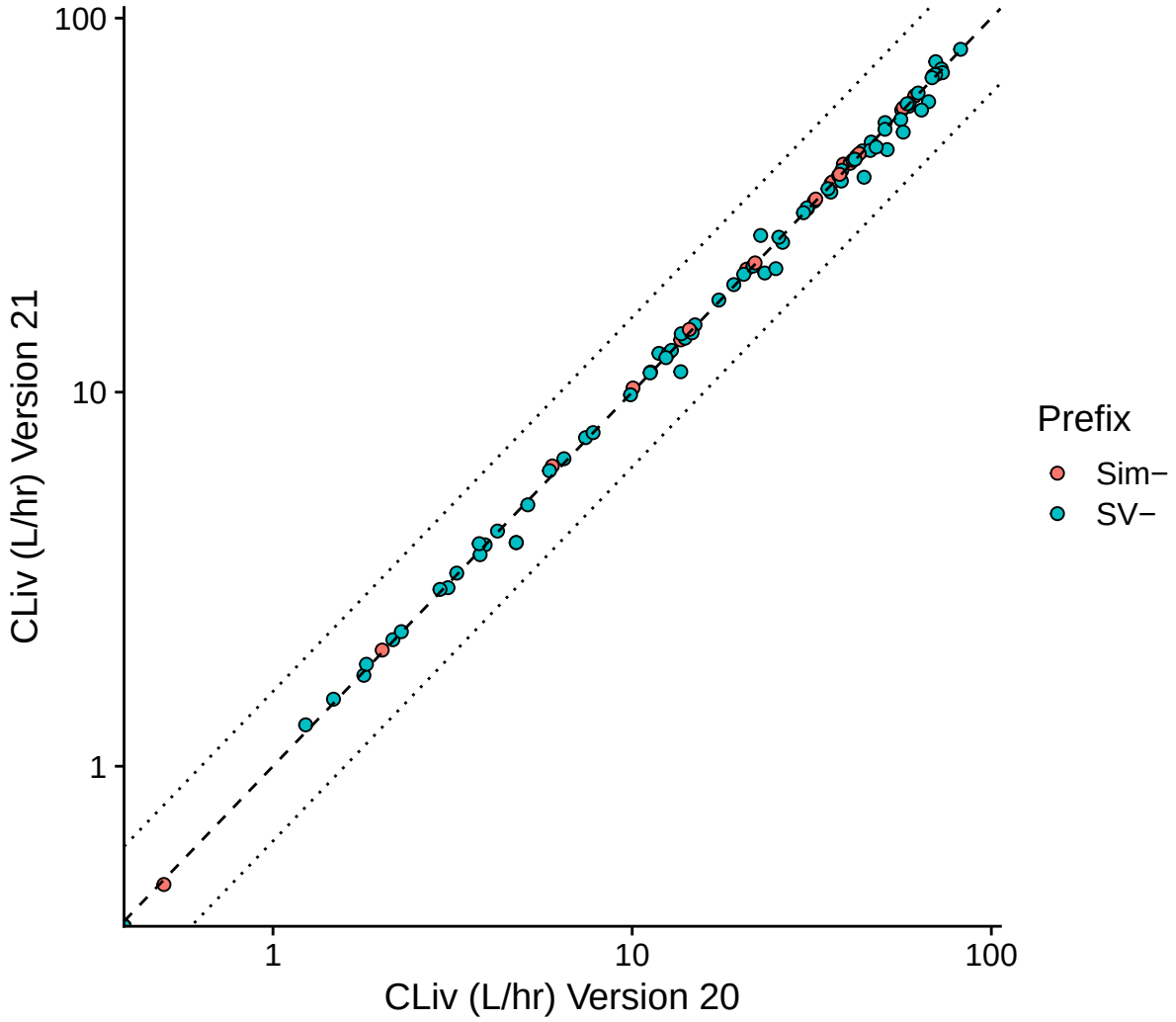

Figure 5. Mean simulated CLiv (L/hr) for the Sim-(red) and SV-(blue) compound files using the Simcyp Simulator Version 20 release 1 or Version 21 release 1.

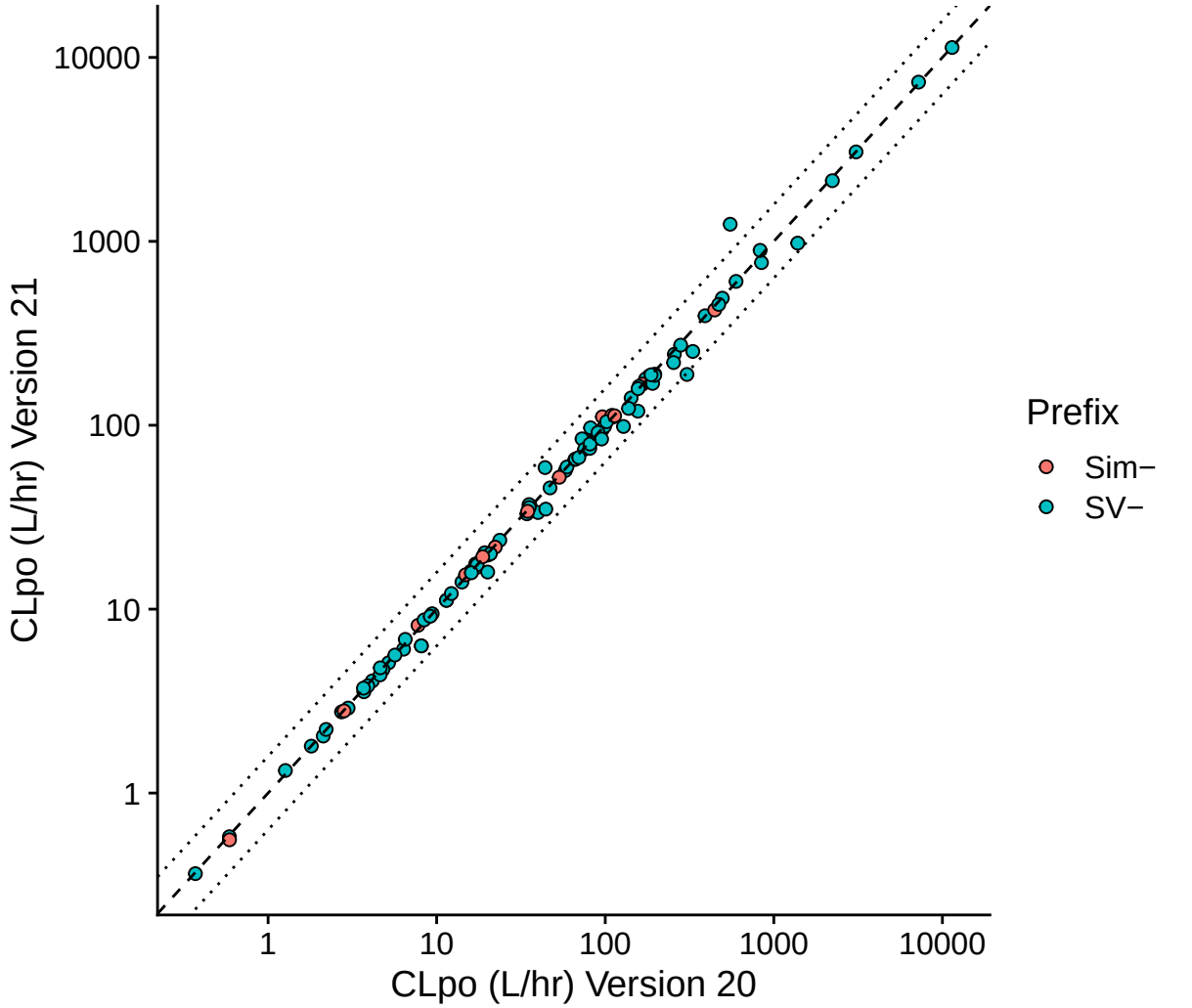

Figure 6. Mean simulated CLpo (L/hr) for the Sim-(red) and SV-(blue) compound files using the Simcyp Simulator Version 20 release 1 or Version 21 release 1.

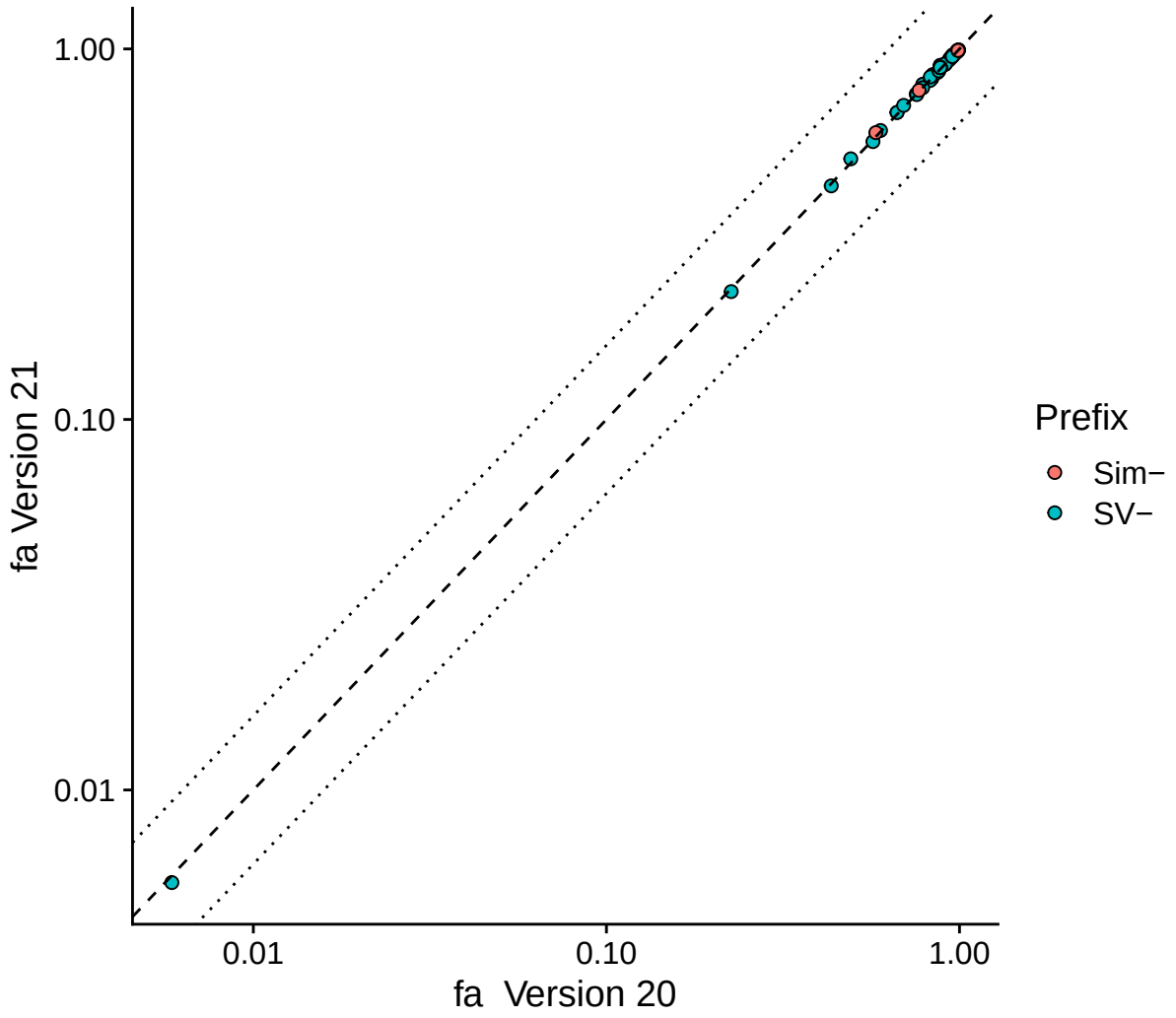

Figure 7. Mean simulated fa for the Sim-(red) and SV-(blue) compound files using the Simcyp Simulator Version 20 release 1 or Version 21 release 1.

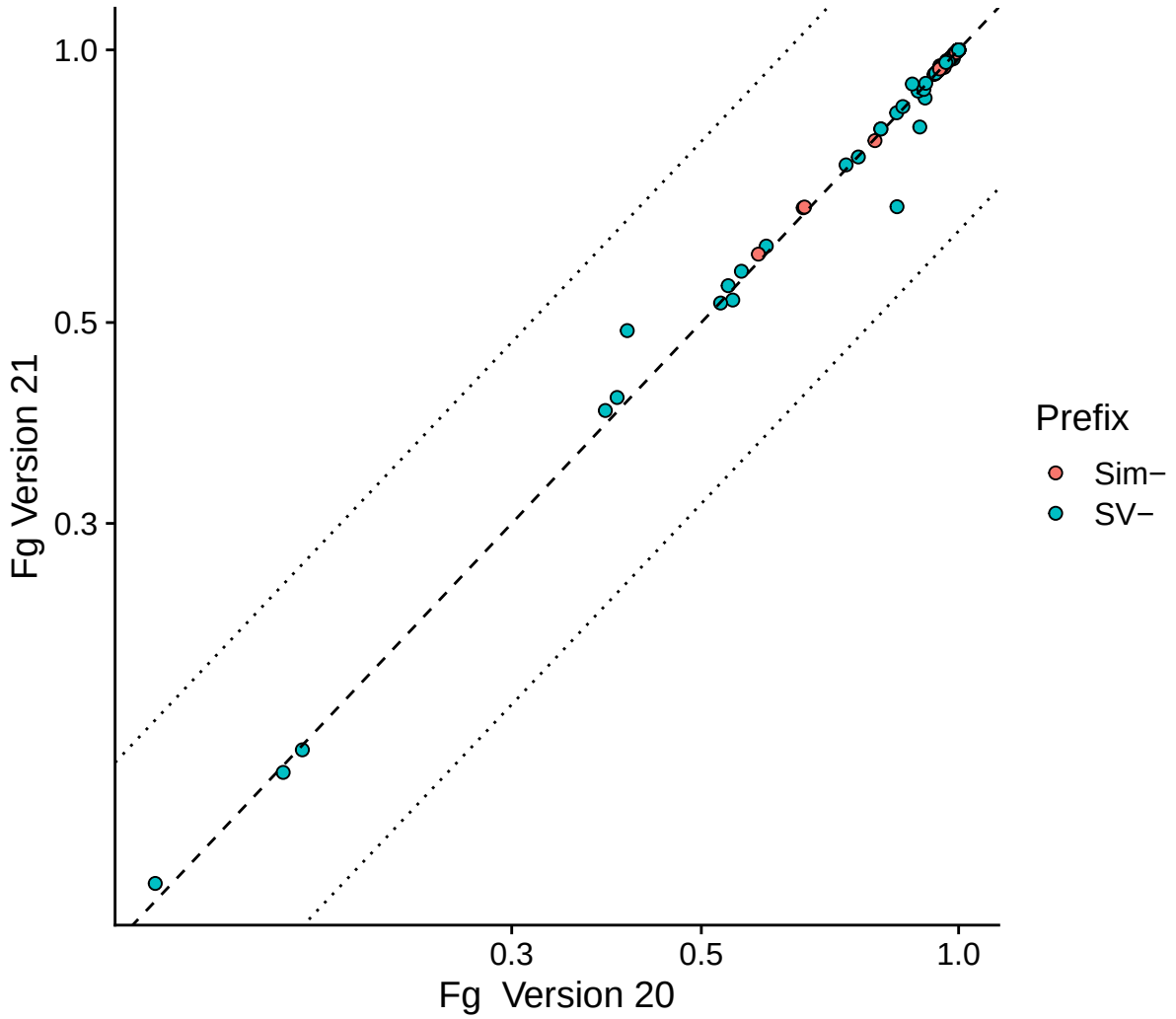

Figure 8. Mean simulated F_g for the Sim-(red) and SV-(blue) compound files using the Simcyp Simulator Version 20 release 1 or Version 21 release 1.

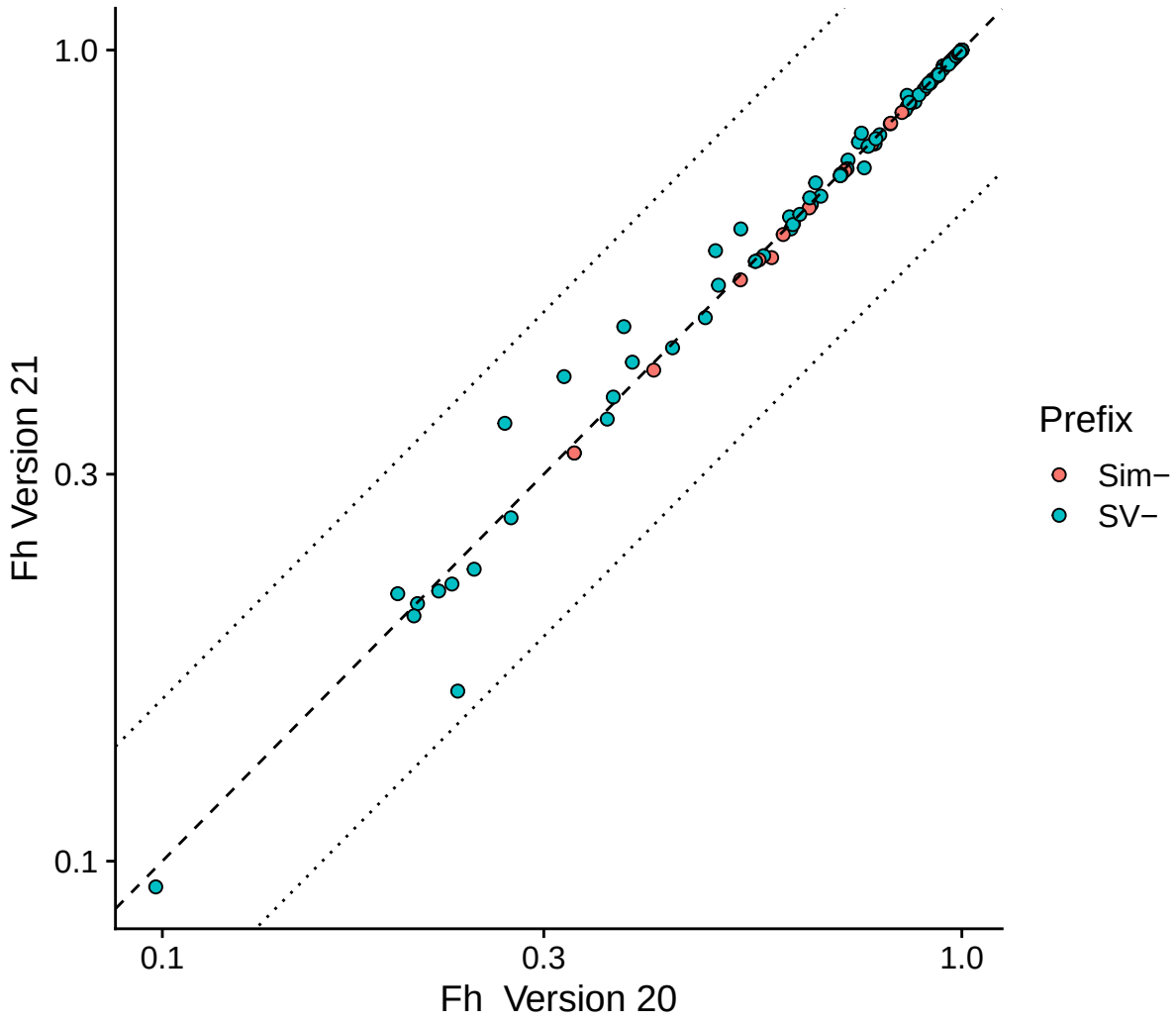

Figure 9. Mean simulated F_H for the Sim-(red) and SV-(blue) compound files using the Simcyp Simulator Version 20 release 1 or Version 21 release 1.

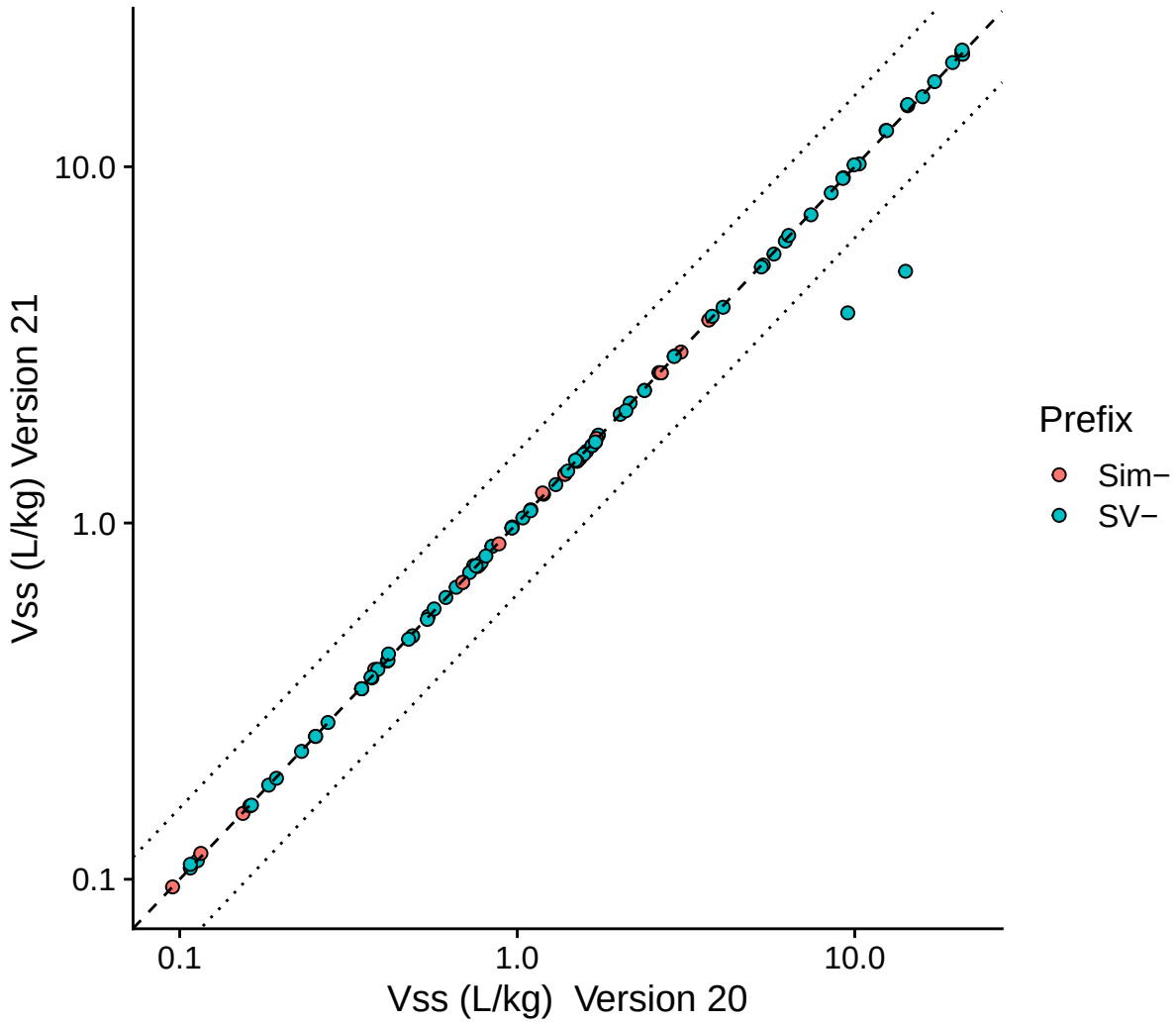

Figure 10. Mean simulated V_{ss} (L/kg) for the Sim-(red) and SV-(blue) compound files using the Simcyp Simulator Version 20 release 1 or Version 21 release 1.

Deviations

The table below shows the relative difference in pharmacokinetic parameters for the SV and Sim Compound files when they are run in V20 and V21. Results are presented as a percentage with 100% meaning no difference in the results for that compound between V20 and V21.

	PKPD Parameters						PKPD Profiles			
Name	**CLiv**	**CLpo**	**Fa**	**Fg**	**Fh**	**Vss**	**Cmax**	**Tmax**	**AUC**	**Dose/AUC**
Alfentanil	101	100	100	102	99	99	103	99	100	101
Alprazolam	101	98	101	100	100	99	101	99	96	99
Atazanavir	101	102	100	100	99	99	98	100	96	102
Atomoxetine	115	134	101	97	95	102	88	97	92	134
Atomoxetine-PM	100	98	101	100	100	102	97	100	98	99
Atorvastatin	101	95	102	104	99	99	102	99	101	97

(continued)

Name	CLiv	CLpo	Fa	Fg	Fh	Vss	Cmax	Tmax	AUC	Dose/AUC
Bufuralol	105	116	101	99	96	99	95	98	96	116
Bufuralol-PM	101	98	101	100	100	99	100	98	91	98
Bupropion-SR	99	86	101	99	102	99	100	100	100	87
Caffeine	106	105	101	100	100	103	96	100	97	105
Carbamazepine	101	97	102	100	100	99	100	99	96	97
Carbamazepine epoxide	NaN	98	102	100	100	99	102	99	102	98
Celecoxib	96	98	100	100	102	99	108	100	108	96
Cimetidine	101	100	102	100	100	100	98	99	98	98
Cinacalcet	101	101	100	100	97	102	94	101	95	101
Ciproflxacin	104	116	100	100	98	101	100	99	99	115
Clarithromycin	101	98	101	101	99	101	97	100	95	98
Clozapine	102	102	101	100	99	99	101	99	97	102
Crizotinib	101	103	99	100	99	100	98	99	93	101
Cyclosporine-Neoral	101	97	101	102	99	99	98	99	93	97
Cyclosporine-M1	98	96	101	100	100	99	100	100	97	95
Cyclosporine-M17	98	96	101	100	100	99	100	100	96	96
Dabigatran Etexilate	100	102	99	99	100	99	99	99	96	100
Dabigatran	99	97	101	100	100	100	99	100	101	98
Desipramine	85	77	101	101	114	99	116	106	146	77
Desipramine-PM	102	100	101	100	100	99	100	99	99	98
Desmethyl diltiazem	101	99	101	100	99	100	97	100	96	99
Dexamethasone	101	100	100	100	100	99	98	99	94	100
Dextromethorphan	109	225	101	91	69	103	85	46	45	225
Dextromethorphan-PM	107	103	101	100	99	104	168	87	63	106
Dextrorphan	101	99	101	100	97	41	213	71	95	99
Digoxin	101	101	100	100	100	99	99	100	97	102
Diltiazem	101	100	100	100	98	99	98	100	95	100
Efavirenz-MD	83	78	101	100	101	99	101	97	99	91
Efavirenz-SD	83	78	101	100	101	99	106	100	102	90
Erythromycin	101	99	101	101	100	102	97	100	98	99
Erythromycin-EC	101	98	101	101	99	100	97	100	96	98
Esomeprazole	96	92	100	100	102	100	102	101	102	92
Esomperazole-PM	101	100	100	100	100	100	98	100	98	101
Ethinylestradiol	101	105	100	97	100	99	107	98	94	105
Fluconazole	105	105	100	100	100	100	99	99	99	103
Fluoxetine	83	79	101	100	103	99	103	103	107	90
Fluvoxamine	89	84	101	100	104	102	101	104	108	87
Gemfibrozil-glucuronide	101	99	101	100	100	100	99	100	100	100
Gemfibrozil	102	104	100	99	100	99	98	98	94	102
3-HydroxyMorphinan	100	91	101	100	95	101	89	99	87	91
Ibrutinib	100	100	100	104	95	102	97	100	96	100
Imipramine	96	88	100	100	106	101	104	102	108	88
Itraconazole-fasted solution	101	97	101	100	97	99	101	99	93	95
Itraconazole-fed capsule	101	95	103	100	97	99	100	99	94	90
Ketoconazole 200mg BD	NaN	98	101	100	100	99	102	100	102	98
Ketoconazole 200mg QD	NaN	98	101	100	100	99	102	100	102	98
Ketoconazole 400mg QD	NaN	98	101	100	100	99	102	100	102	98
Lansoprazole	100	96	100	100	100	100	96	99	67	97

(continued)

Name	CLiv	CLpo	Fa	Fg	Fh	Vss	Cmax	Tmax	AUC	Dose/AUC
Lorazepam	103	104	100	100	100	99	99	101	97	104
S-Mephenytoin	87	62	101	104	121	99	127	104	140	62
S-Mephenytoin-PM	103	100	101	100	100	99	101	100	100	100
Metformin	101	99	101	100	99	101	98	99	98	99
3-Methoxymorphinan	85	79	101	100	105	36	263	94	153	71
Metoprolol	87	76	101	101	115	101	118	107	145	76
Metoprolol-PM	100	98	101	100	100	101	98	100	100	98
Midazolam	101	96	101	102	99	99	100	98	95	97
Mirabegron	101	103	100	100	99	101	99	100	97	101
Nebivolol	98	108	100	99	108	101	108	103	118	108
Nebivolol-PM	101	101	100	100	100	101	98	100	78	120
Nifedipine	101	100	100	102	99	99	99	99	95	100
Norfluoxetine	98	95	101	100	100	101	98	100	98	96
Norverapamil	102	99	101	101	98	101	99	99	94	100
Hydroxybupropion	97	95	101	100	100	99	101	100	97	96
Hydroxyitraconazole	101	97	101	100	99	99	98	98	93	98
3-Hydroxyquinidine	NaN	98	101	100	100	101	100	101	101	98
Ompeprazole	96	90	100	100	103	99	103	101	101	90
Omeprazole-PM	100	100	100	100	100	99	100	99	97	100
Ondansetron	100	96	102	100	100	100	100	100	99	99
Paroxetine	89	71	100	120	129	102	128	107	152	70
Phenacetin	101	103	101	100	99	99	99	99	97	103
Phenobarbital	NaN	98	100	100	100	99	102	100	102	98
Phenytoin	102	98	102	100	100	101	98	100	98	99
Pravastatin	100	100	100	100	100	100	99	99	99	102
Probenecid	101	101	100	100	100	100	99	99	95	101
Quinidine	101	98	101	100	100	101	98	100	96	98
Raltegravir	96	118	100	79	102	101	82	102	82	119
Repaglinide	105	105	100	100	99	99	97	99	94	105
Rifabutin	100	103	101	98	100	99	99	100	98	102
Rifampicin-MD	99	99	100	100	100	103	101	101	101	100
Rifampicin-SD	101	101	100	100	100	100	100	100	102	100
Ritonavir-ADAM	101	101	100	100	99	98	94	98	93	111
Ritonavir-FO	101	95	103	100	99	98	99	105	99	84
Rosiglitazone	105	105	100	100	100	100	98	98	95	106
Rosuvastatin	101	101	98	100	100	100	106	100	107	88
Sildenafil	101	99	100	102	99	102	97	100	95	99
Simvastatin	101	96	101	105	97	101	99	100	97	96
Sulphaphenazole	NaN	98	101	100	100	99	103	100	101	98
Theophylline	105	104	101	100	100	99	101	99	98	104
Ticlopidine	102	96	100	100	93	98	100	99	92	94
Tolbutamide	103	100	101	100	100	102	98	102	102	101
Tolterodine	89	76	101	100	124	99	129	105	155	77
Tolterodine-PM	98	96	101	100	100	99	102	100	103	97
Triazolam	101	97	101	101	100	100	98	100	94	98
Trimethoprim	NaN	100	100	100	100	101	100	98	101	100
Valsartan	101	99	101	100	100	100	112	91	105	93

(continued)

Name	CLiv	CLpo	Fa	Fg	Fh	Vss	Cmax	Tmax	AUC	Dose/AUC
Verapamil	101	101	100	102	97	99	96	99	95	102
S-Warfarin	97	94	101	100	100	102	98	103	109	96
Zidovudine-glucuronide	100	99	96	100	100	100	100	100	100	100
Zidovudine	101	101	101	100	98	100	96	100	95	100
Zolpidem	102	103	100	100	100	99	100	99	96	103
5-Hydroxymethyltolerodine	95	88	101	100	105	99	107	102	110	88

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

Discussion

During the V21 development cycle the phenotype frequencies and abundancies have been updated for CYP2A6, 2B6, 2C9, 2C19 and 2D6. The abundance values for CYP2C18 (liver), 2J2 (liver and intestine) and UGT1A1 (liver, intestine and kidney) have been updated. The genotypes frequency and abundance have been updated for CYP2C9 and added for CYP2B6.

As a consequence of these changes several library files were updated during the V21 development cycle. These include atomoxetine, bufuralol, efavirenz, fluvoxamine, bupropion, nebivolol and S-mephenytoin. The compound files for dextromethorphan and its metabolites have been extensively revised. The dextromethorphan compound file has been modified to use the peripheral sampling site option. Some performance verification for the revised dextromethorphan file are included below. In addition to the changes noted above a P-gp Ki value has been added to the Itraconazole library file and the Trimethoprim interaction parameters have been revised. There are some differences in the Lansoprazole AUC between V20 and V21 but the performance of the file is acceptable in v21 if the simulated subjects are matched to the phenotypes of the clinical study that is being simulated. Due to the changes in UGT1A1 abundance in the V21 populations there are some differences in the simulated pharmacokinetics for Raltegravir between V20 and V21 but the overall performance of the Raltegravir file when compared to clinical data is satisfactory. Although the first order ritonavir file shows a 16% difference in mean Dose/AUC this is the result of big differences in Dose/AUC for a few subjects as there is minimal difference in the AUC between versions and the geometric mean Dose/AUC varies by 6% between versions. The paroxetine file shows differences due to the changes in CYP2D6 phenotypes in V21 but when the trial design in V21 is matched to the phenotype frequency of the subjects in the clinical trial there is good agreement between the simulated and observed concentration time profiles (Figure 13).

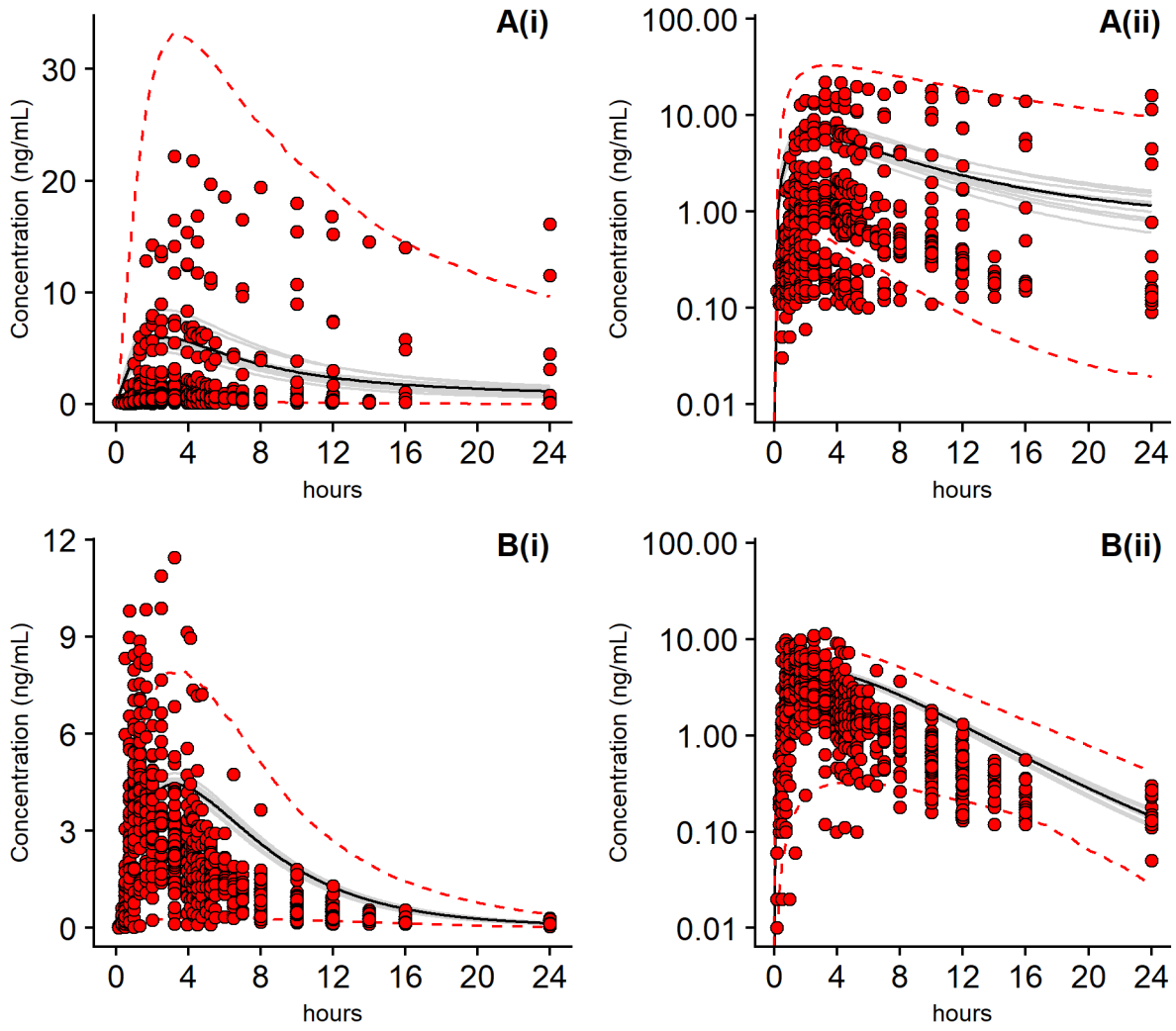

Figure 11: Simulated (black line) and observed (data points) individual plasma concentration-time profiles of **SV-Dextromethorphan** (Ai) and **SV-Dextrorphan** (Bi) after a single oral dose of **30** mg dextromethorphan hydrobromide (HBr) and a virtual population of 10 trials of 36 male subjects (18-49 yrs). Observed data for individual subjects were provided by the authors of the publication from Abduljalil et al. (2010). The grey lines represent the predictions from individual trials. Figure Aii and Bii show the data plotted with the y-axis on a log scale. Dashed lines represent the 5^{th} and 95^{th} percentiles of the total virtual population.This simulation was performed in V21 of the simulator using the V21 population and substrate files.

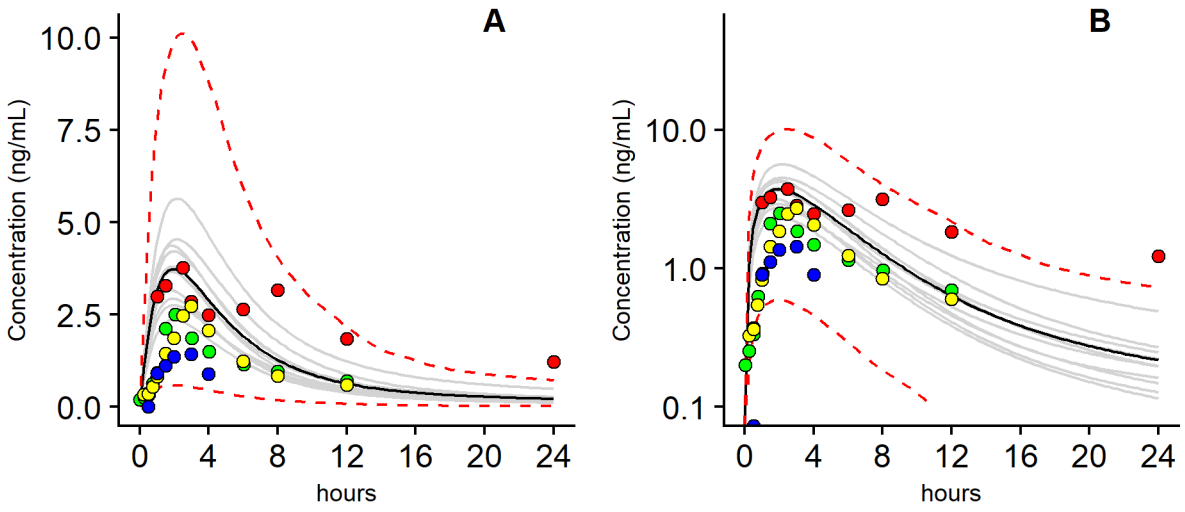

Figure 12: Simulated (black line) and observed (data points) mean plasma concentration-time profiles of **SV-Dextromethorphan** after an oral dose of **30** mg dextromethoprhan hydrobromide (HBr) in CYP2D6 extensive metabolisers (A). Simulations were conducted using a virtual population of 10 trials of 10 subjects, 20-50 yrs, 50% females (with EM, IM1 and UM subjects). Observed data were extracted from Capon et al. (1996) (red circles), Gorski et al. (2004) (green circles), Sager et al. (2014) (yellow circles) and Chen et al. (1990) (blue circles, one subject). The grey lines represent the predictions from individual trials. Figure B show the data plotted with the y-axis on a log scale. Dashed lines represent the 5^{th} and 95^{th} percentiles of the total virtual population.This simulation was performed in V21 of the simulator using the V21 population and substrate files.

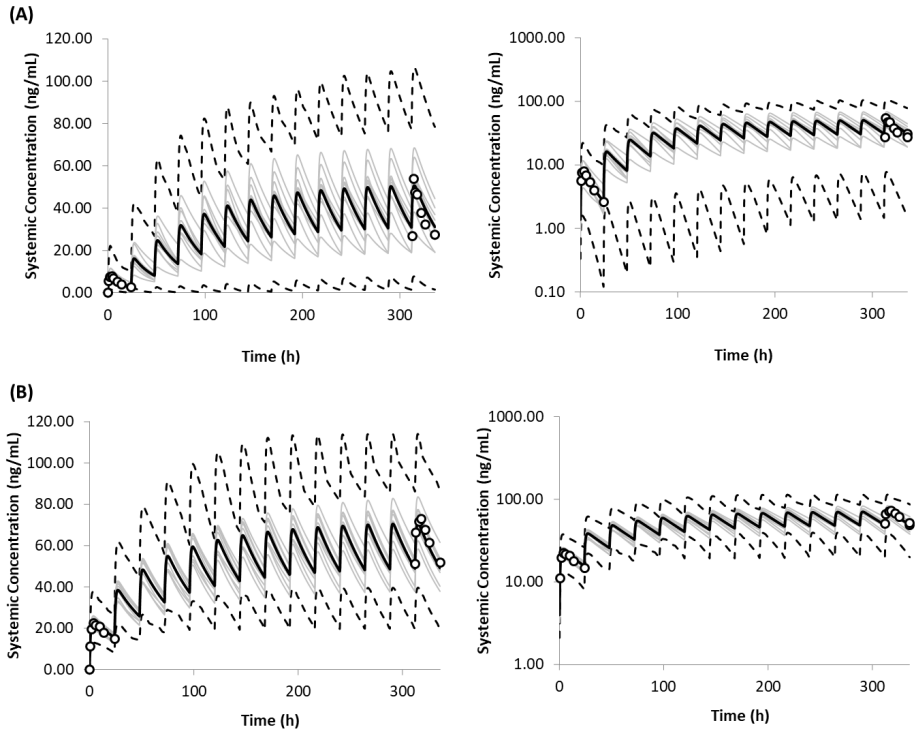

Figure 13: Simulated (black line) and observed (data points, Sindrup et al. (1992) mean plasma concentration-

time profile of SV-Paroxetine after oral dose of 30mg every 24 hours for 14 days (14 doses) in (A) CYP2D6 EMs and (B) CYP2D6 PMs. The grey lines represent the predictions from individual trials (10 trials x 9 male healthy volunteers (EMs), 20 – 30 years; and 10 trials x 8 male HVs (PMs), 23 - 39 years). Dashed lines represent the 5^{th} and 95^{th} percentile of the total virtual population. The right hand panel shows a semi-log plot of the data.This simulation was performed in V21 of the simulator using the V21 population and substrate files.

New compounds for V21

During the development of V21 of the Simcyp simulator new compound files were developed for Atezolizumab (SB), Buprenorphine (SV), Drospirenone (SV), Flurbiprofen (SV), Montelukast (SV), Siponimod (SV) and Pioglitazone (SV). In addition, research (RES-) files have been developed for Glibenclamide (Glyburide), Tenofovir, Rivaroxaban, Clopidogrel and its acyl glucuronide metabolite, Dasabuvir, Levonogestrel, Maraviroc, Atenolol and Prasugrel and its two metabolites (R-95913, R-138727) and will be made available for download from the Members area.

References

Abduljalil, Khaled, Dorothee Frank, Andrea Gaedigk, Tobias Klaassen, Dorota Tomalik-Scharte, Alexander Jetter, Ulrich Jaehde, Julia Kirchheiner, and Uwe Fuhr (2010). "Assessment of activity levels for CYP2D6* 1, CYP2D6* 2, and CYP2D6* 41 genes by population pharmacokinetics of dextromethorphan". In: *Clinical Pharmacology and Therapeutics* 88.5, pp. 643–651. ISSN: 0009-9236.

Capon, Deborah A, Felix Bochner, Nicole Kerry, Gerd Mikus, Catherine Danz, and Andrew A Somogyi (1996). "The influence of CYP2D6 polymorphism and quinidine on the disposition and antitussive effect of dextromethorphan in humans". In: *Clinical Pharmacology and Therapeutics* 60.3, pp. 295–307. ISSN: 0009-9236.

Chen, ZR, AA Somogyi, and F Bochner (1990). "Simultaneous determination of dextromethorphan and three metabolites in plasma and urine using high-performance liquid chromatography with application to their disposition in man". In: *Therapeutic drug monitoring* 12.1, pp. 97–104. ISSN: 0163-4356.

Gorski, J Christopher, Shiew-Mei Huang, Amar Pinto, Mitchell A Hamman, Janna K Hilligoss, Narjis A Zaheer, Mehul Desai, Margaret Miller, and Stephen D Hall (2004). "The effect of echinacea (Echinacea purpurea root) on cytochrome P450 activity in vivo". In: *Clinical Pharmacology and Therapeutics* 75.1, pp. 89–100. ISSN: 0009-9236.

Sager, Jennifer E, Justin D Lutz, Robert S Foti, Connie Davis, Kent L Kunze, and Nina Isoherranen (2014). "Fluoxetine-and Norfluoxetine-Mediated Complex Drug–Drug Interactions: In Vitro to In Vivo Correlation of Effects on CYP2D6, CYP2C19, and CYP3A4". In: *Clinical Pharmacology and Therapeutics* 95.6, pp. 653–662. ISSN: 0009-9236.

Sindrup, S. H., K. Brosen, L. F. Gram, J. Hallas, E. Skjelbo, A. Allen, G. D. Allen, S. M. Cooper, G. Mellows, T. C. Tasker, and et al. (1992). "The relationship between paroxetine and the sparteine oxidation polymorphism". In: *Clin Pharmacol Ther* 51.3, pp. 278–87. ISSN: 0009-9236 (Print) 0009-9236 (Linking). DOI: 10.1038/clpt.1992.23. URL: https://www.ncbi.nlm.nih.gov/pubmed/1531950.