Population Name:	NEurCaucasian
Prefix:	Sim
Simcyp Version this document relates to:	Version 19 Release 1
File data last updated:	Version 19 Release 1: Addition of FMO IVIVE Scaling Inclusion of the CYP2C19 and CYP2D6 UM Phenotype Update to hepatic transporter abundances (OATP1B1, OCT1, BCRP) Expansion of the ADAM model to account for salts, the addition of mechanistic surface pH calculations, and precipitation of Substrate Primary Metabolite 1

Prepared: May 2025

The **Sim-NEurCaucasian** population is the baseline Simcyp population from which other populations in Simcyp are derived.

The document contains:

1. All parameters relating to this population
2. Performance verification of key population parameters against observed data
3. References illustrating performance verification of this population
4. References to the key parameters
5. Population Lua scripts

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1. Key input parameters relating to this population

Population Characteristics	Parameter	Value	Source
		DEMOGRAPHIC	
Age (years)	Maximum Minimum	95 18	Office for National Statistics in England and Wales, 2002-2010.
Gender	Proportion of females	0.5	
Age Distribution	< 65 years Prop Males < 65 y Prop Females < 65 y > 65 years Male distribution parameter: α Male distribution parameter: β Female distribution parameter: α Female distribution parameter: β	Uniform 0.82 0.784 Weibull 5.47 66.5 5.22 68.57	In-house analysis based on data from Office for National Statistics in England and Wales, 2002-2010.
Height (cm)	Male: height vs age (intercept) Male: height vs age (slope 1) Male: height vs age (slope 2) Male: height vs age (CV %) Female: height vs age (intercept) Female: height vs age (slope 1) Female: height vs age (slope 2) Female: height vs age (CV %)	176.87 0.0743 -0.0021 3.95 161.39 0.1498 -0.0027 4.09	In-house analysis based on Health Survey for England 2008-2009.
Weight (kg)	Male: weight vs height (intercept) Male: weight vs height (slope 1) Male: weight vs height (CV %) Female: weight vs height (intercept) Female: weight vs height (slope 1) Female: weight vs height (CV %)	2.7208 0.0097 16.7 2.936 0.008 19.9	In-house analysis based on Health Survey for England 1998
Body surface area (BSA)	Height exponent Weight exponent C1 parameter	0.725 0.425 0.007184	(Du Bois and Du Bois, 1916)
CYP Phenotype Frequencies	 CYP1A2 CYP2A6 CYP2B6 CYP2C8 CYP2C9 CYP2C18 CYP2C19 CYP2D6 CYP2E1 CYP2J2 CYP3A4 CYP3A5 CYP3A7	**EM/PM/IM/UM** 1/0/0/0 1/0 /0/0 0.89/0.11/0/0 1/0/0/0 0.94/0.06/0/0 1/0/0/0 0.59/0.092/0/0.318 0.865/0.082/0/0.053 1/0/0/0 1/0/0/0 1/0/0/0 0.17/0.83/0/0 0.12/0.88/0/0	In-house meta-analysis based on published data including (Crettol et al., 2005); (Tamminga et al., 1999); Lin *et al.,* 2002 & (Burk et al., 2002).

CYP Genotype Frequencies	CYP2C9 *1/*1	0.672	In-house meta-analysis based on published data including (Yasar et al., 2002).
	CYP2C9 *1/*2	0.186	
	CYP2C9 *1/*3	0.111	
	CYP2C9 *2/*2	0.011	
	CYP2C9 *2/*3	0.017	
	CYP2C9 *3/*3	0.003	
		EM/PM/IM/UM	
UGT Phenotype Frequencies	UGT1A1	0.44/0.11/0.44/0.01	
	UGT1A3	1/0/0/0	In-house meta-analysis based on published data including (Danoff et al., 2004); (Cecchin et al., 2009); (Spierings et al., 2007) & (Swanson et al., 2007).
	UGT1A4	1/0/0/0	
	UGT1A5	1/0/0/0	
	UGT1A6	1/0/0/0	
	UGT1A7	1/0/0/0	
	UGT1A8	1/0/0/0	
	UGT1A9	0.96/0.04/0/0	
	UGT1A10	1/0/0/0	
	UGT2B4	1/0/0/0	
	UGT2B7	1/0/0/0	
	UGT2B10	1/0/0/0	
	UGT2B11	1/0/0/0	
	UGT2B15	0.21/0.28/0.51/0	
	UGT2B17	0.55/0.09/0.36/0	
	UGT2B28	1/0/0/0	
	UserUGT	1/0/0/0	
Cytosolic Phenotype Freq	User Cyt1	1/0/0/0	Default
	User Cyt2	1/0/0/0	
	User Cyt3	1/0/0/0	
	User Cyt4	1/0/0/0	
		ET/PT/IT/UT	
Transporter Phenotype Freq ATP Binding Cassette Transporters	ABCB1 (P-gp/MDR1)	1/0/0/0	
	ABCB11 (BSEP)	1/0/0/0	
	ABCC1 (MRP1)	1/0/0/0	
	ABCC2 (MRP2)	1/0/0/0	
	ABCC3 (MRP3)	1/0/0/0	
	ABCC4 (MRP4)	1/0/0/0	
	ABCC6 (MRP6)	1/0/0/0	
	ABCG2 (BCRP)	0.81/0.02/0.17/0	
		ET/PT/IT/UT	
Solute Carrier Transporters	SLC2A2 (GLUT2)	1/0/0/0	In-house meta-analysis based on published data including (Donnelly et al., 2011, Kobayashi et al., 2005).
	SLC7A5 (LAT1)	1/0/0/0	
	SLC29A1 (ENT1)	1/0/0/0	
	SLC29A2 (ENT2)	1/0/0/0	
	SLC10A1 (NTCP)	1/0/0/0	
	SLC10A1 (ASBT/IBAT)	1/0/0/0	
	SLC15A1 (PepT1)	1/0/0/0	
	SLC16A1 (MCT1)	1/0/0/0	
	SLCO1B1 (OATP1B1)	0.63/0.03/0.27/0.07	
	SLCO1B3 (OATP1B3)	1/0/0/0	
	SLCO2B1 (OATP2B1)	1/0/0/0	
	SLCO4C1 (OATP4C1)	1/0/0/0	

	SLC22A1 (OCT1) SLC22A2 (OCT2) SLC22A3 (OCT3) SLC22A4 (OCTN1) SLC22A6 (OAT1) SLC22A7 (OAT2) SLC22A8 (OAT3) SLC22A9 (OAT7) SLC47A1 (MATE1) Renal SLC47As (Renal MATEs) SLC51A/B (OST-α/β)	0.5404/0.0549/0.4043/0.0004 1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0	
User-defined Transporters	Sinusoidal uptake (Liver) Sinusoidal Efflux (Liver) Canalicular Efflux (Liver) Apical Uptake (Kidney) Basal Efflux (Kidney) Apical Uptake (Intestine) Apical Efflux (Intestine) Basal Influx (Intestine) Basal Efflux (Intestine) Uptake (Tumour) Efflux (Tumour)	1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0	Default
Esterase Phenotype Freq	CES1 CES2 User ES Plasma ES	**EM/PM/IM/UM** 0.999/0.001/0/0 1/0/0/0 1/0/0/0 1/0/0/0	In-house meta-analysis based on published data including (Tarkiainen et al., 2012).
FMO Phenotype Freq	FMO1 FMO3 FMO5 User FMO	1/0/0/0 1/0/0/0 1/0/0/0 1/0/0/0	Default
Gut Luminal Phenotype	Sub>Primary Metabolite 1 Enzyme Primary Metabolite 1>Sub Enzyme	1/0/0/0 1/0/0/0	Default
		LIVER	
Liver volume (L)	Mean BSA (m^2) coefficient BSA (m^2) exponent CV (%)	1.65056 0.722 1.176 12	(Johnson et al., 2005).
Liver density (g/L)	Mean	1080	(Heinemann et al., 1999).
Hepatocellularity (millions of cells/g)	HPGL mean (Older than 20) HPGL mean (Younger than 20) Baseline Age coefficient CV (%) (Older than 20) CV (%) (Younger than 20) P450/10^6 Cells	117.515 125 3.103 -0.655 41.9 20	(Barter et al., 2007).

	Baseline HPGL Coefficient	3.034 -0.506	
Microsomal Protein (mg/g)	MPPGL mean Baseline Age coefficient C1 Age coefficient C2 Age coefficient C3 CV (%)	39.7907 1.407 0.01579 -0.0003824 0.00000237 26.9	(Barter et al., 2008).
Cytosolic Protein (mg/g)	CPPGL mean Baseline Correlation coefficient CV (%)	81.0329 28.8945 1.31032 21.467	In-house meta-analysis based on Unpublished data generated as part of a PhD thesis.
S9 Protein (mg/g)	S9PPGL Mean User S9PPGL Mean CV (%)	120.824 95.0596 30	(Barter, 2006).
Enterohepatic Recirculation Original Model	% Hepatic Bile Entering Gallbladder Mean CV (%) Gallbladder Release Constant (1/h) Fasted Mean Fasted CV (%) Fed Mean Fed CV (%) IMMC Cycle Time (h) Mean IMMC Cycle Time (h) CV (%) Gallbladder Emptied at % of IMMC Gallbladder Residual Volume (%) Fasted Mean Fasted CV (%) Fed Mean Fed CV (%)	 70.3 32.1 0.18 30 0.48 19 1.55 55 30 79.4 13.1 59.9 39.6	(Shaffer et al., 1980) (Degen et al., 2006). (Schmidt et al., 1996). (Ellenbogen et al., 1988).
Advanced Dynamic Bile Salt Model (ADBSM) ADBSM IMMC Parameters	Duration of IMMC Cycle (h) Antral Origin Mean Antral Origin CV (%) Duodenal Origin Probability (%) Duodenal Origin Mean Duodenal Origin CV (%) Duodenal Origin Probability (%)	 2.6 30 60 1.3 60 40	In-house meta-analysis based on published data including (Luiking et al., 1998)
ADBSM Liver Parameters	Hepatic Total Bile Secretion Rate Fasted Mean (mmol/h) Fasted CV (%) Fed Mean (mmol/h) Fed CV (%) % Hepatic Bile Entering Gallbladder Mean CV (%) Bile Salt Weighted Mean MWt (g/mol)	 0.19 69 1.33 45 70.3 32 400	(van Berge Henegouwen and Hofmann, 1978). (Shaffer et al., 1980).

ADBSM Gallbladder Parameters	Gallbladder Residual Volume (%)		
	IMMC Antral Origin Fasted Mean	74	(Stolk et al., 1993).
	IMMC Antral Origin Fasted CV	10	
	IMMC Duodenal Origin Fasted Mean	80.7	
	IMMC Duodenal Origin Fasted CV	17	In-house meta-analysis based on published data including (Portincasa et al., 1994) & (Palasciano et al., 1992)
	Fed Mean	30.67	
	Fed CV	48	
	Maximal Gallbladder Volume		
	Mean (ml)	18.8	
	CV (%)	53	
	Duration of gallbladder emptying (h)		
	Fed Mean	1.17	
	Fed CV	37	
Bile Salts Absorption Passive	Absorption Rate (mmol/h/mM)		
	Jejunum I – II	0.42	(Krag and Phillips, 1974).
	CV (%)	14	
	Ileum I – IV	0	
	CV (%)	30	
	Colon	0.0565	(Mekhjian et al., 1979).
	CV (%)	30	
Active	Jmax (mmol/h)		
	Jejunum I – II	0	(Krag and Phillips, 1974).
	CV (%)	30	
	Ileum I – IV	2.48	
	CV (%)	20	
	Colon	0	
	CV (%)	30	
	Km (mM)		
	Jejunum I – II	0	
	CV (%)	30	
	Ileum I – IV	0.6	
	CV (%)	33	
	Colon	0	
	CV (%)	30	
Bile fraction available for absorption- Passive	Jejunum I	0.15	(Riethorst et al., 2016).
	Jejunum II	0.15	
	Ileum I	0	
	Ileum II	0	
	Ileum III	0	
	Ileum IV	0	
	Colon	1	
Active	Jejunum I	0	
	Jejunum II	0	
	Ileum I	0	
	Ileum II	0	
	Ileum III	0.05	
	Ileum IV	0.05	
	Colon	0	

Average Baseline Bile Salts Concentration: CMC (mM)	Stomach	1	
	Duodenum	1	
	Jejunum I	1	
	Jejunum II	1	
	Ileum I	1	
	Ileum II	1	
	Ileum III	1	
	Ileum IV	1	
	Colon	1	
Bile (mM)	Stomach	0.34	
	CV (%)	134	In-house meta-analysis based on published data including (Schindlbeck et al., 1987); (Perez de la Cruz Moreno et al., 2006) & (Diakidou et al., 2009)
	Duodenum	3.31	
	CV (%)	97	
	Jejunum I	2.3	
	CV (%)	100	
	Jejunum II	3.55	
	CV (%)	42	
	Ileum I	1.25	
	CV (%)	30	
	Ileum II	1.25	
	CV (%)	30	
	Ileum III	1.25	
	CV (%)	30	
	Ileum IV	1.25	
	CV (%)	30	
	Colon	0.12	
	CV (%)	103.56	
	Stomach Bile Salts Concentration Fed State (mM)	0.34	
	CV (%)	216.7	
CYP Phenotype Enzyme Abundances (pmol/mg protein)	CYP1A2 Mean EM (CV %)	52 (67)	
	CYP2A6 Mean EM (CV %)	20 (173)	In-house meta-analysis based on published data including (Rowland-Yeo et al., 2004); (Hofmann et al., 2008); (Haberl et al., 2005) & (Cubitt et al., 2011).
	CYP2B6 Mean EM (CV %)	17 (122)	
	CYP2B6 Mean PM (CV %)	6 (200)	
	CYP2C8 Mean EM (CV %)	24 (81)	
	CYP2C9 Mean EM (CV %)	73 (54)	
	CYP2C9 Mean PM (CV %)	29 (73)	
	CYP2C18 Mean EM (CV %)	1 (106)	
	CYP2C19 Mean EM (CV %)	4.4 (71)	
	CYP2C19 Mean UM (CV %)	8.7 (71)	
	CYP2D6 Mean EM (CV %)	9.4 (65)	
	CYP2D6 Mean UM (CV %)	18.8 (65)	
	CYP2E1 Mean EM (CV %)	61 (61)	
	CYP2J2 Mean EM (CV %)	1.2 (175)	
	CYP3A4 Mean EM (CV %)	137 (41)	
	CYP3A5 Mean EM (CV %)	103 (65)	
	CYP3A7 Mean EM (CV %)	35.4 (61)	
CYP3A4/CYP3A5 correlation	Baseline CYP3A5	62.775	
	Correlation coefficient	0.3934	(Barter et al., 2010)
	CYP3A5 CV (%)	24	

Difference in male/female CYP3A4 contents	Male Mean (CV %) Female Mean (CV%)	126 (35%) 183 (29%)	Default inactive
CYP Turnover rate constant (1/h)	CYP1A2 Mean (CV %) CYP2A6 Mean (CV %) CYP2B6 Mean (CV %) CYP2C8 Mean (CV %) CYP2C9 Mean (CV %) CYP2C18 Mean (CV %) CYP2C19 Mean (CV %) CYP2D6 Mean (CV %) CYP2E1 Mean (CV %) CYP2J2 Mean (CV %) CYP3A4 Mean (CV %) CYP3A5 Mean (CV %) CYP3A7 Mean (CV %)	0.0183 (56) 0.0267 (56) 0.0217 (56) 0.0301 (56) 0.0067 (56) 0.0267 (56) 0.0267 (56) 0.0099 (56) 0.0176 (63) 0.0194 (56) 0.0193 (68) 0.0193 (68) 0.019 (68)	(Yang et al., 2008)
CYP Genotype Abundance (pmol/mg protein)	CYP2C9 *1/*1 Mean (CV %) CYP2C9 *1/*2 Mean (CV %) CYP2C9 *1/*3 Mean (CV %) CYP2C9 *2/*2 Mean (CV %) CYP2C9 *2/*3 Mean (CV %) CYP2C9 *3/*3 Mean (CV %)	83.4 (60.5) 75.8 (63.8) 75.8 (63.8) 75.8 (63.8) 75.8 (63.8) 23 (60)	In-house meta-analysis based on published data including (Coller et al., 2002).
UGT Phenotype Absolute UGT Abundance (pmol/mg protein)	UGT1A1 EM Mean UGT1A3 EM Mean UGT1A4 EM Mean UGT1A5 EM Mean UGT1A6 EM Mean UGT1A7 EM Mean UGT1A8 EM Mean UGT1A9 EM Mean UGT1A10 EM Mean UGT2B4 EM Mean UGT2B7 EM Mean UGT2B10 EM Mean UGT2B11 EM Mean UGT2B15 EM Mean UGT2B17 EM Mean UGT2B28 EM Mean User UGT1 EM Mean	48 23 52 0 20 0 0 31 0.02 54 71 6.5 0 39 5.9 0 0	In-house meta-analysis based on published data including (Harbourt et al., 2012) and unpublished data from the Simcyp Consortium UGT focused group (2013).
Relative UGT Abundances	UGT1A1 EM Mean (CV %) UGT1A1 PM Mean (CV %) UGT1A1 IM Mean (CV %) UGT1A1 UM Mean (CV %) UGT1A3 EM Mean (CV %) UGT1A4 EM Mean (CV %) UGT1A5 EM Mean (CV %) UGT1A6 EM Mean (CV %) UGT1A7 EM Mean (CV %) UGT1A8 EM Mean (CV %) UGT1A9 EM Mean (CV %)	1 (24) 0.42 (50.8) 0.72 (39.9) 1.46 (30) 1 (36) 1(26) 1 (30) 1 (30) 1 (30) 1 (30) 1 (30)	In-house meta-analysis based on published data including (Peterkin et al., 2007); (Villeneuve et al., 2003) & (Swanson et al., 2007).

	UGT1A9 PM Mean (CV %) UGT1A9 IM Mean (CV %) UGT1A10 EM Mean (CV %) UGT2B4 EM Mean (CV %) UGT2B7 EM Mean (CV %) UGT2B10 EM Mean (CV %) UGT2B11 EM Mean (CV %) UGT2B15 EM Mean (CV %) UGT2B15 PM Mean (CV %) UGT2B15 IM Mean (CV %) UGT2B17 EM Mean (CV %) UGT2B17 PM Mean (CV %) UGT2B17 IM Mean (CV %) UGT2B28 EM Mean (CV %) User UGT1 EM Mean (CV %)	0.07 (30) 0.19 (30) 1 (30) 1 (28) 1 (30.4) 1 (30) 1 (30) 1 (34) 0.07 (33) 0.47 (37) 1 (28) 0.08 (40) 0.16 (30) 1 (30) 1 (30)	
UGT Turnover rate (1/h)	UGT1A1 Mean (CV %) UGT1A3 Mean (CV %) UGT1A4 Mean (CV %) UGT1A5 Mean (CV %) UGT1A6 Mean (CV %) UGT1A7 Mean (CV %) UGT1A8 Mean (CV %) UGT1A9 Mean (CV %) UGT1A10 Mean (CV %) UGT2B4 Mean (CV %) UGT2B7 Mean (CV %) UGT2B10 Mean (CV %) UGT2B11 Mean (CV %) UGT2B15 Mean (CV %) UGT2B17 Mean (CV %) UGT2B28 Mean (CV %) User UGT1 EM (CV%)	0.0578 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06	(Emi et al., 2002) & (Ohnishi and Emi, 2003).
Cytosolic Phenotype Relative Abundances compared to wild type and their associated variance	User Cyt1 EM Mean (CV %) User Cyt2 EM Mean (CV %) User Cyt3 EM Mean (CV %) User Cyt4 EM Mean (CV %)	1 (30) 1 (30) 1 (30) 1 (30)	Default
Transporter Phenotype Absolute Abundance (pmol/10^6 hepatocytes)	ABCB1 (P-gp/MDR1) Mean ABCB11 (BSEP) Mean ABCC2 (MRP2) Mean ABCC3 (MRP3) Mean ABCC4 (MRP4) Mean ABCC6 (MRP6) Mean ABCG2 (BCRP) Mean SLC29A1 (ENT1) Mean SLC29A2 (ENT2) Mean SLC10A1 (NTCP) Mean SLC16A1 (MCT1) Mean SLCO1B1 (OATP1B1) Mean SLCo1B3 (OATP1B3) Mean SLCO2B1 (OATP2B1) Mean SLC22A1 (OCT1) Mean	0.246 1 0.59 0.239 0 0.214 0.103 0.0646 0 0.647 0.638 3.1 3.08 1.18 1.27	(Rachumallu et al., 2020)

	SLC22A7 (OAT2) Mean SLC22A9 (OAT7) Mean SLC47A1 (MATE1) Mean SLC51A/B (OST-α/β) Mean Sinusoidal uptake Mean Sinusoidal Efflux Mean Canalicular Efflux Mean	1.25 1.45 0.146 0 0 0 0	
Relative Abundance Compared to Wild Type and their associated Variance	ABCB1 (P-gp/MDR1) ET ABCB11 (BSEP) ET ABCC2 (MRP2 ET ABCC3 (MRP3) ET ABCC4 (MRP4) ET ABCC6 (MRP6) ET ABCG2 (BCRP) ET ABCG2 (BCRP) PT ABCG2 (BCRP) IT SLC29A1 (ENT1) ET SLC29A2 (ENT2) ET SLC10A1 (NTCP) ET SLC16A1 (MCT1) ET SLCO1B1 (OATP1B1) ET SLCO1B1 (OATP1B1) PT SLCO1B1 (OATP1B1) IT SLCO1B1 (OATP1B1) UT SLCO1B3 (OATP1B3) ET SLCO2B1 (OATP2B1) ET SLC22A1 (OCT1) ET SLC22A1 (OCT1) PT SLC22A1 (OCT1) IT SLC22A1 (OCT1) UT SLC22A7 (OAT2) ET SLC22A9 (OAT7) ET SLC47A1 (MATE1) ET SLC51A/B (OST-α/β) ET Sinusoidal uptake ET Sinusoidal Efflux ET Canalicular Efflux ET	1 (59) 1 (131) 1 (88) 1 (65) 1 (60) 1 (46) 1 (30) 0.37 (30) 0.67 (30) 1 (49) 1 (60) 1 (50) 1 (60) 1 (73) 0.37 (30) 0.68 (52) 1.39 (62) 1 (89) 1 (62) 1 (44) 0.01 (44) 0.62 (44) 1.14 (44) 1 (75) 1 (51) 1 (51) 1 (60) 1 (0) 1 (0) 1 (0)	(Rachumallu et al., 2020)
Esterase Phenotype Relative Abundances Compared to Wild Type and their associated Variance	CES1 EM Mean (CV %) CES1 PM Mean (CV %) CES2 EM Mean (CV %) User ES Mean (CV %)	1 (46) 0.11 (30) 1 (35) 1 (30)	In-house meta-analysis based on published data including (Ross et al., 2012).
FMO Phenotype Absolute FMO Abundance (pmol/mg protein)	FMO1 EM Mean FMO3 EM Mean FMO5 EM Mean User FMO EM Mean	0 30 25 0	In-house meta-analysis based on published data including (Haining et al., 1997)
Relative FMO Abundances	FMO1 EM Mean (CV %) FMO3 EM Mean (CV %) FMO5 EM Mean (CV %) UserFMO EM Mean (CV %)	1 (30) 1 (50) 1 (55) 1 (30)	

KIDNEY			
Serum creatinine (µmol/L)	Males (< 61 years) Mean Males (< 61 years) CV (%) Males (> 61 years) Mean Males (< 61 years) CV1 (%) Males (< 61 years) CV2 (%) Females (< 48 years) Mean Females (< 48 years) CV (%) Females (> 48 years) Mean Females (> 48 years) CV1 (%) Females (> 48 years) CV2 (%) Females (> 78 years) Mean Females (> 78 years) CV1 (%) Females (> 78 years) CV2 (%)	76.5 16.1 81.2 27.4 21.2 57 20.4 66.2 26.5 22.8 79.5 38.3 31.6	In-house meta-analysis based on NHANES 1999-2004 dataset
GFR (ml/min/1.73m^2)	GFR Prediction	Method 1 (default selected) Method 2 (default not selected)	(Cockcroft and Gault, 1976). (Levey et al., 2000)
GFR Cap	Less than Greater than Reference value (males) Reference value (females) GFR age limit	400 15 130 120 140	
Kidney Size Parameters	Baseline: Body weight coefficient: Body height coefficient: CV (%): Kidney density (g/L)	15.4 2.04 51.8 23.4 1050	(Price et al., 2003). (ICRP, 2002).
S9 Protein (mg/g)	S9PPGK Mean User S9PPGK Mean CV (%)	12.8 0 30	(Al-Jahdari et al., 2006).
Microsomal Protein (mg/g)	MPPGK Mean CV (%)	12.8 55	
Cytosolic Protein (mg/g)	CPPGK Mean CV (%)	0 30	
UGT Phenotype Absolute UGT Abundance (pmol/mg protein)	UGT1A1 Mean UGT1A3 Mean UGT1A4 Mean UGT1A5 Mean UGT1A6 Mean UGT1A7 Mean UGT1A8 Mean UGT1A9 Mean UGT1A10 Mean UGT2B4 Mean UGT2B7 Mean UGT2B10 Mean UGT2B11 Mean UGT2B15 Mean UGT2B17 Mean UGT2B28 Mean	6.1 0 8.7 0 3.6 13 4.9 79 17 0.3 48 0 0 0.2 0 0	In-house meta-analysis based on published data including (Harbourt et al., 2012) and unpublished data from the Simcyp Consortium UGT focused group (2013).

	User UGT1 Mean	0	
Relative UGT Abundances or probe activity (compared to wild type)	UGT1A1 EM Mean (CV %)	1 (50)	In-house meta-analysis based on published data including (Peterkin et al., 2007); (Villeneuve et al., 2003) & (Swanson et al., 2007).
	UGT1A1 PM Mean (CV %)	0.42 (50)	
	UGT1A1 IM Mean (CV %)	0.72 (50)	
	UGT1A1 UM Mean (CV %)	1.46 (50)	
	UGT1A3 EM Mean (CV %)	1 (50)	
	UGT1A4 EM Mean (CV %)	1 (50)	
	UGT1A5 EM Mean (CV %)	1 (50)	
	UGT1A6 EM Mean (CV %)	1 (50)	
	UGT1A7 EM Mean (CV %)	1 (50)	
	UGT1A8 EM Mean (CV %)	1 (50)	
	UGT1A9 EM Mean (CV %)	1 (50)	
	UGT1A9 PM Mean (CV %)	0.07 (50)	
	UGT1A9 IM Mean (CV %)	0.19 (50)	
	UGT1A10 EM Mean (CV %)	1 (50)	
	UGT2B4 EM Mean (CV %)	1 (50)	
	UGT2B7 EM Mean (CV %)	1 (50)	
	UGT2B10 EM Mean (CV %)	1 (50)	
	UGT2B11 EM Mean (CV %)	1 (50)	
	UGT2B15 EM Mean (CV %)	1 (50)	
	UGT2B15 PM Mean (CV %)	0.07 (50)	
	UGT2B15 IM Mean (CV %)	0.47 (50)	
	UGT2B17 EM Mean (CV %)	1 (50)	
	UGT2B17 PM Mean (CV %)	0.08 (50)	
	UGT2B17 IM Mean (CV %)	0.16 (50)	
	UGT2B28 EM Mean (CV %)	1 (50)	
	User UGT1 EM Mean (CV %)	1 (50)	
UGT Turnover Rate (1/h)	UGT1A1 Mean (CV %)	0.0578	(Emi et al., 2002) & (Ohnishi and Emi, 2003).
	UGT1A3 Mean (CV %)	1E-06	
	UGT1A4 Mean (CV %)	1E-06	
	UGT1A5 Mean (CV %)	1E-06	
	UGT1A6 Mean (CV %)	1E-06	
	UGT1A7 Mean (CV %)	1E-06	
	UGT1A8 Mean (CV %)	1E-06	
	UGT1A9 Mean (CV %)	1E-06	
	UGT1A10 Mean (CV %)	1E-06	
	UGT2B4 Mean (CV %)	1E-06	
	UGT2B7 Mean (CV %)	1E-06	
	UGT2B10 Mean (CV %)	1E-06	
	UGT2B11 Mean (CV %)	1E-06	
	UGT2B15 Mean (CV %)	1E-06	
	UGT2B17 Mean (CV %)	1E-06	
	UGT2B28 Mean (CV %)	1E-06	
Transporter Phenotype Relative Abundances compared to wild type and their associated variances	ABCB1 (P-gp) ET Mean (CV %)	1 (60)	(Neuhoff et al., 2013).
	ABCC4 (MRP4) ET Mean (CV %)	1 (60)	
	SLC22A2 (OCT2) ET Mean (CV %)	1 (60)	
	SLC22A6 (OAT1) ET Mean (CV %)	1 (60)	
	SLC22A8 (OAT3) ET Mean (CV %)	1 (60)	
	SLC47As (MATEs) ET Mean (CV %)	1 (60)	
	Apical Influx (kidney) ET Mean (CV %)	1 (60)	

	Basolateral Efflux (kidney) Mean (CV %)	1 (60)	
		PT-S1/PT-S2/PT-S3	
Relative Abundances along the Proximal Tubular Cells compared to segment 1 values	ABCB1 (P-gp) ET Mean (CV %) ABCC4 (MRP4) ET Mean (CV %) SLC22A2 (OCT2) ET Mean (CV %) SLC22A6 (OAT1) ET Mean (CV %) SLC22A8 (OAT3) ET Mean (CV %) SLC47As (MATEs) Apical Influx (kidney) Basolateral Efflux (kidney)	1/1/1 1/1/1 1/1/1 1/1/1 1/1/1 1/1/1 1/1/1 1/1/1	(Neuhoff et al., 2013).
Cytosolic Phenotype Relative Abundances compared to wild type and their associated variance	User Cyt1 EM Mean (CV %) User Cyt2 EM Mean (CV %) User Cyt3 EM Mean (CV %) User Cyt4 EM Mean (CV %)	1 (30) 1 (30) 1 (30) 1 (30)	
Esterase Phenotype Relative Abundances Compared to Wild Type and their associated Variance	CES1 EM Mean (CV %) CES1 PM Mean (CV %) CES2 EM Mean (CV %) User ES Mean (CV %)	1 (30) 0.11 (30) 1 (30) 1 (30)	In-house meta-analysis based on published data including (Zhu and Markowitz, 2009).
Absolute FMO Abundance (pmol/mg protein)	FMO1 EM Mean FMO3 EM Mean FMO5 EM Mean User FMO Mean	5 0.47 2.6 0	In-house meta-analysis based on published data including (Krause et al., 2003)
FMO Phenotype Relative Abundances Compared to Wild Type and their associated Variance	FMO1 EM Mean (CV %) FMO3 EM Mean (CV %) FMO5 EM Mean (CV %) User FMO Mean (CV %)	1 (35) 1 (79) 1 (57) 1 (30)	
Mech KiM Parameters Kidney Volume	Cortex/Medulla ratio Peritubular Capillary (% volume)	0.92 7	(Neuhoff et al., 2013).
Million Nephrons per Subject	Average value of a 25 year-old male Baseline Kidney weight coefficient	1.61513 0.22693 0.003948	In-house meta-analysis based on published data including (Hoy et al., 2003).
Nephron parameters	Proximal Tubule: Length (mm) Diameter (mm) pH in Tubule Henle' Loop: Length (mm) Diameter (mm) pH in Tubule Distal Tubule: Length (mm) Diameter (mm) pH in Tubule Collecting Duct: Length (mm)	 18 0.06 7.4 7 0.018 7.4 5.5 0.05 7.4 22	 (Neuhoff et al., 2013).

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	Diameter (mm) pH in Tubule	0.2 7.4	
Urine flow rate within nephron ($ml/min/1.73m^2$)	Proximal Tubule (Male/Female) Henle' Loop (Male/Female) Distal Tubule (Male/Female) Collecting Duct (Male/Female) Bladder (Male/Female)	130/120 46.77/43.23 25.97/24.03 12.44/11.56 1/1	(Neuhoff et al., 2013).
Proximal Tubular Cells PTCPGK	Millions of cells/g Kidney Mean: CV (%):	 60 30	(Neuhoff et al., 2013).
Proportion of Blood Bypass	Bypass before glomerulus (% Renal blood flow) Mean (CV %): Bypass to Henle's Loop (% Proximal tubular blood flow) Mean (CV %):	10 (30) 20 (30)	(Hulin, 1997).
Parameters for the mechanistic filtration model	Fraction of hydraulic conductance accounted for by large pores Small pore radius (nm) Large pore radius (nm) Hydrostatic pressure difference across the glomerulus (mm Hg) Colloid osmotic pressure difference across the glomerulus (mm Hg) CLp CL_{mem}	0.0583 4.4 6.11 40 24.9304 141 129.2	In-house analysis based on (Ohlson et al., 2001) & (Blouch et al., 1997).
GI TRACT			
Gastrointestinal Attributes Mean gastric residence time (h)	Stomach Fasted Mean (CV %) Stomach Fed Mean (CV %) Small intestine Weibull parameters α β Mean Colon Mean (CV %)	0.4 (38) 1 (38) 2.92 4.04 3.33873 24 (30)	In-house analysis based on data from (Park et al., 2008). In-house meta-analysis based on published data including (Manabe et al., 2010).
Fluid and dissolved drug mean residence time (MRT) (h)	Stomach Fasted lag time Mean (CV %) Stomach Fasted MRT Mean (CV %)	0 (0) 0.27 (36)	In-house meta-analysis based on published data including (Ziessman et al., 2009).
	Stomach high fat fed lag time Mean (CV %) Stomach high fat fed MRT Mean (CV %) Stomach fed lag time Mean (CV %) Stomach fed MRT Mean (CV %)	0 (0) 1.18 (46.65) 0 (0) 1.18 (46.65)	In-house meta-analysis based on published data including (Siegel et al., 1988).

	Stomach low fat fed lag time Mean (CV %) Stomach low fat fed MRT Mean (CV %) Small intestine fasted Mean (CV %) Small intestine high fat fed Mean (CV %) Small intestine fed Mean (CV %) Small intestine low fat fed Mean (CV %) Whole colon Mean (CV %)- Male Whole colon Mean (CV %)- Female Ascending colon Mean (CV %)- Male Ascending colon Mean (CV %)- Female	0 (0) 1.18 (46.65) 3.4 (9.19) 4.73 (34.67) 4.73 (34.67) 4.73 (34.67) 37.11 (47) 52.87 (47) 18.91 (47) 23.11 (47)	In-house meta-analysis based on published data including (Wilson et al., 2009). In-house meta-analysis based on published data including (Graff et al., 2001).
IMMC Cycle Time (h)	Mean (CV %)	1.55 (55)	(Schmidt et al., 1996).
S9 Protein (mg/small intestine) **Microsomal Protein (mg/small intestine) (mg/colon)** **Cytosolic Protein (mg/small intestine)** **Total Membrane Protein per Intestine (mg/small intestine)** **Total Membrane Protein per colon (mg/colon)**	S9PPI Mean User S9PPI Mean (CV %) MPPI Mean (CV %) MPPC Mean (CV %) CPPI Mean (CV %) TMePPI Mean (CV %) TMePPC Mean (CV %)	5320 0 (30) 2978 (30) 622 (30) 2342 (31) 2737 (0) 112 (0)	In-house analysis based on data from (Paine et al., 1997); (Gibbs et al., 1998) & unpublished data from Mike Coughtrie (University of Dundee, July 2009). (Harwood et al., 2019).
Food Staggering Model Duration of Fed State	Number of gastric emptying half lives	5	
Meal Event Fluid Volumes **High Fat Fed**	Total fluid volume associated with food (ml) Mean (CV %) Time taken to consume meal (T_{et}) (h) Mean (CV %) Zero order filling rate (mL/h) Mean Maximum Stomach Volume (mL)	531.07 (15) 0.335 (30) 1585.28 4000	In-house meta-analysis based on published data including (Grimm et al., 2017).
Fed	Total fluid volume associated with food (ml) Mean (CV %) Time taken to consume meal (T_{et}) (h) Mean (CV %) Zero order filling rate (mL/h) Mean Maximum Stomach Volume (mL)	531.07 (15) 0.335 (30) 1585.28 4000	
Low Fat Fed	Total fluid volume associated with food (ml) Mean (CV %) Time taken to consume meal (T_{et}) (h) Mean (CV %) Zero order filling rate (mL/h) Mean Maximum Stomach Volume (mL)	546 (9) 0.335 (30) 1629.85 4000	
Anatomy of the Intestine	Enterocyte volume in small intestine (L)	0.517	

	Enterocyte volume in colon (L)	0.007	In-house analysis based on (Crowe and Marsh, 1993).
Dependence of Duodenum on BSA	Duodenum length (m) Linear multiplier C1 Exponent Duodenum diameter (m) Linear multiplier C1 Exponent Lower gut length (m) Linear multiplier C1 Exponent CV (%)	0.205 0.55 0.033 0.383 5.231 0.414 20	
Jejunum-Ileum Ratios	Jejunum/Lower gut length Jejunum/Duodenum diameter Ileum/Duodenum diameter	0.4 0.8125 0.725	
Nested Enzyme Within Enterocyte (NEWE) Model	Enterocyte lifespan (h) Mean (CV %) Number of enterocyte groups	120 (30) 100	(Darwich et al., 2019).
CYP Phenotype Intestine Enzyme Abundances (nmol/small intestine)	CYP2C9 Mean EM (CV %) CYP2C9 Mean PM (CV %) CYP2C19 Mean EM (CV %) CYP2C19 Mean UM (CV%) CYP2D6 Mean EM (CV %) CYP2D6 Mean UM (CV %) CYP2J2 Mean EM (CV %) CYP3A4 Mean EM (CV %) CYP3A5 Mean EM (CV %)	12.5 (72) 5 (72) 2 (77) 4 (77) 1.1 (47) 2.1 (47) 7.4 (69) 65.4 (52) 23.3 (32)	In-house meta-analysis based on published data including (Drozdzik et al., 2018) & (Paine et al., 2006).
CYP Turnover Rate Constants (1/h)	CYP2C9 Mean (CV %) CYP2C19 Mean (CV %) CYP2D6 Mean (CV %) CYP2J2 Mean (CV %) CYP3A4 Mean (CV %) CYP3A5 Mean (CV %)	0.03 (20) 0.03 (20) 0.03 (20) 0.03 (20) 0.03 (20) 0.03 (20)	In-house analysis based on (Greenblatt et al., 2003).
CYP Phenotype Colon Enzyme Abundances (nmol/colon)	CYP2C9 Mean EM (CV %) CYP2C19 Mean EM (CV %) CYP2D6 Mean EM (CV %) CYP2J2 Mean EM (CV %) CYP3A4 Mean EM (CV %) CYP3A5 Mean EM (CV %)	0 (0) 0 (0) 0 (0) 0 (0) 1.99 (30) 0.74 (30)	In-house analysis based on published data from (de Waziers et al., 1991) & (Gervot et al., 1996).
CYP Genotype Abundance	CYP2C9 *1/*1 Mean (CV %) CYP2C9 *1/*2 Mean (CV %) CYP2C9 *1/*3 Mean (CV %) CYP2C9 *2/*2 Mean (CV %) CYP2C9 *2/*3 Mean (CV %) CYP2C9 *3/*3 Mean (CV %)	12.5 (72) 11.4 (72) 11.4 (72) 11.4 (72) 11.4 (72) 3.4 (72)	In-house meta-analysis based on published data including (Drozdzik et al., 2018) & (Paine et al., 2006).
UGT Phenotype Absolute UGT Abundance (pmol/mg protein)	UGT1A1 Mean UGT1A3 Mean UGT1A4 Mean UGT1A5 Mean	8.5 0.4 1.9 0.3	In-house meta-analysis based on published data including (Harbourt

	UGT1A6 Mean UGT1A7 Mean UGT1A8 Mean UGT1A9 Mean UGT1A10 Mean UGT2B4 Mean UGT2B7 Mean UGT2B10 Mean UGT2B11 Mean UGT2B15 Mean UGT2B17 Mean UGT2B28 Mean User UGT1 Mean	1.3 7.1 5.6 5.9 4.3 0 4.5 0.1 0 0.1 11 0 0	et al., 2012) & unpublished data from the Simcyp Consortium UGT focused group (2013).
Relative UGT Abundances or probe activity (compared to wild type)	UGT1A1 EM Mean (CV %) UGT1A1 PM Mean (CV %) UGT1A1 IM Mean (CV %) UGT1A1 UM Mean (CV %) UGT1A3 EM Mean (CV %) UGT1A4 EM Mean (CV %) UGT1A5 EM Mean (CV %) UGT1A6 EM Mean (CV %) UGT1A7 EM Mean (CV %) UGT1A8 EM Mean (CV %) UGT1A9 EM Mean (CV %) UGT1A9 PM Mean (CV %) UGT1A9 IM Mean (CV %) UGT1A10 EM Mean (CV %) UGT2B4 EM Mean (CV %) UGT2B7 EM Mean (CV %) UGT2B10 EM Mean (CV %) UGT2B11 EM Mean (CV %) UGT2B15 EM Mean (CV %) UGT2B15 PM Mean (CV %) UGT2B15 IM Mean (CV %) UGT2B17 EM Mean (CV %) UGT2B17 PM Mean (CV %) UGT2B17 IM Mean (CV %) UGT2B28 EM Mean (CV %) User UGT1 EM Mean (CV %)	1 (60) 0.42 (60) 0.72 (60) 1.46 (60) 1 (60) 1 (60) 1 (60) 1 (60) 1 (60) 1 (60) 1 (60) 0.07 (60) 0.19 (60) 1 (60) 1 (60) 1 (60) 1 (60) 1 (60) 1 (60) 0.07 (60) 0.47 (60) 1 (60) 0.08 (60) 0.16 (60) 1 (60) 1 (60)	In-house meta-analysis based on published data including (Peterkin et al., 2007); (Villeneuve et al., 2003) & (Swanson et al., 2007).
UGT Turnover Rate (1/h)	UGT1A1 Mean (CV %) UGT1A3 Mean (CV %) UGT1A4 Mean (CV %) UGT1A5 Mean (CV %) UGT1A6 Mean (CV %) UGT1A7 Mean (CV %) UGT1A8 Mean (CV %) UGT1A9 Mean (CV %) UGT1A10 Mean (CV %) UGT2B4 Mean (CV %) UGT2B7 Mean (CV %) UGT2B10 Mean (CV %) UGT2B11 Mean (CV %) UGT2B15 Mean (CV %)	0.0578 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06 1E-06	(Barter et al., 2007) & (Ohnishi and Emi, 2003).

	UGT2B17 Mean (CV %) UGT2B28 Mean (CV %)	1E-06 1E-06	
Cytosolic Phenotype Relative Abundances compared to wild type and their associated variance	User Cyt1 EM Mean (CV %) User Cyt2 EM Mean (CV %) User Cyt3 EM Mean (CV %) User Cyt4 EM Mean (CV %)	1 (60) 1 (60) 1 (60) 1 (60)	Default
Transporter Expression Absolute Abundance (pmol/mg total membrane protein)- Jejunum I	ABCB1 (P-gp/MDR1) ABCC1 (MRP1) ABCC2 (MRP2) ABCC3 (MRP3) ABCC4 (MRP4) ABCG2 (BCRP) SLC2A2 (GLUT2) SLC10A2 (ASBT/IBAT) SLC15A1 (PepT1) SLC16A1 (MCT1) SLCO2B1 (OATP2B1) SLCO4C1 (OATP4C1) SLC22A1 (OCT1) SLC22A3 (OCT3) SLC22A4 (OCTN1) SLC51A/B (OST-α/β) Apical Influx Apical Efflux Basal Influx Basal Efflux	0.4 0 0.86 0.58 0 0.34 0 0.01 3.69 0 0.4 0 0.65 0.06 0 0.47 0 0 0 0	(Harwood et al., 2019).
Relative Abundances along the GI tract compared to jejunum values- Duodenum	ABCB1 (P-gp/MDR1) ABCC1 (MRP1) ABCC2 (MRP2) ABCC3 (MRP3) ABCC4 (MRP4) ABCG2 (BCRP) SLC2A2 (GLUT2) SLC10A2 (ASBT/IBAT) SLC15A1 (PepT1) SLC16A1 (MCT1) SLCO2B1 (OATP2B1) SLCO4C1 (OATP4C1) SLC22A1 (OCT1) SLC22A3 (OCT3) SLC22A4 (OCTN1) SLC51A/B (OST-α/β) Apical Influx Apical Efflux Basal Influx Basal Efflux	0.51 0.45 1.41 2.15 1.02 0.68 1 16.49 0.94 1.25 0.73 1 1.03 1.19 0.46 0.56 1 1 1 1	(Harwood et al., 2019).
Jejunum I	ABCB1 (P-gp/MDR1) ABCC1 (MRP1) ABCC2 (MRP2) ABCC3 (MRP3) ABCC4 (MRP4)	1 1 1 1 1	(Harwood et al., 2019).

	ABCG2 (BCRP) SLC2A2 (GLUT2) SLC10A2 (ASBT/IBAT) SLC15A1 (PepT1) SLC16A1 (MCT1) SLCO2B1 (OATP2B1) SLCO4C1 (OATP4C1) SLC22A1 (OCT1) SLC22A3 (OCT3) SLC22A4 (OCTN1) SLC51A/B (OST-α/β) Apical Influx Apical Efflux Basal Influx Basal Efflux	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	
Jejunum II	ABCB1 (P-gp/MDR1) ABCC1 (MRP1) ABCC2 (MRP2) ABCC3 (MRP3) ABCC4 (MRP4) ABCG2 (BCRP) SLC2A2 (GLUT2) SLC10A2 (ASBT/IBAT) SLC15A1 (PepT1) SLC16A1 (MCT1) SLCO2B1 (OATP2B1) SLCO4C1 (OATP4C1) SLC22A1 (OCT1) SLC22A3 (OCT3) SLC22A4 (OCTN1) SLC51A/B (OST-α/β) Apical Influx Apical Efflux Basal Influx Basal Efflux	1.46 0.88 1 0.89 1.22 1 1 4 1.06 1 0.94 1 0.87 1.11 0.63 1.89 1 1 1 1	(Harwood et al., 2019).
Ileum I	ABCB1 (P-gp/MDR1) ABCC1 (MRP1) ABCC2 (MRP2) ABCC3 (MRP3) ABCC4 (MRP4) ABCG2 (BCRP) SLC2A2 (GLUT2) SLC10A2 (ASBT/IBAT) SLC15A1 (PepT1) SLC16A1 (MCT1) SLCO2B1 (OATP2B1) SLCO4C1 (OATP4C1) SLC22A1 (OCT1) SLC22A3 (OCT3) SLC22A4 (OCTN1) SLC51A/B (OST-α/β) Apical Influx Apical Efflux	1.5 0.86 0.6 1.54 1.71 0.78 1 98.44 1.23 1.29 1.28 1 1.29 1.08 0.78 1.08 1 1	(Harwood et al., 2019).

	Basal Influx Basal Efflux	1 1	
Ileum II	ABCB1 (P-gp/MDR1) ABCC1 (MRP1) ABCC2 (MRP2) ABCC3 (MRP3) ABCC4 (MRP4) ABCG2 (BCRP) SLC2A2 (GLUT2) SLC10A2 (ASBT/IBAT) SLC15A1 (PepT1) SLC16A1 (MCT1) SLCO2B1 (OATP2B1) SLCO4C1 (OATP4C1) SLC22A1 (OCT1) SLC22A3 (OCT3) SLC22A4 (OCTN1) SLC51A/B (OST-α/β) Apical Influx Apical Efflux Basal Influx Basal Efflux	1.51 0.86 0.6 1.54 1.71 0.78 1 98.44 1.23 1.29 1.28 1 1.29 1.08 0.78 1.08 1 1 1 1	(Harwood et al., 2019).
Ileum III	ABCB1 (P-gp/MDR1) ABCC1 (MRP1) ABCC2 (MRP2) ABCC3 (MRP3) ABCC4 (MRP4) ABCG2 (BCRP) SLC2A2 (GLUT2) SLC10A2 (ASBT/IBAT) SLC15A1 (PepT1) SLC16A1 (MCT1) SLCO2B1 (OATP2B1) SLCO4C1 (OATP4C1) SLC22A1 (OCT1) SLC22A3 (OCT3) SLC22A4 (OCTN1) SLC51A/B (OST-α/β) Apical Influx Apical Efflux Basal Influx Basal Efflux	1.52 0.89 0.6 1.6 1.2 0.78 1 109.18 1.24 1.29 1.28 1 1.3 1.23 0.8 0.93 1 1 1 1	(Harwood et al., 2019).
Ileum IV	ABCB1 (P-gp/MDR1) ABCC1 (MRP1) ABCC2 (MRP2) ABCC3 (MRP3) ABCC4 (MRP4) ABCG2 (BCRP) SLC2A2 (GLUT2) SLC10A2 (ASBT/IBAT) SLC15A1 (PepT1) SLC16A1 (MCT1)	1.51 0.89 0.6 1.6 1.2 0.78 1 108 1.24 1.29	(Harwood et al., 2019)

	SLCO2B1 (OATP2B1)	1.28	
	SLCO4C1 (OATP4C1)	1	
	SLC22A1 (OCT1)	1.3	
	SLC22A3 (OCT3)	1.23	
	SLC22A4 (OCTN1)	0.8	
	SLC51A/B (OST-α/β)	0.93	
	Apical Influx	1	
	Apical Efflux	1	
	Basal Influx	1	
	Basal Efflux	1	
Colon	ABCB1 (P-gp/MDR1)	0.57	(Harwood et al., 2019)
	ABCC1 (MRP1)	0.93	
	ABCC2 (MRP2)	0.02	
	ABCC3 (MRP3)	5.95	
	ABCC4 (MRP4)	1.76	
	ABCG2 (BCRP)	0.57	
	SLC2A2 (GLUT2)	1	
	SLC10A2 (ASBT/IBAT)	1.1	
	SLC15A1 (PepT1)	0.03	
	SLC16A1 (MCT1)	4.72	
	SLCO2B1 (OATP2B1)	1.06	
	SLCO4C1 (OATP4C1)	1	
	SLC22A1 (OCT1)	2.77	
	SLC22A3 (OCT3)	1.88	
	SLC22A4 (OCTN1)	0.24	
	SLC51A/B (OST-α/β)	0.71	
	Apical Influx	1	
	Apical Efflux	1	
	Basal Influx	1	
	Basal Efflux	1	
Phenotype: Jejunum I: Relative Abundances Compared to Wild Type and their associated Variance	ABCB1 (P-gp) ET Mean (CV %)	1 (65)	In-house meta-analysis based on published data. See (Harwood et al., 2019) for details of references used.
	ABCC1 (MRP1) ET Mean (CV %)	1 (88)	
	ABCC2 (MRP2) ET Mean (CV %)	1 (79)	
	ABCC3 (MRP3) ET Mean (CV %)	1 (64)	
	ABCC4 (MRP4) ET Mean (CV %)	1 (106)	
	ABCG2 (BCRP) ET Mean (CV %)	1 (63)	
	ABCG2 (BCRP) PT Mean (CV %)	0.37 (63)	
	ABCG2 (BCRP) IT Mean (CV %)	0.67 (63)	
	SLC2A2 (GLUT2) ET Mean (CV %)	1 (31)	
	SLC10A2 (ASBT/IBAT) ET Mean (CV)	1 (43)	
	SLC15A1 (PepT1) ET Mean (CV %)	1 (41)	
	SLC16A1 (MCT1) ET Mean (CV %)	1 (75)	
	SLCO2B1 (OATP2B1) ET Mean (CV %)	1 (74)	
	SLCO4C1 (OATP4C1) ET Mean (CV %)	1 (60)	
	SLC22A1 (OCT1) ET Mean (CV %)	1 (49)	
	SLC22A1 (OCT1) PT Mean (CV %)	0.01 (49)	
	SLC22A1 (OCT1) IT Mean (CV %)	0.62 (49)	
	SLC22A1 (OCT1) UT Mean (CV %)	1.14 (49)	
	SLC22A3 (OCT3) ET Mean (CV %)	1 (74)	
	SLC22A4 (OCTN1) ET Mean (CV %)	1 (106)	
	SLC51A/B (OST-α/β) ET Mean (CV %)	1 (99)	
	Apical Influx ET Mean (CV %)	1 (0)	
	Apical Efflux ET Mean (CV %)	1 (0)	

	Basal Influx ET Mean (CV %) Basal Efflux ET Mean (CV %)	1 (0) 1 (0)	
Esterase Phenotype Relative Abundances Compared to Wild Type and their associated Variance	CES1 EM Mean (CV %) CES1 PM Mean (CV %) CES2 EM Mean (CV %) User ES Mean (CV %)	1 (30) 0.11 (30) 1 (30) 1 (30)	In-house meta-analysis based on published data including (Zhu and Markowitz, 2009).
Luminal Metabolism Substrate- Expression Relative Activity along the GI tract compared to reference segment selected on the Elimination screen	Substrate -> Primary Metabolite 1 Enzyme user Stomach Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon	 1 1 1 1 1 1 1 1 1	Default
-Phenotype Reference segment selected on Elimination screen: Relative Activity compared to Wild Type and their associated variability	Substrate -> Primary Metabolite 1 Enzyme user EM Mean (CV %)	 1 (30)	Default
Substrate- Expression Relative Activity along the GI tract compared to reference segment selected on the Elimination screen	Primary Metabolite 1 -> Substrate Enzyme user Stomach Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon	 1 1 1 1 1 1 1 1 1	Default
-Phenotype Reference segment selected on Elimination screen: Relative Activity compared to Wild Type and their associated variability	Primary Metabolite 1 -> Substrate Enzyme user EM Mean (CV %)	 1 (30)	Default
FMO Phenotype Absolute FMO Abundance (pmol/mg protein)	FMO1 EM FMO3 EM FMO5 EM User FMO FMO1 EM (CV%) FMO3 EM (CV%)	0 0 0 0 1 (30) 1 (30)	Default

Relative FMO Abundances or probe activity (compared to wild type)	FMO5 EM (CV%)	1 (30)	
	User FMO	1 (30)	
ADAM Model Parameters Achlorhydrics	Achlorhydric subjects (%) Coefficient	8	
	Age Power	0	
	Maximum (%)	8	
General Duodenum	Blood Flow (Q_{villi} %)	8.8	In-house analysis based on published data including (Paine et al., 1997).
	Transit Time (Total %)	4.6	
	CYP 3A (Total %)	13.76	
	S9PPI (Total %)	14.88	
	MPPI (Total %)	13.76	
	CPPI (Total %)	14.88	
Jejunum I	Blood Flow (Q_{villi} %)	24.2	
	Transit Time (Total %)	17.3	
	CYP 3A (Total %)	27.24	
	S9PPI (Total %)	26.9	
	MPPI (Total %)	27.24	
	CPPI (Total %)	26.9	
Jejunum II	Blood Flow (Q_{villi} %)	24.2	
	Transit Time (Total %)	17.3	
	CYP 3A (Total %)	27.24	
	S9PPI (Total %)	26.9	
	MPPI (Total %)	27.24	
	CPPI (Total %)	26.9	
Ileum I	Blood Flow (Q_{villi} %)	10.7	
	Transit Time (Total %)	15.2	
	CYP 3A (Total %)	7.94	
	S9PPI (Total %)	7.83	
	MPPI (Total %)	7.94	
	CPPI (Total %)	7.83	
Ileum II	Blood Flow (Q_{villi} %)	10.7	
	Transit Time (Total %)	15.2	
	CYP 3A (Total %)	7.94	
	S9PPI (Total %)	7.83	
	MPPI (Total %)	7.94	
	CPPI (Total %)	7.83	
Ileum III	Blood Flow (Q_{villi} %)	10.7	
	Transit Time (Total %)	15.2	
	CYP 3A (Total %)	7.94	
	S9PPI (Total %)	7.83	
	MPPI (Total %)	7.94	
	CPPI (Total %)	7.83	
Ileum IV	Blood Flow (Q_{villi} %)	10.7	
	Transit Time (Total %)	15.2	
	CYP 3A (Total %)	7.94	
	S9PPI (Total %)	7.83	
	MPPI (Total %)	7.94	
	CPPI (Total %)	7.83	

Enzyme Abundances (nmol) **CYP2C9**	Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon	1.72 3.41 3.41 0.99 0.99 0.99 0.99 0	In-house meta-analysis based on published data including (Drozdzik et al., 2018), (Paine et al., 2006) & (Paine et al., 1997).
CYP2C19	Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon	0.28 0.54 0.54 0.16 0.16 0.16 0.16 0	In-house meta-analysis based on published data including (Drozdzik et al., 2018), (Paine et al., 2006) & (Paine et al., 1997).
CYP2D6	Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon	0.15 0.3 0.3 0.09 0.09 0.09 0.09 0	In-house meta-analysis based on published data including (Drozdzik et al., 2018), (Paine et al., 2006) & (Paine et al., 1997).
CYP2J2	Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon	1.02 2.02 2.02 0.59 0.59 0.59 0.59 0	In-house meta-analysis based on published data including (Paine et al., 1997) & (Paine et al., 2006).
CYP3A4	Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon	9.0 17.81 17.81 5.19 5.19 5.19 5.19 1.99	In-house meta-analysis based on published data including (Paine et al., 1997) & (Paine et al., 2006).
CYP3A5	Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon	3.21 6.35 6.35 1.85 1.85 1.85 1.85 0.74	In-house meta-analysis based on published data including (Paine et al., 1997) & (Paine et al., 2006).
	Duodenum	791.62	In-house analysis based on published

S9PPI (mg)	Jejunum I	1431.08	(Paine et al., 1997)
	Jejunum II	1431.08	& unpublished data
	Ileum I	416.56	(Mike Coughtrie,
	Ileum II	416.56	University of
	Ileum III	416.56	Dundee, July 2009).
	Ileum IV	416.56	In-house analysis
			based on (Paine et
			al., 1997).
	Duodenum	409.77	
MPPI/MPPC (mg)	Jejunum I	811.21	
	Jejunum II	811.21	
	Ileum I	236.45	
	Ileum II	236.45	
	Ileum III	236.45	
	Ileum IV	236.45	
	Colon	622	In-house analysis
			based on published
	Duodenum	348.49	(Paine et al., 1997)
CPPI (mg)	Jejunum I	630	& unpublished data
	Jejunum II	630	(Mike Coughtrie,
	Ileum I	183.38	University of
	Ileum II	183.38	Dundee, July 2009).
	Ileum III	183.38	
	Ileum IV	183.38	
			In-house analysis
			based on published
	Ionic Product (Kw) ($10^{-14}mol^2/dm^6$)	2.4	data from (Zeebee,
Water Physicochemical	Aqueous Diffusion Coefficients		2011).
Properties (37˚C)	($10^{-4}cm^2/min$)		
	H^+	6.94	
	OH^-	7.2	
	Water Concentration (mM)	55560	In-house analysis
			based on published
	pH Fasted Mean (CV %)	1.5 (38)	data from
Luminal pH	pH High Fat Fed Mean (CV %)	4.39 (24.1)	(Fallingborg et al.,
Stomach	pH Fed Mean (CV %)	5 (25)	1989) & (Koziolek
	pH Low Fat Fed Mean (CV %)	5 (25)	et al., 2015).
	$pH_{fed,initial}$ Mean (CV %)	4.39 (24)	
Time-Dependent Gastric pH	k (h^{-1}) Mean (CV %)	0.467 (97.8)	
High Fat Fed	pH_{fasted}	0.5367779	
	pH Fasted Mean (CV %)	1.5 (38)	
	$pH_{fed,initial}$ Mean (CV %)	5 (25)	
Fed	Age < 65 Tff (h) Mean (CV %)	1.8 (65)	
	Age < 65 Tff (h) Mean (CV %)	3 (80)	
	K (h^{-1})	0.668877	
	Slope	1.166667	
	pH Fasted Mean (CV %)	1.5 (38)	
	$pH_{fed,initial}$ Mean (CV %)	5 (25)	
Low Fat Fed	Age < 65 Tff (h) Mean (CV %)	1.8 (65)	
	Age < 65 Tff (h) Mean (CV %)	3 (80)	
	K (h^{-1})	0.668874	
	Slope	1.166667	In-house analysis
	pH Fasted Mean (CV %)		based on published
	Duodenum	6.4 (16)	data from

Small Intestine - Static pH Model	Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV pH High Fat Fed Mean (CV %) Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV pH Fed Mean (CV %) Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV pH Low Fat Fed Mean (CV %) Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV	6.5 (13) 6.6 (11) 6.8 (10) 7 (10) 7.1 (7) 7.3 (6) 5.4 (11) 6.5 (13) 6.6 (11) 6.8 (10) 7 (10) 7.1 (7) 7.3 (6) 5.4 (11) 6.5 (13) 6.6 (11) 6.8 (10) 7 (10) 7.1 (7) 7.3 (6) 5.4 (11) 6.5 (13) 6.6 (11) 6.8 (10) 7 (10) 7.1 (7) 7.3 (6)	(Fallingborg et al., 1989).
Small Intestine -Dynamic pH Model	Fasted K A B C D a b c Fed (High Fat/Fed/Low Fat) K A B C D a b c	 8.50336 0.881696 8.23296 2.96836 2.32041 2.35408 -0.737846 7.19977 4.73512 1.5348 4.09878 6.46013 -4.45833 2 -1 15	In-house analysis based on published data including (Fallingborg et al., 1989) & (Koziolek et al., 2015).
	pH Fasted Mean (CV %) pH High Fat Fed Mean (CV %)	6.6 (13.3) 6.33 (11.78)	In-house meta-analysis based on published data

Colon	pH Fed Mean (CV %) pH Low Fat Fed Mean (CV %)	6.33 (11.78) 6.33 (11.78)	including (Schneider et al., 2016).
Luminal Bicarbonate-Luminal Fluid Total Bicarbonate Buffer Concentration (mM)	Fasted (CV %) Stomach Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon Fed (CV %) Stomach Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon	 7.3 (30) 6.53 (30) 9.94 (30) 9.94 (30) 30 (30) 30 (30) 30 (30) 30 (30) 90.87 (30) 42.46 (30) 34.19 (30) 17.34 (30) 17.34 (30) 30 (30) 30 (30) 30 (30) 30 (30) 44.43 (30)	In-house meta-analysis based on published data including (Fadda et al., 2009).
Bicarbonate Physicochemical Parameters	pKa 1 Acidic pKa 2 Acidic Measured pKa at 37°C Ionic Strength (I) 0.15M pKa 1 Acidic pKa 2 Acidic Effective pKa Aqueous Diffusion Coefficients ($10^{-4}cm^2/min$) H_2CO_3 HCO_3^- CO_3^{2-}	6.05 9.79 4.2 9.79 17.72 9.85 6.98	In-house analysis based on published data from (Zeebee, 2011).
Luminal Fluid Velocity (m/s)	Fasted (CV %) Stomach Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon Fed (CV %) Stomach Duodenum Jejunum I Jejunum II Ileum I Ileum II	 0.032 (30) 0.005 (30) 0.0013 (56) 0.0013 (56) 0.0013 (56) 0.0013 (56) 0.0013 (56) 0.0013 (56) 0.0013 (56) 0.032 (30) 0.005 (30) 0.0013 (56) 0.0013 (56) 0.0013 (56) 0.0013 (56)	In-house meta-analysis based on published data including (Gutzeit et al., 2010).

	Ileum III Ileum IV Colon	0.0013 (56) 0.0013 (56) 0.0013 (56)	
Endogenous Ions	Chloride (CL^{-}) Mean (Min, Max) Stomach Duodenum Jejunum I Jejunum II Illeum I Illeum II Illeum III Illeum IV Colon Stomach CV Small Intestine CV Colon CV	 102 (48,173) 102.4 (64.6,158.8) 126 (92,181) 126 (92,181) 113.3 (80.4,157.5) 100.5 (71.4,139.7) 84 (59.6,116.7) 67.4 (58,79) 13 (7,20) 27.5 15.1 13	
	Sodium (Na^{+}) Mean (Min, Max) Stomach Duodenum Jejunum I Jejunum II Illeum I Illeum II Illeum III Illeum IV Colon Stomach CV Small Intestine CV Colon CV	 68 (19,122) 118.4 (89.6,155.1) 142 (111,165) 142 (111,165) 136.3 (107.4,171.8) 130.5 (102.8,164.6) 128.9 (101.5,162.5) 127.2 (112,138) 30 (6,93) 42.6 9.2 42	
	Potassium (K^{+}) Mean (Min, Max) Stomach Duodenum Jejunum I Jejunum II Illeum I Illeum II Illeum III Illeum IV Colon Stomach CV Small Intestine CV Colon CV	 13.4 (8.4,19.3) 11.2 (3.4,32.1) 5.4 (1.7,11.6) 5.4 (1.7,11.6) 6.1 (4.6,8) 6.7 (5,8.8) 6.3 (4.7,8,3) 5.9 (5.3,6.5) 77 (40,108) 22.4 38.9 11	
	Calcium (Ca^{2+}) Mean (Min, Max) Stomach Duodenum Jejunum I Jejunum II Illeum I Illeum II Illeum III Illeum IV	 0.6 (0.3,1.2) 0.5 (0.1,1.3) 0.5 (0.1, 1.3) 0.5 (0.1, 1.3) 0.5 (0.1, 1.3) 0.5 (0.1, 1.3) 0.5 (0.1, 1.3) 0.5 (0.1, 1.3)	

	Colon Stomach CV Small Intestine CV Colon CV	20 (7,85) 33.3 60 34	
Luminal Bile Salts (mM)	CMC Fasted Stomach Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon [Bile] Fasted Mean (CV %) Stomach Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon CMC Fed Stomach Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon [Bile] Fed Mean (CV %) Stomach Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon	 1 1 1 1 1 1 1 1 1 0.34 (134) 3.31 (97) 2.3 (100) 3.55 (42) 1.25 (30) 1.25 (30) 1.25 (30) 1.25 (30) 0.12 (104) 1 1 1 1 1 1 1 1 1 0.34 (216.7) 8.74 (79) 10.03 (73) 4.79 (66) 5.86 (84) 8.61 (88) 8.06 (65) 5.96 (65) 0.59 (70)	In-house meta-analysis based on published data including (Perez de la Cruz Moreno et al., 2006) & (Schindlbeck et al., 1987).
GI Morphology **Villi**	Channel Depth (µm) Mean (CV %) Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV	 522.78 (32.72) 448.81 (21.82) 448.81 (21.82) 289.94 (49.37) 289.94 (49.37) 289.94 (49.37) 289.94 (49.37)	In-house meta-analysis based on published data including (Trbojevic-Stankovic et al., 2010).

	Channel Width (μm) Mean (CV %) Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV	 28.03 (28.69) 22.44 (31.68) 22.44 (31.68) 56.19 (30) 56.19 (30) 56.19 (30) 56.19 (30)	
	Thickness (μm) Mean (CV %) Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV	 128.35 (8.1) 137.7 (14.42) 137.7 (14.42) 127 (30) 127 (30) 127 (30) 127 (30)	
	Apply Villus Accessible Surface Area	Active	Default
Plicae Circulares	Fold Expansion Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon	 1 (0) 1.97 (24.54) 1.38 (20.19) 1.1 (9.15) 1.1 (9.15) 1.08 (16.07) 1.04 (12.4) 1 (0)	 In-house meta-analysis based on published data from (Wilson, 1967).
Paracellular	Pore Radius[2] Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon Paracellular Scalar Pore Electric Gradient Potential Drop (mV)	 8.6 (0) 8.6 (0) 8.6 (0) 8.6 (0) 8.6 (0) 8.6 (0) 8.6 (0) 8.6 (0) 0.00039 -64.145	 (Sugano, 2009).
Luminal Boundary	Unstirred Layer Thickness (μm) Mean (CV %) Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon	 170 (22.35) 123 (3) 123 (3) 480 (10) 480 (10) 480 (10) 480 (10) 830 (13)	 (Atuma et al., 2001).

	Unstirred Layer pH Mean (CV %)		
	Duodenum	6.5 (0.5)	
	Jejunum I	6.5 (0.5)	
	Jejunum II	6.5 (0.5)	
	Ileum I	6.5 (0.5)	
	Ileum II	6.5 (0.5)	
	Ileum III	6.5 (0.5)	
	Ileum IV	6.5 (0.5)	
	Colon	6.5 (0.5)	
	Force gut unstirred boundary layer pH to equal bulk lumen pH	inactive	Default
Viscosity	Apparent Viscosity (cP) Fasted Mean (CV %)		In-house analysis based on published data from (Pedersen et al., 2013).
	Stomach	3 (71)	
	Duodenum	3 (71)	
	Jejunum I	3 (71)	
	Jejunum II	3 (71)	
	Ileum I	3 (71)	
	Ileum II	3 (71)	
	Ileum III	3 (71)	
	Ileum IV	3 (71)	
	Colon	3 (71)	
	Apparent Viscosity (cP) Fed Mean (CV %)		In-house analysis based on published data from (Radwan et al., 2012).
	Stomach	232 (32)	
	Duodenum	65 (27)	
	Jejunum I	33 (36)	
	Jejunum II	12 (14)	
	Ileum I	9 (2)	
	Ileum II	3 (71)	
	Ileum III	3 (71)	
	Ileum IV	3 (71)	
	Colon	3 (71)	
Luminal Fluid Volume Fluid Volume Dynamics (FVD) Model	Initial volume of stomach fluid (mL)		In-house analysis based on published data from (ICRP, 2002) & (Schiller et al., 2005).
	Fasted Mean (CV %)	50 (30)	
	Fed Mean (CV %)	1000 (30)	
	User Defined Intestinal Baseline Fluid Volumes- Fasted Mean (CV %)	inactive	
	Duodenum	34.35	
	Jejunum I	21.1	
	Jejunum II	21.1	
	Ileum I	12.6	
	Ileum II	12.6	
	Ileum III	12.6	
	Ileum IV	12.6	
	Total Jej I to Ile IV	92.6 (37)	
	Colon	13 (4.4)	
	Fed Mean (CV %)		
	Duodenum	34.35	
	Jejunum I	21.1	
	Jejunum II	21.1	
	Ileum I	12.6	
	Ileum II	12.6	

	Ileum III Ileum IV Total Jej I to Ile IV Colon	12.6 12.6 92.6 (37) 13 (4.4)	
Advanced Fluid Volume Dynamics (aFVD) Model Baseline Volumes	Basal (Steady State) Fluid Volumes (mL) Mean (CV %) Stomach Small Intestine Colon	 31.36 (97) 85.8 (65) 11.92 (90)	In-house meta-analysis based on published data including (Schiller et al., 2005).
	Basal Distribution of Water Within Small Intestine- % of Total Volume Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Volume in mL Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV	 10.55 15.55 22.6 13.53 13.53 12.12 12.12 9.0519 13.3419 19.3908 11.6087 11.6087 10.399 10.399	In-house analysis based on published data from (Mudie et al., 2014) & (Schiller et al., 2005).
Secretions **Fluid Secretion Rates**	Stomach (Fasted Mean)- Saliva Secretion Rate (mL/h) Gastric Juice Secretion Rate (mL/h) Stomach High Fat Fed/Fed/Low Fat Fed Secretion Rates- Time Dependent Saliva Secretion $R_{saliva, fasted}$ (mL/h) Mean T_{et} (h) Mean (CV %) $R_{saliva, max}$ (mL/h) Mean (CV %) T_{ss} (h) Mean (CV %) Slope (mL/h/h) K_s (1/h) Time Dependent Gastric Secretion $R_{gastric, fasted}$ (mL/h) Mean $T_{g\ max}$ (h) Mean (CV %) $R_{gastric, max}$ (mL/h) Mean (CV %) T_{gs} (h) Mean (CV %) Slope (mL/h/h) K_s (1/h)	 33.3229 82.82524 33.3229 0.335 (30) 199.36 (52) 2.4 (16) 495.6331 0.8662794 82.82525 0.63 (26) 209.67 (57) 3.2 (14.28) 201.3409 0.361402	In-house analysis based on published data including (Richardson and Feldman, 1986).
	Duodenum Secretion Rates (mL/h) Pancreatic Juice Mean (CV %) Bile Mean (CV %) Brunner's Fasted/Fed Mean (CV %) Other Secretion (TOS * $f_{surface,duo}$)	 26.28 (66) 29.2/10.051 (30) 5.21 (30) 4.728084	In-house analysis based on published data including (Malagelada et al., 1979) & (Gullo et al., 1988). Bile secretion rate

	Time Dependent Pancreatic Secretion (High Fat Fed/Fed/Low Fat Fed) $R_{pancreatic, fasted}$ (mL/h) Mean (CV %) $T_{p,max}$ (h) Mean (CV %) $R_{pancreatic, max}$ (mL/h) Mean (CV %) T_{ps} (h) Mean (CV %) Slope (mL/h/h) K_s (1/h) Time Dependent Bile Secretion Rest of SI Secretion Rates (mL/h) Fasted Mean (CV %) Total Other Secretion (TOS) Other Secretion (TOS * (1-$f_{surface,duo}$)) Fed Mean (CV %) Total Other Secretion (TOS) Other Secretion (TOS * (1-$f_{surface,duo}$)) Colonic Secretion Rates (mL/h) Fasted Mean (CV %) Fed Mean (CV %)	26.28 (66) 0.48 (30) 78.18 (42) 3.38 (30) 108.125 0.375933 Defined in liver tab 79.17 (30) 74.44191 79.17 (30) 74.44191 5.42 (30) 5.42 (30)	depends on the enterohepatic recirculation model selected. In-house meta-analysis based on published data including (ICRP, 2002).
Water Absorption Rate Constants (h^{-1})	Mean Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon	14.1094/11.8695 3.92724 0.380685 1.92378 1.01863 1.36233 1.13713 2.116475	Values are back-calculated from fasted residence times, secretions and baseline fluid volumes. Duodenal water absorption rate depends on what bile salt model is selected.
Luminal Content Weight	Fasted (grams) Mean (CV %) Stomach Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon Fed (grams) Mean (CV %) Stomach Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Colon	50 (30) 34 (30) 23 (30) 23 (30) 14 (30) 14 (30) 14 (30) 14 (30) 133.29 (62.2) 1000 (30) 34 (30) 23 (30) 23 (30) 14 (30) 14 (30) 14 (30) 14 (30) 133.29 (62.2)	Luminal content for stomach to ileum are assumed to be the baseline fluid volume for a population representative corrected using a density of 1g/ml (see reference above). For colon: In-house meta-analysis based on published data including (Cummings, 2011)
TISSUE COMPOSITION			

Adipose	Relative Volume of Wet Tissue (%)-		
	EW	14.1	In-house analysis
	IW	3.9	based on (Poulin
	NL	79	and Theil, 2002).
	NP	0.2	
	Subcellular	0	
	AP (mg/g)	0.4	(Rodgers et al.,
	Binding Proteins-		2005)
	KP_{ALB}	0.037	(Rodgers and
	KP_{LPP}	0.068	Rowland, 2006)
	Tissue volume fold scalar	1	
	IW pH[2]-		
	Local	7	(Coffey and De
	Subcellular	5	Duve, 1968)
	Membrane Potential (mV)-		(Roos and Boron,
	Local	-41	1981)
	Subcellular	10	(Van Dyke, 1988)
	Ve (fraction tissue volume)	0.001925	
Bone	Relative Volume of Wet Tissue (%)-		
	EW	9.8	In-house analysis
	IW	34.1	based on (Poulin
	NL	7.4	and Theil, 2002).
	NP	0.11	
	Subcellular	0	
	AP (mg/g)	0.67	(Rodgers et al.,
	Binding Proteins-		2005)
	KP_{ALB}	0.1	(Rodgers and
	KP_{LPP}	0.05	Rowland, 2006)
	Tissue volume fold scalar	1	
	IW pH[2]-Local	7	(Coffey and De
	Subcellular	5	Duve, 1968)
	Membrane Potential (mV)-		(Roos and Boron,
	Local	-41	1981)
	Subcellular	10	(Van Dyke, 1988)
	Ve (fraction tissue volume)	0.001375	
Brain	Relative Volume of Wet Tissue (%)-		
	EW	9.2	In-house analysis
	IW	67.8	based on (Poulin
	NL	5.1	and Theil, 2002).
	NP	5.65	
	Subcellular	0	
	AP (mg/g)	0.4	(Rodgers et al.,
	Binding Proteins-		2005)
	KP_{ALB}	0.048	(Rodgers and
	KP_{LPP}	0.041	Rowland, 2006)
	Tissue volume fold scalar	1	
	IW pH[2]-		(Shen et al.,
	Local	7.12	2004)
	Subcellular	5	(Coffey and De
			Duve, 1968)
	Membrane Potential (mV)-		(Roos and Boron,
	Local	-41	1981)
	Subcellular	10	

	Ve (fraction tissue volume)	0.0025	(Van Dyke, 1988)
Gut	Relative Volume of Wet Tissue (%)-		
	EW	26.7	
	IW	45.1	In-house analysis
	NL	4.87	based on (Poulin
	NP	1.63	and Theil, 2002).
	Subcellular	0	
	AP (mg/g)	2.84	
	Binding Proteins-		
	KP_{ALB}	0.158	
	KP_{LPP}	0.141	(Rodgers and
	Tissue volume fold scalar	1	Rowland, 2006)
	IW pH[2]-		
	Local	7	
	Subcellular	5	(Coffey and De
	Membrane Potential (mV)-		Duve, 1968)
	Local	-41	(Roos and Boron,
	Subcellular	10	1981)
	Ve (fraction tissue volume)	0.001375	(Van Dyke, 1988)
Heart	Relative Volume of Wet Tissue (%)-		
	EW	31.3	In-house analysis
	IW	44.5	based on (Poulin
	NL	1.15	and Theil, 2002).
	NP	1.66	
	Subcellular	0	
	AP (mg/g)	3.07	
	Binding Proteins-		
	KP_{ALB}	0.157	(Rodgers and
	KP_{LPP}	0.16	Rowland, 2006)
	Tissue volume fold scalar	1	
	IW pH[2]-		
	Local	7	(Coffey and De
	Subcellular	5	Duve, 1968)
	Membrane Potential (mV)-		(Roos and Boron,
	Local	-41	1981)
	Subcellular	10	(Van Dyke, 1988)
	Ve (fraction tissue volume)	0.001155	
Kidney	Relative Volume of Wet Tissue (%)-		
	EW	28.3	
	IW	50	In-house analysis
	NL	2.07	based on (Poulin
	NP	1.62	and Theil, 2002).
	Subcellular	1	
	AP (mg/g)	2.48	(Logan et al.,
	Binding Proteins-		2013)
	KP_{ALB}	0.13	
	KP_{LPP}	0.137	(Rodgers and
	Tissue volume fold scalar	1	Rowland, 2006)
	IW pH[2]-		
	Local	7.2	
			(Dudley and
	Subcellular	5	Brown, 1995)

	Membrane Potential (mV)- Local Subcellular Ve (fraction tissue volume)	 -70 10 0.001925	(Coffey and De Duve, 1968) (Roos and Boron, 1981) (Van Dyke, 1988)
Liver	Relative Volume of Wet Tissue (%)- EW IW NL NP Subcellular AP (mg/g) Binding Proteins- KP_{ALB} KP_{LPP} Tissue volume fold scalar IW pH[2]- Local Subcellular Membrane Potential (mV)- Local Subcellular Ve (fraction tissue volume)	 16.5 58.6 3.48 2.52 1 5.09 0.086 0.161 1 7 5 -41 10 0.001375	In-house analysis based on (Poulin and Theil, 2002). (Logan et al., 2013) (Rodgers and Rowland, 2006) (Coffey and De Duve, 1968) (Roos and Boron, 1981) (Van Dyke, 1988)
Lung	Relative Volume of Wet Tissue (%)- EW IW NL NP Subcellular AP (mg/g) Binding Proteins- KP_{ALB} KP_{LPP} Tissue volume fold scalar IW pH[2]- Local Subcellular Membrane Potential (mV)- Local Subcellular Ve (fraction tissue volume)	 34.8 46.3 0.3 0.9 1 0.5 0.212 0.168 1 6.7 5 -41 10 0.0050985	In-house analysis based on (Poulin and Theil, 2002). (Logan et al., 2013) (Rodgers and Rowland, 2006) (Effros and Chinard, 1969) (Coffey and De Duve, 1968) (Roos and Boron, 1981) (Van Dyke, 1988)
Muscle	Relative Volume of Wet Tissue (%)- EW IW NL NP Subcellular AP (mg/g) Binding Proteins-	 9.1 66.9 2.38 0.72 0 2.49	In-house analysis based on published data including (Poulin and Theil, 2002) & (Bergstrom et al., 1974).

	KP_{ALB} KP_{LPP} Tissue volume fold scalar IW pH[2]- Local Subcellular Membrane Potential (mV)- Local Subcellular Ve (fraction tissue volume)	0.034 0.059 1 7 5 -41 10 0.001375	(Rodgers and Rowland, 2006) (Coffey and De Duve, 1968) (Roos and Boron, 1981) (Van Dyke, 1988)
Pancreas	Relative Volume of Wet Tissue (%)- EW IW NL NP Subcellular AP (mg/g) Binding Proteins- KP_{ALB} KP_{LPP} Tissue volume fold scalar IW pH[2]- Local Subcellular Membrane Potential (mV)- Local Subcellular Ve (fraction tissue volume)	 12 66.4 4.1 0.93 0 1.67 0.06 0.06 1 7 5 -41 10 0.001375	(Rodgers and Rowland, 2006) (Kawai et al., 1994) (Coffey and De Duve, 1968) (Roos and Boron, 1981) (Van Dyke, 1988)
Skin	Relative Volume of Wet Tissue (%)- EW IW NL NP Subcellular AP (mg/g) Binding Proteins- KP_{ALB} KP_{LPP} Tissue volume fold scalar IW pH[2]- Local Subcellular Membrane Potential (mV)- Local Subcellular Ve (fraction tissue volume)	 62.3 9.47 2.84 1.11 0 1.32 0.277 0.096 1 7 5 -41 10 0.00275	In-house analysis based on (Poulin and Theil, 2002). (Rodgers et al., 2005) (Rodgers and Rowland, 2006) (Coffey and De Duve, 1968) (Roos and Boron, 1981) (Van Dyke, 1988)
Spleen	Relative Volume of Wet Tissue (%)- EW IW NL NP	 20.8 57.9 2.01 1.98	In-house analysis based on (Poulin and Theil, 2002).

	Subcellular AP (mg/g) Binding Proteins- KP_{ALB} KP_{LPP} Tissue volume fold scalar IW pH[2]- Local Subcellular Membrane Potential (mV)- Local Subcellular Ve (fraction tissue volume)	0 2.81 0.097 0.207 1 7 5 -41 10 0.001375	 (Rodgers et al., 2005) (Rodgers and Rowland, 2006) (Coffey and De Duve, 1968) (Roos and Boron, 1981) (Van Dyke, 1988)
Plasma	Relative Volume of Wet Tissue (%)- EW IW NL NP AP (mg/g) Tissue volume fold scalar IW pH[2]- Local	 94.5 0 0.35 0.23 0.04 1 7.4	In-house analysis based on (Poulin and Theil, 2002). (Boon et al., 1969) (Rodgers et al., 2005)
RBC	Relative Volume of Wet Tissue (%)- EW IW NL NP AP (mg/g) Tissue volume fold scalar IW pH[2]- Local Membrane Potential (mV)- Local	 0 66.6 0.17 0.29 0.44 1 7.22 -10	In-house analysis based on published data including (Bollmann et al., 1979), (Rodgers et al., 2005) & (Boon et al., 1969)
TISSUE FLOW RATES			
Define Cardiac Output	Lua Script Cardiac Output Scalar	User defined Lua Script (See section 5). 1	
Tissue blood flow rates (% of cardiac output)	 Adipose Bone Brain Stomach & Oesophagus Small Intestine Villi Large Intestine Heart Kidney Liver (Arterial) Liver (Portal) Lung	**Male/Female** 5/8.5 5/5 12/12 1/1 10/11 6/6 4/5 4/5 19/17 6.5/6.5 19/21.5 100/100	(ICRP, 2002).

	Muscle Pancreas Skin Spleen Cervix Vagina Additional Organ SC Site	17/12 1/1 5/5 2/3 NA/0.15 NA/0.24 0.65/0.65 0.016/0.016	
Lymph Flow Rate (% total lymph flow)	Adipose Bone Brain Stomach & Oesophagus Heart Kidney Liver (Arterial) Lung Muscle Pancreas Skin Spleen Additional Organ SC Site	12.8 0 1.05 12 1 8.5 33 3 16 0.3 7.3 1 0 0.039	(Gill et al., 2016).
Lymph Flow Rate (pop rep) (L/h)	Adipose Bone Brain Stomach & Oesophagus Heart Kidney Liver (Arterial) Lung Muscle Pancreas Skin Spleen Additional Organ SC Site	0.0454908 0 0.00373167 0.0426476 0.00355397 0.0302087 0.117281 0.0106619 0.0568635 0.00106619 0.025944 0.00355397 0 0.000138605	
Time-dependent Small Intestine Blood Flow Fed/Fasted ratio	High Fat Fed/Fed/Low Fat Fed: Qmax Mean (CV %) Tmax (h) Mean (CV %) kQ (1/h) Mean (CV %) Cap on Portal Vein Blood Flow Fed/Fasted Ratio	 4 (20) 0.693147 (30) 1.25 (30) 10	(Rose et al., 2017).
BLOOD			
Blood Composition **Haematocrit (%)** **Alpha-1-acid-glycoprotein (g/L)**	Male Mean (CV %) Female Mean (CV %) Male Mean (CV %) Female Mean (CV %)	43 (6.5) 38 (7.1) 0.793 (23) 0.715 (24)	(ICRP, 2002). In-house meta-analysis based on published data

Albumin (g/L)	Male: C0 (Intercept) Male: C1 (Age) Male: C2 (BMI) Male: CV% Female: C0 (Intercept) Female: C1 (Age) Female: C2 (BMI) Female: CV% User-defined plasma binding component (µM) Male Mean (CV %) Female Mean (CV %)	50.34 -0.0575 -0.0738 10 49.38 -0.037 -0.1286 10 0 (0) 0 (0)	including (Blain et al., 1985). Analysis based on NHANES dataset 1999-2004 generated as part of a PhD thesis; (Baker, 2014).
Plasma Esterase Phenotype-Relative Abundances Compared to Wild Type and their associated Variance	Plasma ES EM Mean (CV %)	1 (30)	

2. Performance verification of the population against observed data

2.1. Physiological Parameters

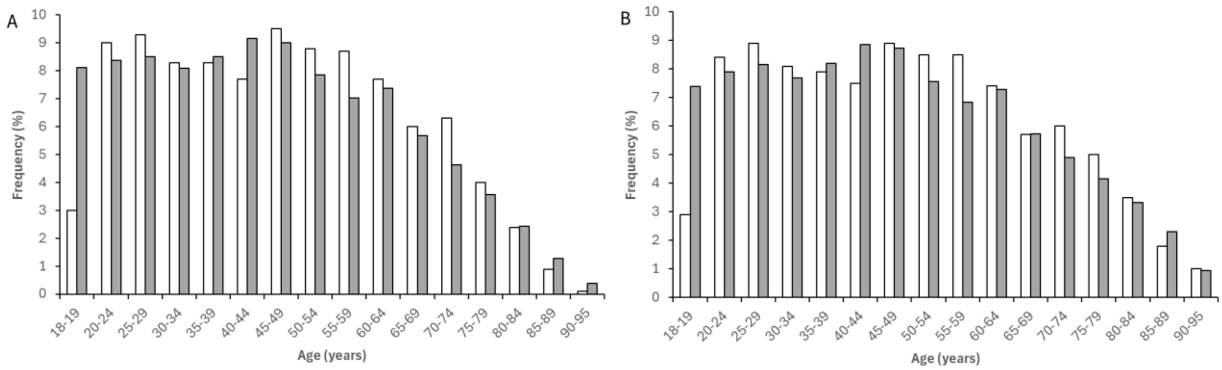

Figure 1: Age Distribution. (open bars; Simulated 10 trials x 100 North European Caucasians, 18-95 years, 100% male (A), 100% female (B)), and observed (closed bars) age distribution of the Sim-NEurCaucasian population. Observed data from are from the UK Office of National Statistics 2010 population estimates.

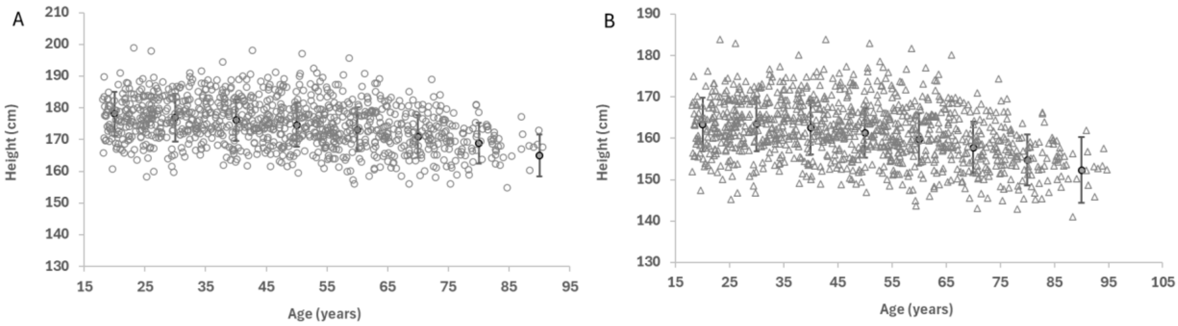

Figure 2: Height versus Age. Simulated (10 trials x 100 North European Caucasians, 18-95 years, 100% male (open circles) (A), 100% female (open triangles) (B)) and observed mean and standard deviation (male: closed circles, female: closed triangle) height (cm) of the Sim-NEurCaucasian population. Observed data are from the Health Survey for England 2008 and 2009.

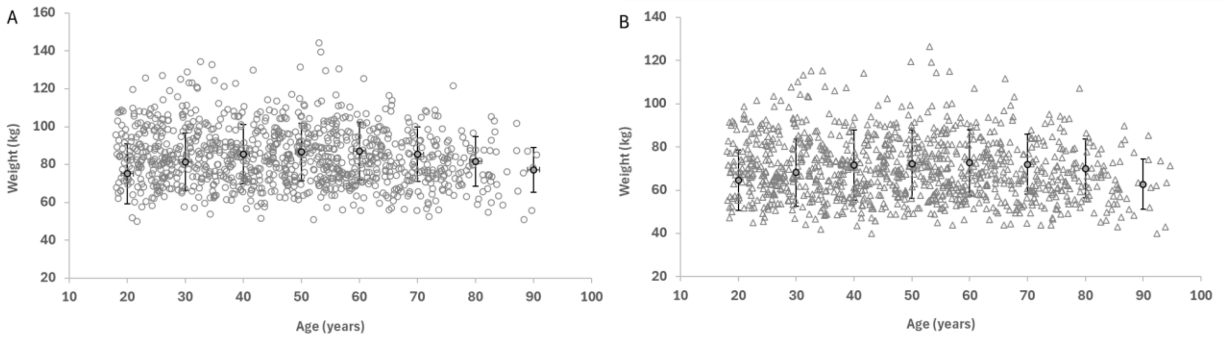

Figure 3: Weight versus Age. Simulated (10 trials x 100 North European Caucasians, 18-95 years, 100% male (open circles) (A), 100% female (open triangles) (B)) and observed mean and standard deviation (male: closed circles, female: closed triangle) weight (kg) of the Sim-NEurCaucasian population. Observed data are from the Health Survey for England 2008 and 2009.

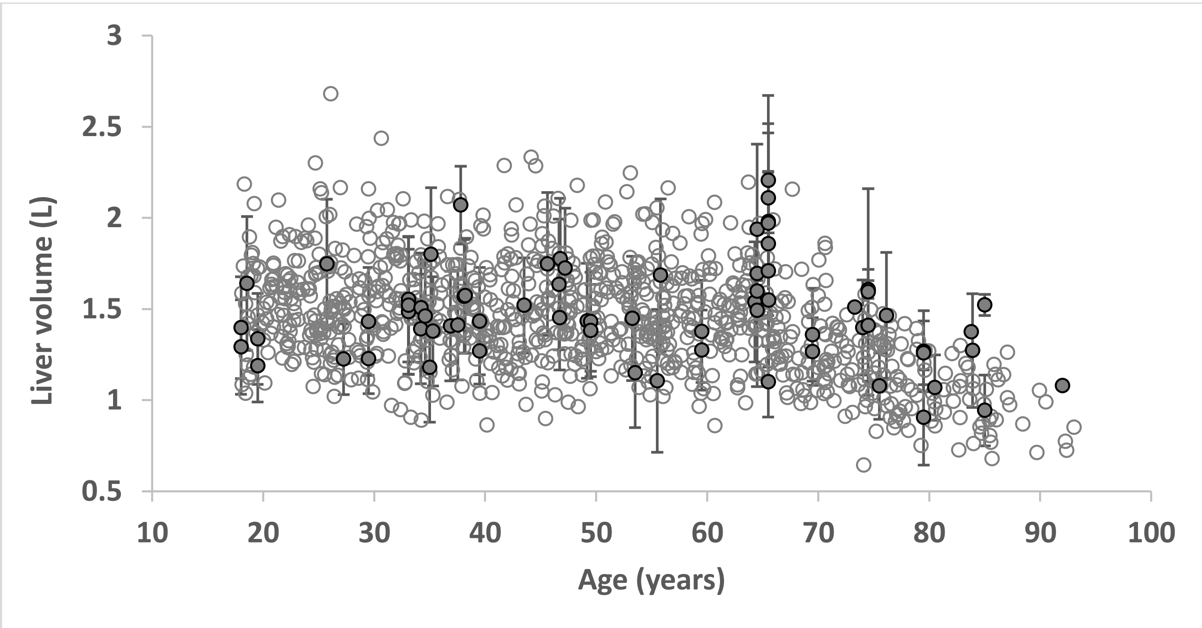

Figure 4: Liver volume versus Age. Simulated (10 trials x 100 North European Caucasians, 18-95 years, 50% females (open circles) and observed mean and standard deviation (closed circles) liver volume (L) of the Sim-NEurCaucasian population. Observed data are from Small *et al.,* 2017.

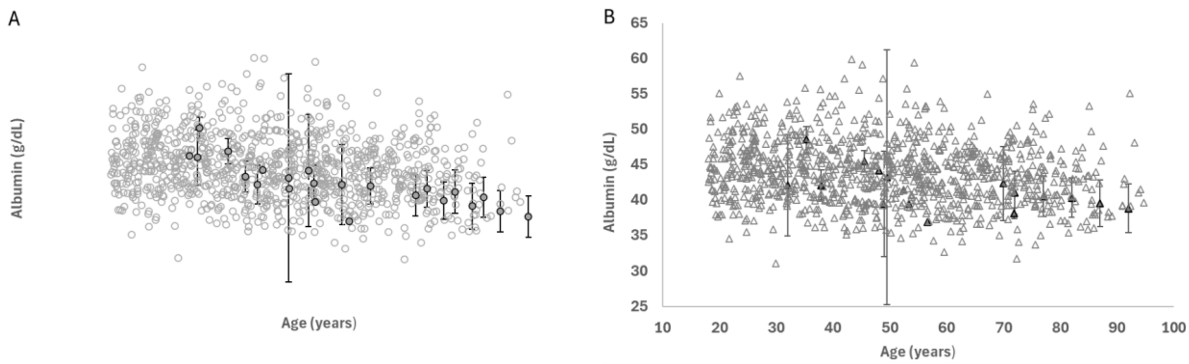

Figure 5: Serum Albumin versus Age. Simulated (10 trials x 100 North European Caucasians, 18-95 years, 100% male (open circles) (A), 100% female (open triangles) (B)) and observed mean and

standard deviation (male: closed circles, female: closed triangles) albumin levels (g/dl) of the Sim-NEurCaucasian population. Observed data are independent literature searches carried out in Mark Baker's PhD thesis (2003).

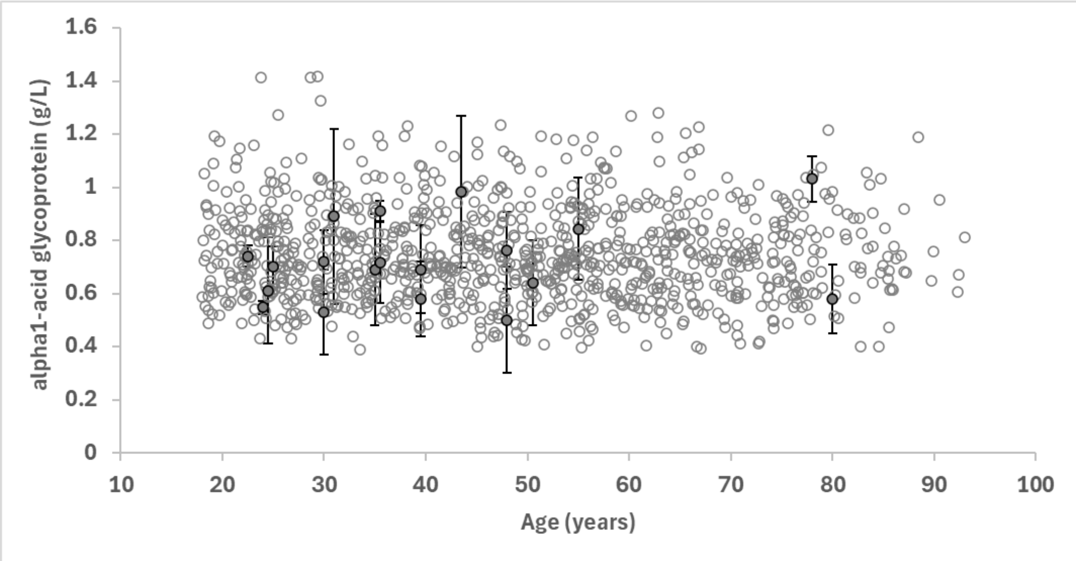

Figure 6: Alpha-1-acid glycoprotein versus Age. Simulated (10 trials x 100 North European Caucasians, 18-95 years, 50% females (open circles) and observed mean and standard deviation (closed circles) α-acid glycoprotein (g/L) of the Sim-NEurCaucasian population. Observed data are from a meta-analysis of published data including Veering et al., 1989 & Zini et al., 1990.

3. References illustrating performance verification of this population

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This paper describes the development and performance verification of the North European Caucasian population in Simcyp.

Plowchalk DR & Rowland-Yeo K. 2012. Prediction of drug clearance in a smoking population: Modeling the impact of variable cigarette consumption on the induction of CYP1A2. *European Journal of Clinical Pharmacology* 68(6), 951- 960.
This study used the North European Caucasian population within the Simcyp Simulator to predict the clearances of CYP1A2 substrates. It then derived estimates of CYP1A2 abundance as a function of daily cigarette consumption and use these values to predict the clearances of CYP1A2 substrates in smokers.

Chetty M, Mattison D, Rostami-Hodjegan A. 2012. Sex differences in the clearance of CYP3A4 substrates: Exploring possible reasons for the substrate dependency and lack of consensus. *Current Drug Metabolism* 13(6), 778-786.
The aim of the current study was to use *in vitro* data on a number of CYP3A4 substrates to develop mechanistic population pharmacokinetic models using the North European Caucasian population to estimate the statistical power of *in vivo* studies designed to discern sex differences in the clearance of CYP3A4 substrates.

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This study utilised the ADAM model of both the adult and paediatric North European Caucasian populations to predict the systemic exposure of different formulations of quetiapine.

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5. Lua Scripts

Cardiac Output:

```
function DefineCardiacOutput(age, WT, BSA)

   if age <= 25 then
      CO = BSA * (110 + (184.974*(math.exp(-0.0378 * age) - math.exp(-0.2477 * age))))
   else
      CO = BSA * 60 * (3 - 0.01 * (age - 20))
   end

   return CO
end
```