

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	Paramotor	Value	Sourco	
r opulation	Falameter	value	Source	
Characteristics				
DEMOGRAPHIC				
Age (years)	Maximum	95	Office for National	
	Minimum	18	Statistics in England	
			and Wales, 2002-	
Gender	Proportion of females	0.5	2010.	
Age Distribution	< 65 years	Uniform	In-house analysis	
	Prop Males < 65 y	0.82	based on data from	
	Prop Females < 65 y	0.784	Office for National	
	> 65 years	Weibull	Statistics in England	
	Male distribution parameter: α	5.47	and Wales, 2002-	
	Male distribution parameter: β	66.5	2010.	
	Female distribution parameter: α	5.22		
	Female distribution parameter: β	68.57		
Height (cm)	Male: height vs age (intercept)	176.87	In-house analysis	
	Male: height vs age (slope 1)	0.0743	based on Health	
	Male: height vs age (slope 2)	-0.0021	Survey for England	
	Male: height vs age (CV %)	3.95	2008-2009.	
	Female: height vs age (intercept)	161.39		
	Female: height vs age (slope 1)	0.1498		
	Female: height vs age (slope 2)	-0.0027		
	Female: height vs age (CV %)	4.09		
Weight (kg)	Male: weight vs height (intercept)	2.7208	In-house analysis	
	Male: weight vs height (slope 1)	0.0097	based on Health	
	Male: weight vs height (CV %)	16.7	Survey for England	
	Female: weight vs height		1998	
	(intercept)	2.936		
	Female: weight vs height (slope 1)	0.008		
	Female: weight vs height (CV %)	19.9		
			/ · · · -	
Body surface area	Height exponent	0.725	(Du Bois and Du	
(BSA)	Weight exponent	0.425	Bois, 1916)	
	C1 parameter	0.007184		
		FM/PM/IM/IIM		
CVP Phenotype	CVP1A2	1/0/0/0	In-house meta-	
Frequencies	CYP2A6	1/0/0/0	analysis based on	
requencies	CVP2B6	0.89/0.11/0/0	nublished data	
	CYP2C8	1/0/0/0	including (Crettal et	
		0.94/0.06/0/0		
		1/0/0/0	(Tamminga et al	
		0.59/0.092/0/0.318	1999). Lin et al	
		0.865/0.022/0/0.310	2002 & (Burk of al	
		1/0/0/0	2002 & (BUIK et al.,	
		1/0/0/0	2002].	
		1/0/0/0		
		0.12/0.88/0/0		
	CIP3A/	0.12/0.88/0/0		





CYP Genotype	CYP2C9 *1/*1	0.672	In-house meta-
Frequencies	CYP2C9 *1/*2	0.186	analysis based on
-	CYP2C9 *1/*3	0.111	published data
	CYP2C9 *2/*2	0.011	including (Yasar et
	CYP2C9 *2/*3	0.017	al 2002)
	CYP2C9 *3/*3	0.003	uii, 2002).
		0.005	
LIGT Phonotype			
		1/0/0/0	la haven mate
Frequencies	UGTIAS	1/0/0/0	m-nouse meta-
	UGTIA4	1/0/0/0	analysis based on
	UGTIAS	1/0/0/0	published data
	UGI1A6	1/0/0/0	including (Danoff et
	UGT1A7	1/0/0/0	al., 2004); (Cecchin
	UGT1A8	1/0/0/0	et al., 2009);
	UGT1A9	0.96/0.04/0/0	(Spierings et al.,
	UGT1A10	1/0/0/0	2007) & (Swanson
	UGT2B4	1/0/0/0	et al., 2007).
	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	
		_, _, _, _, _	
Cvtosolic Phenotype	User Cvt1	1/0/0/0	Default
Frea	User Cvt2	1/0/0/0	
	User Cvt3	1/0/0/0	
	User Cvt4	1/0/0/0	
		_, ;, ;, ;	
		ET/PT/IT/UT	
Transporter	ABCB1 (P-gn/MDR1)	1/0/0/0	
Phenotyne Fred	ABCB11 (BSEP)	1/0/0/0	
ATP Binding Cassette	ABCC1 (MPD1)	1/0/0/0	
Transporters		1/0/0/0	
mansporters		1/0/0/0	
	ABCC3 (IVIRPS)	1/0/0/0	
		1/0/0/0	
	ABCCD (INIRPO)		
	ABCG2 (BCRP)	0.81/0.02/0.17/0	
		ET /DT /IT /I IT	
Solute Carrier	SLC2A2 (GLU12)	1/0/0/0	In-nouse meta-
Transporters	SLC7A5 (LAT1)	1/0/0/0	analysis based on
	SLC29A1 (ENT1)	1/0/0/0	published data
	SLC29A2 (ENT2)	1/0/0/0	including (Donnelly
	SLC10A1 (NTCP)	1/0/0/0	et al., 2011,
	SLC10A1 (ASBT/IBAT)	1/0/0/0	Kobayashi et al.,
	SLC15A1 (PepT1)	1/0/0/0	2005).
	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)	0.5404/0.0549/0.4043/0.0004	
	SLC22A2 (OCT2)	1/0/0/0	
	SLC22A3 (OCT3)	1/0/0/0	
	SI C22A4 (OCTN1)	1/0/0/0	
	SI C22A6 (OAT1)	1/0/0/0	
	SIC22A7 (OAT2)	1/0/0/0	
	SIC22A8 (OAT3)	1/0/0/0	
		1/0/0/0	
	SLC2ZRJ (ORT7) SLC2ZRJ (MATE1)	1/0/0/0	
	Bonal SI CATAs (Bonal MATEs)	1/0/0/0	
	$SLCE1A/B(OST \alpha/B)$	1/0/0/0	
	SLCSIA/B (OSI-u/p)	1/0/0/0	
the surd office and	Circus side Loutslas (Lines)	4/0/0/0	Defeult
User-defined	Sinusoidal uptake (Liver)	1/0/0/0	Default
Transporters		1/0/0/0	
	Canalicular Efflux (Liver)	1/0/0/0	
	Apical Uptake (Kidney)	1/0/0/0	
	Basal Efflux (Kidney)	1/0/0/0	
	Apical Uptake (Intestine)	1/0/0/0	
	Apical Efflux (Intestine)	1/0/0/0	
	Basal Influx (Intestine)	1/0/0/0	
	Basal Efflux (Intestine)	1/0/0/0	
	Uptake (Tumour)	1/0/0/0	
	Efflux (Tumour)	1/0/0/0	
		EM/PM/IM/UM	In-house meta-
Esterase Phenotype	CES1	0.999/0.001/0/0	analysis based on
Freq	CES2	1/0/0/0	published data
	User ES	1/0/0/0	including
	Plasma ES	1/0/0/0	(Tarkiainen et al.,
			2012).
FMO Phenotype Freq	FM01	1/0/0/0	Default
	FMO3	1/0/0/0	
	FMO5	1/0/0/0	
	User FMO	1/0/0/0	
Gut Luminal	Sub>Primary Metabolite 1 Enzyme	1/0/0/0	Default
Phenotype	Primary Metabolite 1>Sub Enzyme	1/0/0/0	
Liver velume (L)	Moon	1 65056	(Johnson at al
	$PSA(m^2)$ coefficient	1.03030	
	BSA (m ²) ovperant	1.176	2005].
	BSA (III-) exponent	1.1/0	
	CV (%)	12	
Liver density (g/L)	Mean	1080	(Heinemann et al
Liver defisity (g/L)	Weath	1080	1999)
Hepatocellularity	HPGL mean (Older than 20)	117.515	(Barter et al., 2007).
(millions of cells/g)	HPGL mean (Younger than 20)	125	
(Baseline	3 103	
	Age coefficient	-0.655	
	CV (%) (Older than 20)	/1 9	
	CV(%) (Vounger than 20)	20	
		20	
	P450/10/10 Cells		l





	Baseline	3.034	
	HPGL Coefficient	-0.506	
Microsomal Protein	MPPGL mean	39.7907	(Barter et al., 2008).
(mg/g)	Baseline	1.407	· · · ·
(Age coefficient C1	0.01579	
	Age coefficient C2	-0.0003824	
	Age coefficient C3	0.00000237	
	Age coefficient co	26.0	
		20.9	
Cutocolio Duotoin	CDDCI maan	81 0330	
	CPPGL mean	81.0329	in-nouse meta-
(mg/g)	Baseline	28.8945	analysis based on
	Correlation coefficient	1.31032	Unpublished data
	CV (%)	21.467	generated as part
			of a PhD thesis.
S9 Protein (mg/g)	S9PPGL Mean	120.824	(Barter, 2006).
	User S9PPGL Mean	95.0596	
	CV (%)	30	
Enterohepatic	% Hepatic Bile Entering Gallbladder		
Recirculation	Mean	70.3	(Shaffer et al.,
Original Model	CV (%)	32.1	1980)
	Gallbladder Release Constant (1/h)		,
	Easted Mean	0.18	(Degen et al
	Easted CV (%)	30	2006)
	Fed Mean	0.48	2000).
	End CV (%)	10	
	INANC Cycle Time (b) Mean	1 5	(Schmidt at al
	INIVIC Cycle Time (II) Mean	1.55	
	INIVIC Cycle Time (n) CV (%)	55	1996).
	Galibladder Emptied at % of IMMC	30	
	Gallbladder Residual Volume (%)		
	Fasted Mean	79.4	(Ellenbogen et al.,
	Fasted CV (%)	13.1	1988).
	Fed Mean	59.9	
	Fed CV (%)	39.6	
Advanced Dynamic	Duration of IMMC Cycle (h)		In-house meta-
Bile Salt Model	Antral Origin Mean	2.6	analysis based on
(ADBSM)	Antral Origin CV (%)	30	published data
ADBSM IMMC	Duodenal Origin Probability (%)	60	including
Parameters	Duodenal Origin Mean	1.3	(Luiking et al.,
	Duodenal Origin CV (%)	60	1998)
	Duodenal Origin Probability (%)	40	
ADBSM Liver	Hepatic Total Bile Secretion Rate		
Parameters	Fasted Mean (mmol/h)	0.19	(van Berge
	Easted CV (%)	69	Henegouwen and
	Fed Mean (mmol/b)	1 33	Hofmann 1978)
	Eed CV (%)	15	1011111, 1970j.
	% Hopatic Pilo Entering Callbladder	<u>ر</u> ۲	
	Moon	70.2	(Shaffar at al
		70.3	
		32	1980).
	Bile Salt weighted Mean MWt	400	
	(g/mol)	400	
			1





ADBSM Gallbladder	Gallbladder Residual Volume (%)		
Parameters	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-
	Fed Mean	30.67	analysis based on
	Fed CV	48	nublished data
	Maximal Gallbladder Volume		including
	Mean (ml)	18.8	(Portincasa et al
	CV(%)	52	(FOITINGasa et al.,
	Duration of gallbladdor omptying	- 55	(Palassiano et al
			(Falasciario et al.,
	(II) Fod Moon	1 17	1992)
	Fed ()(1.17	
	Fed CV	57	
Bile Salts Absorption	Absorption Rate (mmol/h/mM)		
Passive	Jejunum I – II	0.42	(Krag and Phillips,
	CV (%)	14	1974).
	lleum I – IV	0	
	CV (%)	30	
	Colon	0.0565	(Mekhjian et al.,
	CV (%)	30	1979).
Active	Jmax (mmol/h)		/
	Jeiunum I – II	0	(Krag and Phillips.
	CV (%)	30	1974).
	lleum I – IV	2.48	- ,
	CV (%)	20	
	Colon	0	
	CV (%)	30	
	Km (mM)		
	leiunum I – II	0	
	CV (%)	30	
	lleum I – IV	0.6	
	CV (%)	33	
	Colon	0	
	CV (%)	30	
Bile fraction available	Jeiunum I	0.15	(Riethorst et al.,
for absorption-	leiunum II	0.15	2016)
Passive	lleum I	0	2010).
	lleum II	0	
	lleum III	0	
	lleum IV	0	
	Colon	1	
Active			
Active	leiunum II	0	
	lleum l	0	
	lleum II	0	
	lleum III	0.05	
	lleum IV	0.05	
	Colon	0.05	





Average Baseline Bile	Stomach	1	
Salts Concentration:	Duodenum	1	
CMC (mM)	Jejunum I	1	
	Jejunum II	1	
	lleum I	1	
	lleum II	1	
	lleum III	1	
	lleum IV	1	
	Colon	1	
Bile (mM)	Stomach	0.34	
	CV (%)	134	In-house meta-
	Duodenum	3 31	analysis based on
	CV (%)	97	nublished data
		23	including
		100	(Schindlbeck et al
		3 55	1987). (Perez de la
		42	Cruz Moreno et al
		1 25	2006)
		20	8. (Diakidou et al
		1 25	
		1.25	2009)
		30	
		1.25	
		30	
		1.25	
	CV (%)	30	
	Colon	0.12	
	CV (%)	103.56	
	Stomach Bile Salts Concentration		
	Fed State (mM)	0.34	
	CV (%)	216.7	
		52 (67)	
CYP Phenotype	CYP1A2 Mean EM (CV %)	52 (67)	
Enzyme Abundances	CYP2A6 Mean EM (CV %)	20 (173)	In-nouse meta-
(pmol/mg protein)	CYP2B6 Mean EM (CV %)	17 (122)	analysis based on
	CYP2B6 Mean PM (CV %)	6 (200)	published data
	CYP2C8 Mean EM (CV %)	24 (81)	including (Rowland-
	CYP2C9 Mean EM (CV %)	73 (54)	Yeo et al., 2004);
	CYP2C9 Mean PM (CV %)	29 (73)	(Hofmann et al.,
	CYP2C18 Mean EM (CV %)	1 (106)	2008); (Haberl et
	CYP2C19 Mean EM (CV %)	4.4 (71)	al., 2005) & (Cubitt
	CYP2C19 Mean UM (CV %)	8.7 (71)	et al., 2011).
	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	Baseline CYP3A5	62.775	
correlation	Correlation coefficient	0.3934	(Barter et al., 2010)
	CYP3A5 CV (%)	24	





Difference in	Male Mean (CV %)	126 (35%)	Default inactive
male/female CYP3A4	Female Mean (CV%)	183 (29%)	Deraute materive
contents		103 (2370)	
contents			
CYP Turnover rate	CYP1A2 Mean (CV %)	0 0183 (56)	(Yang et al. 2008)
constant (1/b)	CVP2A6 Mean $(CV %)$	0.0267 (56)	(1011g ct 01., 2000)
	CVP2P6 Moon $(CV %)$	0.0207 (50)	
	CVP2C8 Moon $(CV %)$	0.0217 (50)	
	CVP2C0 Mean $(CV %)$	0.0301 (30)	
	CYP2C18 Maan (CV %)	0.0007 (50)	
		0.0267 (56)	
		0.0207 (56)	
	CYP2D6 Mean (CV %)	0.0099 (56)	
		0.0176 (63)	
		0.0194 (56)	
	CYP3A4 Mean (CV %)	0.0193 (68)	
	CYP3A5 Mean (CV %)	0.0193 (68)	
	CYP3A7 Mean (CV %)	0.019 (68)	
CVP Genetyme	CVP2CQ *1/*1 Mean (CV/ %)	83 4 (60 5)	In-house moto
Abundance (nmol/mg	CVP2C0 *1/*2 Moon (CV %)	75 9 (62 9)	analysis based on
Abunuance (phioi/ing	CVP2C0 *1/*2 Mean (CV %)	75.8 (05.8)	allalysis based off
protein)	CYP2C9 *1/*3 Mean (CV %)	75.8 (63.8)	published data
	CYP2C9 *2/*2 Mean (CV %)	75.8 (63.8)	
	CYP2C9 *2/*3 Mean (CV %)	75.8 (63.8)	al., 2002).
	CYP2C9 *3/*3 Mean (CV %)	23 (60)	
UGT Phenotype	UGT1A1 FM Mean	48	In-house meta-
Absolute LIGT	UGT1A3 FM Mean	23	analysis based on
Abundance (nmol/mg	UGT1A4 FM Mean	52	nublished data
nrotein)	UGT1A5 FM Mean	0	including (Harbourt
protein	UGT1A6 EM Mean	20	et al 2012) and
	UGT1A7 FM Mean	0	unnublished data
	UGT1A8 FM Mean		from the Simcyn
	LIGT1A9 FM Mean	31	Consortium LIGT
	UGT1A10 FM Mean	0.02	focused group
	LIGT2B4 FM Mean	54	(2013)
	UGT2B7 EM Mean	71	(2020).
	UGT2B10 FM Mean	65	
	UGT2B11 EM Mean	0	
	UGT2B15 FM Mean	39	
	UGT2B17 EM Mean	5.9	
	UGT2B28 EM Mean	0	
	User UGT1 EM Mean	0	
Relative UGT	UGT1A1 EM Mean (CV %)	1 (24)	In-house meta-
Abundances	UGT1A1 PM Mean (CV %)	0.42 (50.8)	analysis based on
	UGT1A1 IM Mean (CV %)	0.72 (39.9)	published data
	UGT1A1 UM Mean (CV %)	1.46 (30)	including (Peterkin
	UGT1A3 EM Mean (CV %)	1 (36)	et al., 2007);
	UGT1A4 EM Mean (CV %)	1(26)	(Villeneuve et al.,
	UGT1A5 EM Mean (CV %)	1 (30)	2003) & (Swanson
	UGT1A6 EM Mean (CV %)	1 (30)	et al., 2007).
	UGT1A7 EM Mean (CV %)	1 (30)	
	UGT1A8 EM Mean (CV %)	1 (30)	
	UGT1A9 EM Mean (CV %)	1 (30)	





	UGT1A9 PM Mean (CV %)	0.07 (30)	
	UGT1A9 IM Mean (CV %)	0.19 (30)	
	UGT1A10 EM Mean (CV %)	1 (30)	
	UGT2B4 EM Mean (CV %)	1 (28)	
	UGT2B7 EM Mean (CV %)	1 (30.4)	
	UGT2B10 EM Mean (CV %)	1 (30)	
	UGT2B11 EM Mean (CV %)	1 (30)	
	UGT2B15 EM Mean (CV %)	1 (34)	
	UGT2B15 PM Mean (CV %)	0.07 (33)	
	UGT2B15 IM Mean (CV %)	0.47 (37)	
	UGT2B17 EM Mean (CV %)	1 (28)	
	UGT2B17 PM Mean (CV %)	0.08 (40)	
	UGT2B17 IM Mean (CV %)	0.16 (30)	
	UGT2B28 EM Mean (CV %)	1 (30)	
	User UGT1 EM Mean (CV %)	1 (30)	
		1 (00)	
UGT Turnover rate	UGT1A1 Mean (CV %)	0.0578	(Emietal 2002) &
(1/h)	UGT1A3 Mean (CV %)	1F-06	(Ohnishi and Emi
(-/)	UGT1A4 Mean (CV %)	1F-06	2003)
	UGT1A5 Mean (CV %)	1E-06	2003).
	UGT1A6 Mean (CV %)	1F-06	
	UGT1A7 Mean (CV %)	15-06	
	UGT1A8 Mean (CV %)	1E-06	
	UGT1A9 Mean (CV %)	15-06	
	LIGT1A10 Mean (CV %)	15-06	
	UGT2B4 Mean (CV %)	1E-06	
	UGT2B7 Mean (CV %)	15-06	
	UGT2B10 Mean (CV %)	1E-06	
	LIGT2B11 Mean (CV %)	15-06	
	LIGT2B15 Mean (CV %)	15-06	
	LIGT2B17 Mean (CV %)	15-06	
	LIGT2B28 Mean (CV %)	15-06	
	User LIGT1 EM ($CV\%$)	15-06	
		11-00	
Cytosolic Phenotyne	User Cvt1 FM Mean (CV %)	1 (30)	Default
Relative Abundances	User Cyt2 EM Mean (CV %)	1 (30)	Delault
compared to wild type	User Cyt2 EM Mean (CV %)	1 (30)	
and their associated	User Cyt4 EM Mean (CV %)	1 (30)	
variance	User Cyte Ein Mean (CV 70)	1 (30)	
Transporter	ABCB1 (P-gp/MDB1) Mean	0 246	(Rachumallu et al
Phenotyne	ABCB11 (BSEP) Mean	1	2020)
	ABCC2 (MRP2) Mean	0.59	2020)
(pmol/10 ⁶	ABCC3 (MRP3) Mean	0.239	
henatocytes)	ABCC4 (MRP4) Mean	0	
neputocytes/	ABCC6 (MRP6) Mean	0 214	
	ABCG2 (BCRP) Mean	0 103	
	SIC29A1 (FNT1) Mean	0.0646	
	SIC29A2 (ENT2) Mean	0	
	SIC10A1 (NTCP) Mean	0.647	
	SIC16A1 (MCT1) Mean	0.638	
	SICO1B1 (OATP1B1) Maan	3 1	
	SICO1B3 (OATP1R3) Mean	3.08	
	SLCO2B1 (OATP2B1) Mean	1 18	
	SLC22A1 (OCT1) Mean	1 27	
	JLCZZAT (UCIT) WEAL	1.21	1





	SLC22A7 (OAT2) Mean	1.25	
	SLC22A9 (OAT7) Mean	1.45	
	SLC47A1 (MATE1) Mean	0.146	
	SLC51A/B (OST- α/β) Mean	0	
	Sinusoidal uptake Mean	0	
	Sinusoidal Efflux Mean	0	
	Canalicular Efflux Mean	0	
Relative Abundance	ABCB1 (P-gp/MDR1) FT	1 (59)	(Rachumallu et al.,
Compared to Wild	ABCB11 (BSEP) FT	1 (131)	2020)
Type and their	ABCC2 (MRP2 FT	1 (88)	,
associated Variance	ABCC3 (MRP3) FT	1 (65)	
	ABCC4 (MRP4) FT	1 (60)	
	ABCC6 (MRP6) FT	1 (46)	
	ABCG2 (BCRP) FT	1 (30)	
	ABCG2 (BCRP) PT	0 37 (30)	
	ABCG2 (BCRP) IT	0.67 (30)	
	SI C29A1 (FNT1) FT	1 (49)	
	SIC29A2 (ENT2) ET	1 (60)	
	SIC10A1 (NTCP) FT	1 (50)	
	SIC16A1 (MCT1) FT	1 (60)	
	SICO1B1 (OATP1B1) FT	1 (73)	
	SICO1B1 (OATP1B1) PT	0 37 (30)	
		0.68 (52)	
	SICO1B1 (OATP1B1) IIT	1 39 (62)	
	SICO1B3 (OATP1B3) FT	1 (89)	
	SLCO2B1 (OATP2B1) ET	1 (62)	
	SICO2DI (OCT1) ET	1(02)	
	SIC22A1 (OCT1) ET	1(44)	
		0.01(44)	
		1 14 (44)	
	SIC22AT (OCT1) OT	1 (75)	
	SIC22A7 (OAT2) ET	1 (51)	
	SLC2ZAG (OAT7) LT	1 (51)	
	SLC47AI (MATEI) ET	1 (51)	
	Sicusoidal untake ET	1(00)	
		1(0)	
	Canalicular Efflux ET	1(0)	
		1(0)	
Esterase Phenotyne	CES1 EM Mean (CV %)	1 (46)	In-house meta-
Relative Abundances	CEST PM Mean (CV %)	1 (+0)	analysis based on
Compared to Wild	CES2 FM Mean (CV %)	1 (35)	nublished data
Type and their	User FS Mean (CV %)	1 (30)	including (Ross et
associated Variance		1 (50)	al 2012)
associated variance			al., 2012).
FMO Phenotype	FMO1 EM Mean	0	In-house meta-
Absolute FMO	FMO3 FM Mean	30	analysis based on
Abundance (pmol/mg	FMO5 EM Mean	25	published data
protein)	User FMO EM Mean	0	including (Haining
/			et al., 1997)
Relative FMO	FMO1 EM Mean (CV %)	1 (30)	- , ,
Abundances	FMO3 EM Mean (CV %)	1 (50)	
	FMO5 EM Mean (CV %)	1 (55)	
	UserFMO EM Mean (CV %)	1 (30)	





KIDNEY			
Serum creatinine	Males (< 61 years) Mean	76.5	In-house meta-
(µmol/L)	Males (< 61 years) CV (%)	16.1	analysis based on
	Males (> 61 years) Mean	81.2	NHANES 1999-2004
	Males (< 61 years) CV1 (%)	27.4	dataset
	Males (< 61 years) CV2 (%)	21.2	
	Females (< 48 years) Mean	57	
	Females (< 48 years) CV (%)	20.4	
	Females (> 48 years) Mean	66.2	
	Females (> 48 years) CV1 (%)	26.5	
	Females (> 48 years) CV2 (%)	22.8	
	Females (> 78 years) Mean	79.5	
	Females (> 78 years) CV1 (%)	38.3	
	Females (> 78 years) CV2 (%)	31.6	
GFR (ml/min/1.73m ²)	GFR Prediction	Method 1 (default selected)	(Cockcroft and Gault, 1976).
		Method 2 (default not	(Levev et al., 2000)
		selected)	
GFR Cap	Less than	400	
	Greater than	15	
	Reference value (males)	130	
	Reference value (females)	120	
	GFR age limit	140	
Kidney Size	Baseline:	15.4	(Price et al., 2003).
Parameters	Body weight coefficient:	2.04	
	Body height coefficient:	51.8	
	CV (%):	23.4	
	Kidney density (g/L)	1050	(ICRP, 2002).
S9 Protein (mg/g)	S9PPGK Mean	12.8	(Al-Jahdari et al
55 Hotelli (116/ 5/	User S9PPGK Mean	0	2006)
	CV (%)	30	
Microsomal Protein	MPPGK Mean	12.8	
(mg/g)	CV (%)	55	
Cytosolic Protein	CPPGK Mean	0	
(mg/g)	CV (%)	30	
UGT Phenotype	UGT1A1 Mean	6.1	In-house meta-
Absolute UGT	UGT1A3 Mean	0	analysis based on
Abundance (pmol/mg	UGT1A4 Mean	8.7	published data
protein)	UGT1A5 Mean	0	including (Harbourt
	UGT1A6 Mean	3.6	et al., 2012) and
	UGT1A7 Mean	13	unpublished data
	UGT1A8 Mean	4.9	from the Simcyp
	UGT1A9 Mean	79	Consortium UGT
	UGT1A10 Mean	17	focused group
	UGT2B4 Mean	0.3	(2013).
	UGT2B7 Mean	48	
	UGT2B10 Mean	0	
	UGT2B11 Mean	0	
	UGI2B15 Mean	0.2	
	UGI2B17 Mean	0	
	UG12B28 Mean	U	





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





	Basolateral Efflux (kidney) Mean	1 (60)	
	(CV %)		
		PT-S1/PT-S2/PT-S3	
Relative Abundances	ABCB1 (P-gp) ET Mean (CV %)	1/1/1	(Neuhoff et al.,
along the Proximal	ABCC4 (MRP4) ET Mean (CV %)	1/1/1	2013).
Tubular Cells	SLC22A2 (OCT2) ET Mean (CV %)	1/1/1	
compared to segment	SLC22A6 (OAT1) ET Mean (CV %)	1/1/1	
1 values	SLC22A8 (OAT3) ET Mean (CV %)	1/1/1	
	SLC47As (MATEs)	1/1/1	
	Apical Influx (kidney)	1/1/1	
	Basolateral Efflux (kidney)	1/1/1	
Cytosolic Phenotype	User Cyt1 EM Mean (CV %)	1 (30)	
Relative Abundances	User Cyt2 EM Mean (CV %)	1 (30)	
compared to wild type	User Cyt3 EM Mean (CV %)	1 (30)	
and their associated	User Cyt4 EM Mean (CV %)	1 (30)	
variance			
Esterase Phenotype	CES1 EM Mean (CV %)	1 (30)	In-house meta-
Relative Abundances	CES1 PM Mean (CV %)	0.11 (30)	analysis based on
Compared to Wild	CES2 EM Mean (CV %)	1 (30)	published data
Type and their	User ES Mean (CV %)	1 (30)	including (Zhu and
associated Variance			Markowitz, 2009).
Absolute EMO	EMO1 EM Mean	5	In-house meta-
Abundance (nmol/mg	FMO3 FM Mean	0.47	analysis based on
nrotein)	EMOS EM Mean	2.6	nublished data
proteiny	Liser FMO Mean	0	including (Krause et
FMO Phenotype	FMO1 FM Mean (CV %)	1 (35)	al 2003)
Relative Abundances	FMO3 FM Mean (CV %)	1 (79)	, 2000,
Compared to Wild	FMO5 EM Mean (CV %)	1 (57)	
Type and their	User FMO Mean (CV %)	1 (30)	
associated Variance		- ()	
Mech KiM Parameters	Cortex/Medulla ratio	0.92	(Neuhoff et al.,
Kidney Volume	Peritubular Capillary (% volume)	7	2013).
Million Nephrons per	Average value of a 25 year-old male	1.61513	In-house meta-
Subject	Baseline	0.22693	analysis based on
	Kidney weight coefficient	0.003948	published data
			Including (Hoy et
Nonbron neverators	Brovinal Tubula:		di., 2003).
Nephron parameters	Proximal Tubule:	10	(Nouhoff at al
	Diamator (mm)	18	(Neunon et al.,
			2013).
	Honlo' Loon:	7.4	
	Length (mm)	7	
	Diameter (mm)	, 0.018	
	nH in Tubule	74	
	Distal Tubule:	/ · · · ·	
	Length (mm)	5 5	
	Diameter (mm)	0.05	
	pH in Tubule	7.4	
	Collecting Duct:		
	Length (mm)	22	





	Diame pH in	eter (mm) Tubule	0.2 7.4		
Urine flow rate within nephron (ml/min/1.73m ²)	Proxin Henle Distal Collec Bladd	mal Tubule (Male/Female) [?] Loop (Male/Female) Tubule (Male/Female) ting Duct (Male/Female) er (Male/Female)	130/12 46.77/ 25.97/ 12.44/ 1/1	20 (43.23 (24.03 (11.56	(Neuhoff et al. <i>,</i> 2013).
Proximal Tubular Cells PTCPGK	Millio Mean CV (%	ns of cells/g Kidney :):	60 30		(Neuhoff et al. <i>,</i> 2013).
Proportion of Blood Bypass	Bypas blood Mean Bypas tubula Mean	is before glomerulus (% Renal flow) (CV %): is to Henle's Loop (% Proximal ar blood flow) (CV %):	10 (30 20 (30)	(Hulin, 1997).
Parameters for the mechanistic filtration model	Fracti accou Small Large Hydrc across Colloi across Clp	on of hydraulic conductance inted for by large pores pore radius (nm) pore radius (nm) ostatic pressure difference s the glomerulus (mm Hg) d osmotic pressure difference s the glomerulus (mm Hg)	0.0583 4.4 6.11 40 24.930 141)4	In-house analysis based on (Ohlson et al., 2001) & (Blouch et al., 1997).
	CLmem		129.2		
		GI TRAC	Т		
Gastrointestinal Attribu Mean gastric residence (h)	tes time	Stomach Fasted Mean (CV %) Stomach Fed Mean (CV %) Small intestine Weibull param α β Mean Colon Mean (CV %)	eters	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 Mea %) Stomach Fasted MRT Mean (C	n (CV 0 (0) V %) 0.27 (36)		In-house meta- analysis based on published data including (Ziessman et al., 2009).
		Stomach high fat fed lag time (CV %) Stomach high fat fed MRT Me %) Stomach fed lag time Mean (C Stomach fed MRT Mean (CV %	Mean an (CV CV %) 6)	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	0 (0)	
	(CV %)		In-house meta-
	Stomach low fat fed MRT Mean (CV	1.18 (46.65)	analysis based on
	%)	3.4 (9.19)	published data
	Small intestine fasted Mean (CV %)		including (Wilson
	Small intestine high fat fed Mean	4.73 (34.67)	et al., 2009).
	(CV %)	4.73 (34.67)	
	Small intestine fed Mean (CV %)		
	Small intestine low fat fed	4.73 (34.67)	In-house meta-
	Mean (CV %)	37.11 (47)	analysis based on
	Whole colon Mean (CV %)- Male	52.87 (47)	published data
	Whole colon Mean (CV %)- Female	18.91 (47)	including (Graff et
	Ascending colon Mean (CV %)- Male		al., 2001).
	Ascending colon Mean (CV %)-	23.11 (47)	
	Female		
IMMC Cycle Time (h)	Mean (CV %)	1.55 (55)	(Schmidt et al.,
			1996).
CO Drotoin /ma/amall		E220	In house analysis
sy protein (mg/small	SPPPI Mean	5320	In-nouse analysis
Microsomal Protoin	User SSPPT Weatt (CV %)	0 (50)	(Daine et al. 1007)
(mg/small intesting)	MPPI Mean (CV %)	2078 (20)	(Faille et al., 1997), (Gibbs et al. 1998)
(mg/colon)	MPPC Mean (CV %)	622 (30)	& unnublished data
(mg/small		022 (30)	from Mike
intestine)	CPPI Mean (CV %)	2342 (31)	Coughtrie
intestine)		2342 (31)	(University of
Total Membrane Protein per	TMePPI Mean (CV %)	2737 (0)	Dundee. July 2009).
Intestine (mg/small intestine)		- (-)	(Harwood et al.,
Total Membrane Protein per	TMePPC Mean (CV %)	112 (0)	2019).
colon (mg/colon)			
Food Staggering Model	Number of gastric emptying half	5	
Duration of Fed State	lives		
Mool Event Fluid Volumos	Total fluid volume accessized with		In house moto
High Eat Ead	food (ml) Moon (C)(%)	551.07 (15)	analysis based on
ingii rat reu	Time taken to consume meal (T)	0 335 (30)	nublished data
	(h) Mean (CV %)	0.555 (50)	including (Grimm
	Zero order filling rate (ml /h) Mean	1585 28	et al 2017)
	Maximum Stomach Volume (ml.)	4000	ct di., 2017 j.
Fed	Total fluid volume associated with	531 07 (15)	
	food (ml) Mean (CV %)	001.07 (10)	
	Time taken to consume meal (T _{et})	0.335 (30)	
	(h) Mean (CV %)		
	Zero order filling rate (mL/h) Mean	1585.28	
	Maximum Stomach Volume (mL)	4000	
Low Fat Fed	Total fluid volume associated with	546 (9)	
	food (ml) Mean (CV %)		
	Time taken to consume meal (T _{et})	0.335 (30)	
	(h) Mean (CV %)	1629.85	
	Zero order filling rate (mL/h) Mean		
	Maximum Stomach Volume (mL)	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** Duodenum length (m) 0.205 on BSA Linear multiplier C1 0.55 Exponent Duodenum diameter (m) Linear multiplier C1 0.033 0.383 Exponent Lower gut length (m) Linear multiplier C1 5.231 0.414 Exponent CV (%) 20 0.4 **Jejunum-Ileum Ratios** Jejunum/Lower gut length Jejunum/Duodenum diameter 0.8125 Ileum/Duodenum diameter 0.725 **Nested Enzyme Within** Enterocyte lifespan (h) Mean (CV %) 120 (30) (Darwich et al., Enterocyte (NEWE) Model Number of enterocyte groups 100 2019). **CYP** Phenotype Intestine CYP2C9 Mean EM (CV %) 12.5 (72) In-house meta-**Enzyme Abundances** CYP2C9 Mean PM (CV %) 5 (72) analysis based on (nmol/small intestine) CYP2C19 Mean EM (CV %) 2 (77) published data CYP2C19 Mean UM (CV%) 4 (77) including (Drozdzik CYP2D6 Mean EM (CV %) et al., 2018) & 1.1 (47) (Paine et al., 2006). CYP2D6 Mean UM (CV %) 2.1 (47) CYP2J2 Mean EM (CV %) 7.4 (69) CYP3A4 Mean EM (CV %) 65.4 (52) CYP3A5 Mean EM (CV %) 23.3 (32) **CYP Turnover Rate Constants** CYP2C9 Mean (CV %) 0.03 (20) In-house analysis (1/h) CYP2C19 Mean (CV %) 0.03 (20) based on (Greenblatt et al., CYP2D6 Mean (CV %) 0.03 (20) CYP2J2 Mean (CV %) 0.03 (20) 2003). CYP3A4 Mean (CV %) 0.03 (20) CYP3A5 Mean (CV %) 0.03 (20) **CYP** Phenotype Colon CYP2C9 Mean EM (CV %) 0 (0) In-house analysis **Enzyme Abundances** CYP2C19 Mean EM (CV %) 0(0) based on published (nmol/colon) CYP2D6 Mean EM (CV %) 0 (0) data from (de CYP2J2 Mean EM (CV %) 0(0) Waziers et al., 1991) & (Gervot et CYP3A4 Mean EM (CV %) 1.99 (30) CYP3A5 Mean EM (CV %) 0.74 (30) al., 1996). **CYP Genotype Abundance** CYP2C9 *1/*1 Mean (CV %) 12.5 (72) In-house meta-CYP2C9 *1/*2 Mean (CV %) analysis based on 11.4 (72) CYP2C9 *1/*3 Mean (CV %) 11.4 (72) published data CYP2C9 *2/*2 Mean (CV %) 11.4 (72) including (Drozdzik CYP2C9 *2/*3 Mean (CV %) 11.4 (72) et al., 2018) & CYP2C9 *3/*3 Mean (CV %) 3.4 (72) (Paine et al., 2006). **UGT Phenotype** UGT1A1 Mean 8.5 In-house meta-**Absolute UGT Abundance** UGT1A3 Mean 0.4 analysis based on 1.9 (pmol/mg protein) UGT1A4 Mean published data UGT1A5 Mean 0.3 including (Harbourt



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UGT1A7 Mean7.1unpublished dataUGT1A8 Mean5.6from the SimcypUGT1A9 Mean5.9Consortium UGTUGT1A10 Mean4.3focused groupUGT2B4 Mean0(2013)
UGT1A8 Mean5.6from the SimcypUGT1A9 Mean5.9Consortium UGTUGT1A10 Mean4.3focused groupUGT2B4 Mean0(2013)
UGT1A9 Mean5.9Consortium UGTUGT1A10 Mean4.3focused groupUGT2B4 Mean0(2013)
UGT1A10 Mean 4.3 focused group
LIGT2B4 Mean 0 (2013)
UGT2B7 Mean 4.5
UGT2B10 Mean 0 1
UGT2B11 Mean 0
LIGT2B15 Mean 0 1
LIGT2B17 Mean 11
LIGT2B28 Mean
User LIGT1 Mean
alative LIGT Abundances or LIGT1A1 EM Mean (CV/%) 1 (60)
rative OGT Abundances of OGTIAT Elvi Mean (CV %) 1 (00) 11-1003e meta-
$\frac{1}{10} \frac{1}{10} \frac$
UCT1A1 INI Mean (CV 76) 0.72 (00) published data
$\begin{array}{c} \text{UGTIA3 EM Mean (CV \%)} \\ \text{UGTIA4 EM Mean (CV \%)} \\ \text{I (60)} \\ I ($
UGT1A5 EM Mean (CV %) 1 (60) 2003) & (Swanson
UGT1A6 EM Mean (CV %) 1 (60) et al., 2007).
UGT1A7 EM Mean (CV %) 1 (60)
UGT1A8 EM Mean (CV %) 1 (60)
UGT1A9 EM Mean (CV %) 1 (60)
UGT1A9 PM Mean (CV %) 0.07 (60)
UGT1A9 IM Mean (CV %) 0.19 (60)
UGT1A10 EM Mean (CV %) 1 (60)
UGT2B4 EM Mean (CV %) 1 (60)
UGT2B7 EM Mean (CV %) 1 (60)
UGT2B10 EM Mean (CV %) 1 (60)
UGT2B11 EM Mean (CV %) 1 (60)
UGT2B15 EM Mean (CV %) 1 (60)
UGT2B15 PM Mean (CV %) 0.07 (60)
UGT2B15 IM Mean (CV %) 0.47 (60)
UGT2B17 EM Mean (CV %) 1 (60)
UGT2B17 PM Mean (CV %) 0.08 (60)
UGT2B17 IM Mean (CV %) 0.16 (60)
UGT2B28 EM Mean (CV %) 1 (60)
User UGT1 EM Mean (CV %) 1 (60)
GT Turnover Rate (1/h) UGT1A1 Mean (CV %) 0.0578 (Barter et al., 2007)
UGT1A3 Mean (CV %) 1E-06 & (Ohnishi and
UGT1A4 Mean (CV %) 1E-06 Emi, 2003).
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 %) 1F-06
UGT2B11 Mean (CV %) 1F-06
UGT2B15 Mean (CV %) 1F-06





	UGT2B17 Mean (CV %)	1E-06	
	UGT2B28 Mean (CV %)	1E-06	
Cytosolic Phenotyne Relative	User Cyt1 FM Mean (CV %)	1 (60)	Default
Abundances compared to	User Cyt2 EM Mean $(CV \%)$	1 (60)	Delutit
Abundances compared to	User Cyt2 ENANAser (C)(2)	1 (00)	
wild type and their	User Cyt3 EIVI Mean (CV %)	1 (60)	
associated variance	User Cyt4 EM Mean (CV %)	1 (60)	
Transporter Expression	ABCB1 (P-gp/MDR1)	0.4	(Harwood et al.,
Absolute Abundance	ABCC1 (MRP1)	0	2019).
(pmol/mg total membrane	ABCC2 (MRP2)	0.86	
protein)- Jeiunum I	ABCC3 (MRP3)	0.58	
, , ,	ABCC4 (MRP4)	0	
		0.34	
		0.54	
		0	
	SLCIUAZ (ASBI/IBAT)	0.01	
	SLC15A1 (PepT1)	3.69	
	SLC16A1 (MCT1)	0	
	SLCO2B1 (OATP2B1)	0.4	
	SLCO4C1 (OATP4C1)	0	
	SLC22A1 (OCT1)	0.65	
	SLC22A3 (OCT3)	0.06	
	SI C22A4 (OCTN1)	0	
	$SIC51A/B (OST-\alpha/B)$	0.47	
	Anical Influx	0.47	
		0	
	Apical Efflux	0	
	Basal Influx	0	
	Basal Efflux	0	
Relative Abundances along	ABCB1 (P-gp/MDR1)	0.51	(Harwood et al.,
the GI tract compared to	ABCC1 (MRP1)	0.45	2019).
jejunum values- Duodenum	ABCC2 (MRP2)	1.41	
	ABCC3 (MRP3)	2.15	
	ABCC4 (MRP4)	1.02	
	ABCG2 (BCBP)	0.68	
		1	
		16.40	
	SLCIUAZ (ASBI/IBAT)	10.49	
	SLC15A1 (Pep11)	0.94	
	SLC16A1 (MCT1)	1.25	
	SLCO2B1 (OATP2B1)	0.73	
	SLCO4C1 (OATP4C1)	1	
	SLC22A1 (OCT1)	1.03	
	SLC22A3 (OCT3)	1.19	
	SLC22A4 (OCTN1)	0.46	
	SI C51A/B (OST- α/β)	0.56	
	Anical Influx	1	
	Apical Efflux	1	
	Recal Influx	1	
		1	
		1	
Jejunum I	ABCB1 (P-gp/MDR1)	1	(Harwood et al.,
	ABCC1 (MRP1)	1	2019).
	ABCC2 (MRP2)	1	
	ABCC3 (MRP3)	1	
	ABCC4 (MRP4)	1	





	ABCG2 (BCRP)	1	
	SLC2A2 (GLUT2)	1	
	SLC10A2 (ASBT/IBAT)	1	
	SLC15A1 (PepT1)	1	
	SLC16A1 (MCT1)	1	
	SLCO2B1 (OATP2B1)	1	
	SICOAC1 (OATPAC1)	1	
		1	
		1	
	SLC22A3 (OCT3)		
	SLC22A4 (OCIN1)	1	
	SLC51A/B (OST-α/β)	1	
	Apical Influx	1	
	Apical Efflux	1	
	Basal Influx	1	
	Basal Efflux	1	
leiunum II	ABCB1 (P-gn/MDB1)	1 46	(Harwood et al
	ABCC1 (MRP1)	0.88	2019)
		1	2015).
		1	
	ABCC3 (IVIRP3)	0.89	
	ABCC4 (MRP4)	1.22	
	ABCG2 (BCRP)	1	
	SLC2A2 (GLUT2)	1	
	SLC10A2 (ASBT/IBAT)	4	
	SLC15A1 (PepT1)	1.06	
	SLC16A1 (MCT1)	1	
	SLCO2B1 (OATP2B1)	0.94	
	SLCO4C1 (OATP4C1)	1	
	SLC22A1 (OCT1)	0.87	
	SLC22A1 (OCT1)	1 11	
	SLC22AS(OCTS)	1.11	
	SLC22A4 (OCTN1)	0.63	
	SLC51A/B (US1- α/β)	1.89	
	Apical Influx	1	
	Apical Efflux	1	
	Basal Influx	1	
	Basal Efflux	1	
lleum I	ABCB1 (P-gp/MDR1)	1.5	(Harwood et al.,
	ABCC1 (MRP1)	0.86	2019).
	ABCC2 (MRP2)	0.6	/
	ABCC3 (MRP3)	1 54	
	ABCCA (MRDA)	1 71	
		1.71	
		0.78	
	SLC2A2 (GLUT2)		
	SLC10A2 (ASBT/IBAT)	98.44	
	SLC15A1 (PepT1)	1.23	
	SLC16A1 (MCT1)	1.29	
	SLCO2B1 (OATP2B1)	1.28	
	SLCO4C1 (OATP4C1)	1	
	SLC22A1 (OCT1)	1.29	
	SLC22A3 (OCT3)	1.08	
	SLC22A4 (OCTN1)	0.78	
	$SIC51A/B (OST-\alpha/B)$	1.08	
	Anical Influx	1	
		⊥ 1	
	Apical Elliux	L T	1





	Basal Influx	1	
	Basal Efflux	1	
lleum II	ABCB1 (P-gp/MDR1)	1.51	(Harwood et al
	ABCC1 (MRP1)	0.86	2019)
	ABCC2 (MRP2)	0.6	2013).
		1 5/	
	ABCC3 (MINFS)	1.34	
		1./1	
	ABCG2 (BCRP)	0.78	
	SLC2A2 (GLUT2)	1	
	SLC10A2 (ASB1/IBA1)	98.44	
	SLC15A1 (PepT1)	1.23	
	SLC16A1 (MCT1)	1.29	
	SLCO2B1 (OATP2B1)	1.28	
	SLCO4C1 (OATP4C1)	1	
	SLC22A1 (OCT1)	1.29	
	SLC22A3 (OCT3)	1.08	
	SLC22A4 (OCTN1)	0.78	
	SLC51A/B (OST- α/β)	1.08	
	Apical Influx	1	
	Apical Efflux	1	
	Basal Influx	1	
	Basal Efflux	1	
	Basar Errax	-	
lleum III	ABCB1 (P-gp/MDB1)	1 5 2	(Harwood et al
		0.80	2010)
		0.85	2019].
		1.6	
	ABCCS (MIRPS)	1.0	
	ABCC4 (MRP4)	1.2	
	ABCG2 (BCRP)	0.78	
	SLC2A2 (GLU12)	1	
	SLC10A2 (ASB1/IBA1)	109.18	
	SLC15A1 (PepT1)	1.24	
	SLC16A1 (MCT1)	1.29	
	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	
lleum IV	ABCB1 (P-gp/MDR1)	1.51	(Harwood et al.,
	ABCC1 (MRP1)	0.89	2019)
	ABCC2 (MRP2)	0.6	
	ABCC3 (MRP3)	1.6	
	ABCC4 (MRP4)	1.2	
	ABCG2 (BCRP)	0.78	
	SLC2A2 (GLUT2)	1	
	SLC10A2 (ASBT/IBAT)	108	
	SLC15A1 (PepT1)	1.24	
	SLC16A1 (MCT1)	1.29	





	SLCO2B1 (OATP2B1)	1.28	
	SLCO4C1 (OATP4C1)	1	
	SLC22A1 (OCT1)	1.3	
	SIC22A3 (OCT3)	1 23	
	SLC22A4 (OCTN1)	0.8	
	$SIC51A/B (OST_{\alpha}/B)$	0.02	
	Anical Influx	1	
		1	
		1	
	Dasal IIIIux	1	
	Basarelliux	1	
Colon		0.57	(Hanwood at al
COIDII		0.37	(Hai woou et al.,
		0.93	2019)
	ABCC2 (IVIRP2)	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:	ABCB1 (P-gp) ET Mean (CV %)	1 (65)	In-house meta-
Relative Abundances	ABCC1 (MRP1) ET Mean (CV %)	1 (88)	analysis based on
Compared to Wild Type and	ABCC2 (MRP2) ET Mean (CV %)	1 (79)	published data. See
their associated Variance	ABCC3 (MRP3) ET Mean (CV %)	1 (64)	(Harwood et al.,
	ABCC4 (MRP4) ET Mean (CV %)	1 (106)	2019) for details of
	ABCG2 (BCRP) ET Mean (CV %)	1 (63)	references used.
	ABCG2 (BCRP) PT Mean (CV %)	0.37 (63)	
	ABCG2 (BCRP) IT Mean (CV %)	0.67 (63)	
	SLC2A2 (GLUT2) ET Mean (CV %)	1 (31)	
	SI C10A2 (ASBT/IBAT) FT Mean (CV)	1 (43)	
	$SIC15\Delta1$ (PenT1) FT Mean (CV %)	1 (41)	
	SIC16A1 (MCT1) ET Mean (CV %)	1 (75)	
	SLCO2B1 (OATD2B1) ET Mean (CV %)	1(73)	
	SICO2DI (OATRAC1) ET Mean (CV %)	1 (60)	
	SLC22A1 (OCT1) ET Moon (CV %)	1 (40)	
	SIC22A1 (OCT1) ET Maan (CV %)	1 (49) 0 01 (10)	
	SIC22A1 (OCT1) T Maaa (OV $%$)	0.01 (49)	
	1 SUCZAT (OCT1) II Wedfi (UV %)	0.02 (49)	
		1.14 (49)	
		1 (10C)	
	SLC22A4 (UCINI) EI Mean (CV %)	1 (106)	
	SLUSTA/B (USI- α/β) ET Mean (CV %)	T (99)	
	Apical Influx ET Mean (CV %)	1 (0)	
	Apical Efflux ET Mean (CV %)	1 (0)	





	Basal Influx ET Mean (CV %)	1 (0)	
	Basal Efflux ET Mean (CV %)	1 (0)	
		- (-)	
Esterase Phonotype	CES1 EM Mean (CV/%)	1 (30)	In-house meta-
Pelative Abundances	CES1 PM Mean (CV %)	1(30)	analysis based on
Compared to Wild Type and	CES2 EM Moon (CV %)	1 (20)	analysis based on
their associated Marianas		1 (30)	published data
their associated variance	User ES Mean (CV %)	1 (30)	including (Zhu and
			Markowitz, 2009).
Luminal Metabolism	Substrate -> Primary Metabolite 1		
Substrate- Expression	Enzyme user		
Relative Activity along the GI	Stomach	1	Default
tract compared to reference	Duodenum	1	
segment selected on the	Jejunum l	1	
Elimination screen	Jejunum II	1	
	lleum I	1	
	Ileum II	1	
	Ileum III	1	
	lleum IV	1	
	Colon	1	
		-	
Phonotypo	Substrate > Drimary Motabolite 1		
Performence assessment selected	Substrate -> Philling Metabolite 1	1 (20)	Default
Reference segment selected	Enzyme user Eivi weari (CV %)	1 (30)	Default
on Elimination screen:			
Relative Activity compared to			
Wild Type and their			
associated variability			
Substrate-Expression	Primary Metabolite 1 -> Substrate		
Relative Activity along the GI	Enzyme user		
tract compared to reference	Stomach	1	Default
segment selected on the	Duodenum	1	
Elimination screen	Jejunum l	1	
	Jejunum II	1	
	Ileum I	1	
	lleum II	1	
	lleum III	1	
	Ileum IV	1	
	Colon	1	
-Phenotype	Primary Metabolite 1 -> Substrate		
Reference segment selected	Enzyme user EM Mean (CV %)	1 (30)	Default
on Elimination screen:	,	()	
Relative Activity compared to			
Wild Type and their			
associated variability			
FMO Phenotyne	EMO1 EM	0	Default
Absolute EMO Abundanco	EMO3 EM	0	
(nmol/mg protoin)		0	
		U	
		1 (20)	
		1 (30)	
	FIVIO3 EMI (CV%)	1 (30)	





Relative FMO Abundances or	FMO5 EM (CV%)	1 (30)	
probe activity (compared to	User FMO	1 (30)	
wild type)		· · /	
	Achlorhydric subjects (%) Coefficient	8	
ADAM Model Parameters	Age Power	0	
Achlorbydrics	Maximum (%)	8	
Achiornyunes		0	
		0 0	In house analysis
Conorol	Transit Time (Total %)	0.0	haced on published
Duedenum		4.0	date including
Duodenum		13.76	data including
		14.88	(Paine et al., 1997).
		13.76	
	CPPI (Total %)	14.88	
	Blood Flow (Qvilli %)	24.2	
Jejunum I	Transit Time (Total %)	17.3	
	CYP 3A (Total %)	27.24	
	S9PPI (Total %)	26.9	
	MPPI (Total %)	27.24	
	CPPI (Total %)	26.9	
	Blood Flow (Q _{villi} %)	24.2	
Jejunum II	Transit Time (Total %)	17.3	
	CYP 3A (Total %)	27.24	
	S9PPI (Total %)	26.9	
	MPPI (Total %)	27.24	
	CPPI (Total %)	26.9	
	Blood Flow (Q _{villi} %)	10.7	
lleum I	Transit Time (Total %)	15.2	
	CYP 3A (Total %)	7.94	
	S9PPI (Total %)	7.83	
	MPPI (Total %)	7.94	
	CPPI (Total %)	7.83	
	Blood Flow (Q _{villi} %)	10.7	
lleum II	Transit Time (Total %)	15.2	
	CYP 3A (Total %)	7.94	
	S9PPI (Total %)	7.83	
	MPPI (Total %)	7.94	
	CPPI (Total %)	7.83	
	Blood Flow (Q _{villi} %)	10.7	
lleum III	Transit Time (Total %)	15.2	
	CYP 3A (Total %)	7.94	
	S9PPI (Total %)	7.83	
	MPPI (Total %)	7.94	
	CPPI (Total %)	7.83	
	Blood Flow (Qvilli %)	10.7	
lleum IV	Transit Time (Total %)	15.2	
	CYP 3A (Total %)	7.94	
	S9PPI (Total %)	7.83	
	MPPI (Total %)	7 94	
	CPPI (Total %)	7.83	
1			





Duodenum1.72In-house meta- analysis based on published data ileum IICYP2C9Jejunum II3.41published data (Drozdzik ileum III0.99et al., 2018, (Paine et al., 2018), (Paine et al., 2006).CYP2D2Duodenum Jejunum II Ileum II 				
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CYP2C9Jejunum II3.41published data including (Drozdzik Ileum IIIleum II0.99et al., 2018), (Paine et al., 2006).Ileum IV0.99(Paine et al., 2007).Colon00CYP2C19Duodenum Jejunum II0.54 otalysis based on analysis based on analysi	Enzyme Abundances (nmol)	Jejunum I	3.41	analysis based on
Ideum 10.99including (Drozdzik (Paine et al., 2016), Paine et al., 2006), 8Ileum II0.99et al., 2016), Paine et al., 2006), 8CYP2C19Duodenum0.28In-house meta- analysis based on Jejunum IIJejunum II0.54analysis based on analysis based on Jejunum IIIleum II0.16including (Drozdzik analysis based on analysis based on analysis based on Jejunum IIIleum II0.16including (Drozdzik analysis based on analysis based	CYP2C9	Jejunum II	3.41	published data
Ideum II0.99et al., 2018), (Paine et al., 2016)Ileum IV0.99et al., 2016)Colon00Duodenum0.28In-house meta-Jejurum II0.54analysis based onJejurum II0.16et al., 2018), (PaineIleum IV0.16(Paine et al., 1997).Colon00Duodenum0.15In-house meta-Jejurum II0.3published dataIleum IV0.9et al., 2018), (PaineIleum II0.9et al., 2018), (PaineIleum II0.9et al., 2006), &Ileum II0.9et al., 2006), &Ileum II0.9et al., 2018), (PaineIleum II0.9et al., 2018), (PaineIleum III0.9et al., 2018), (PaineIleum III0.9et al., 2018), (PaineJejurum II0.9et al., 2018), (PaineJejurum II0.9et al., 2018), (PaineIleum II1.99al., 1997, (Pain		lleum I	0.99	including (Drozdzik
Ileum II Ileum IV Colon0.99 0(Paine et al., 1997). (Paine et al., 1997).CYP2C19Duodenum Jejunum I Ileum II Ileum II Ileum III Ileum III O.16 OIn-house meta- analysis based on published data Including (Drozdzik Ileum III O.16 (Paine et al., 2006) & (Paine et al., 1997). OCYP2D6Duodenum Jejunum II Ileum III Ileum III Ileum III O.09 (Colon0.15 O OIn-house meta- analysis based on published data Including (Drozdzik Ileum II O.09 (Paine et al., 1997). (ColonCYP2D6Duodenum Jejunum II Ileum II Ileum II Ileum II Ileum II O.09 OIn-house meta- analysis based on published data Including (Drozdzik Ileum II O.09 OCYP2D2Duodenum Jejunum II Ileum II Ileum II Ileum II Ileum II Ileum II O.59 OlonIn-house meta- analysis based on aulysis based on published data including (Paine et al., 1997) & (Paine et al., 2006).CYP3A4Duodenum Jejunum II Jejunum II Jejunum II Jejunum II Jejunum II Ileum III Signam ColonIn-house meta- analysis based on aulysis base		lleum II	0.99	et al., 2018), (Paine
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CYP3A5 Ileum II 5.19 et al., 2006). Ileum IV 5.19 In-house meta- Duodenum 3.21 analysis based on Jejunum I 6.35 published data Jejunum II 6.35 including (Paine et Ileum I 1.85 al., 1997) & (Paine Ileum II 1.85 et al., 2006).			5.19	al., 1997) & (Paine
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Jejunum II6.35including (Paine etIleum I1.85al., 1997) & (PaineIleum II1.85et al., 2006).	CYP3A5		6 35	nublished data
Ileum I1.85al., 1997) & (PaineIleum II1.85et al., 2006).		leiunum II	6 35	including (Daine et
Ileum II 1.85 et al., 2006).		lleum l	1.85	al 1997) & (Daine
		lleum II	1.85	et al 2006)
lleum III 1 85		lleum III	1.85	2000).
		lleum IV	1.85	
Colon 0.74 In-house analysis		Colon	0.74	In-house analysis
Duodenum 791 62 hased on published		Duodenum	791.62	based on published





S9PPI (mg)	Jejunum I	1431.08	(Paine et al., 1997)
	Jejunum II	1431.08	& unpublished data
	lleum I	416.56	(Mike Coughtrie,
	Ileum II	416.56	University of
	lleum 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)	leiunum l	811.21	
	leiunum II	811.21	
	lleum I	236.45	
	lleum II	236.45	
	lleum III	236.45	
	lleum IV	236.45	
	Colon	622	In-house analysis
		022	hased on published
	Duodenum	348 49	(Paine et al 1997)
CPPI (mg)		630	& unnublished data
		630	(Mike Coughtrie
	lleum	182.28	University of
	lleum II	192.29	Dundee July 2009)
		102.20	Dunuee, July 2009).
		103.30	
	neumiv	105.50	In-house analysis
			hased on published
	Ionic Product (Kw) (10-14 mol2/dm6)	24	data from (Zooboo
Water Physicochemical	Aqueous Diffusion Coefficients	2.4	2011)
Properties (27°C)	$(10^{-4} \text{cm}^2/\text{min})$		2011).
Flopencies (37 C)		6.01	
		7.2	
	Water Concentration (mM)	55560	In-house analysis
	water concentration (mw)	55500	hased on nublished
	nH Easted Mean (CV %)	1 5 (38)	data from
Luminal nH	nH High Eat Fed Mean (CV %)	1.3 (30)	(Fallinghorg et al
Stomach	nH Fed Mean (CV %)	5 (25)	
Stomach	nH Low Fat Fed Mean (CV %)	5 (25)	et al 2015)
	nH _{fod} is itial Mean (CV %)	4 39 (24)	ct al., 2013).
Time-Dependent Gastric nH	$k (h^{-1})$ Mean (CV %)	0.467 (97.8)	
High Fat Fed	nHfeeted	0.5367779	
ingii i dei ed	nH Fasted Mean (CV %)	1 5 (38)	
	nHedisial Mean (CV %)	5 (25)	
Fed	Age < 65 Tff (b) Mean (CV %)	1 8 (65)	
100	Age < 65 Tff (h) Mean (CV %)	3 (80)	
	K (h ⁻¹)	0 668877	
	Slope	1 166667	
	nH Fasted Mean (CV %)	1 5 (38)	
	nH _{fod} initial Mean (CV %)	5 (25)	
Low Eat Fed	$\Delta q_{0} < 65$ Tff (b) Mean (CV %)	1 8 (65)	
	$\Delta g_{0} < 65$ Tff (b) Maan (CV %)	3 (80)	
	$A_{ge} < 0.5 \text{ m} \text{ (m) weath (CV /0)}$	0.668874	
	Slope	1 166667	In-house analysis
	nH Easted Mean (CV %)	1.100007	hased on published
	Duodenum	6 1 (16)	data from
	Duouenum	0.4 (10)	





Small Intestine	Jejunum I	6.5 (13)	(Fallingborg et
- Static pH Model	Jejunum II	6.6 (11)	al., 1989).
	lleum I	6.8 (10)	-
	lleum II	7 (10)	
	Ileum III	7.1 (7)	
	lleum IV	7.3 (6)	
	pH High Fat Fed Mean (CV %)		
	Duodenum	5.4 (11)	
	Jejunum l	6.5 (13)	
	Jejunum II	6.6 (11)	
	lleum I	6.8 (10)	
	lleum II	7 (10)	
	lleum III	7.1 (7)	
	lleum IV	7.3 (6)	
	pH Fed Mean (CV %)		
	Duodenum	5.4 (11)	
	Jeiunum I	6.5 (13)	
	Jeiunum II	6.6 (11)	
	lleum I	6.8 (10)	
	lleum II	7 (10)	
	lleum III	7.1 (7)	
	Ileum IV	7.3 (6)	
	pH Low Fat Fed Mean (CV %)		
	Duodenum	5.4 (11)	
	Jejunum I	6.5 (13)	
	Jejunum II	6.6 (11)	
	lleum I	6.8 (10)	
	lleum II	7 (10)	
	lleum III	7.1 (7)	
	Ileum IV	7.3 (6)	
			In-house analysis
	Fasted		based on published
	K	8.50336	data including
Small Intestine	A	0.881696	(Fallingborg et al.,
-Dynamic pH Model	В	8.23296	1989) & (Koziolek
		2.96836	et al., 2015).
		2.32041	
	d b	2.35408	
	D	-0.757640	
	Fed (High Fat/Fed/Low Fat)	7.19977	
	К	4.73512	
	A	1.5348	
	В	4.09878	
	С	6.46013	
	D	-4.45833	
	a	2	
	b	-1	
	с	15	
			In-house meta-
	pH Fasted Mean (CV %)	6.6 (13.3)	analysis based on
	pH High Fat Fed Mean (CV %)	6.33 (11.78)	published data





Colon	nH Fed Mean (CV %)	6 33 (11 78)	including
colon	pH Low Fat Fed Mean (CV %)	6 33 (11 78)	(Schneider et al
		0.55 (11.76)	2016)
			2010).
			In have a marke
	Fasted (CV %)	7.0 (20)	In-nouse meta-
	Stomach	7.3 (30)	analysis based on
Luminal Bicarbonate-	Duodenum	6.53 (30)	published data
Luminal Fluid Total	Jejunum I	9.94 (30)	including (Fadda et
Bicarbonate Buffer	Jejunum II	9.94 (30)	al., 2009).
Concentration (mM)	lleum I	30 (30)	
	lleum II	30 (30)	
	lleum III	30 (30)	
	lleum IV	30 (30)	
	Colon	90.87 (30)	
	Fed (CV %)	, , ,	
	Stomach	42,46 (30)	
	Duodenum	34 19 (30)	
	leiunum l	17 34 (30)	
	leiunum II	17 34 (30)	
	lloum	20 (20)	
		50 (50) 20 (20)	
		30 (30)	
		30 (30)	
	lleum IV	30 (30)	
	Colon	44.43 (30)	
			In-house analysis
Bicarbonate Physicochemical	pKa 1 Acidic	6.05	based on published
Parameters	pKa 2 Acidic Measured pKa at 37°C	9.79	data from (Zeebee,
	Ionic Strength (I) 0.15M		2011).
	pKa 1 Acidic	4.2	
	pKa 2 Acidic Effective pKa	9.79	
	Aqueous Diffusion Coefficients		
	(10 ⁻⁴ cm ² /min)		
	H ₂ CO ₃	17.72	
	HCO ₃ -	9.85	
	CO_3^{2-}	6.98	
Luminal Fluid Velocity (m/s)	Fasted (CV %)		In-house meta-
	Stomach	0 032 (30)	analysis based on
	Duodenum	0.005 (30)	nublished data
	leiunum l	0.0013 (56)	including (Gutzeit
	leiunum II	0.0013 (56)	et al 2010)
	lloum l	0.0013 (50)	ct al., 2010j.
		0.0013 (50)	
		0.0013 (50)	
		0.0013 (50)	
		0.0013 (50)	
	Colon	0.0013 (56)	
	5 1 (0) (0)		
	Fed (CV %)		
	Stomach	0.032 (30)	
	Duodenum	0.005 (30)	
	Jejunum I	0.0013 (56)	
	Jejunum II	0.0013 (56)	
	lleum I	0.0013 (56)	
	lleum II	0.0013 (56)	





	Ileum III	0.0013 (56)	
	Ileum IV	0.0013 (56)	
	Colon	0.0013 (56)	
		0.0010 (00)	
Endogenous lons	Chloride (CL ⁻) Mean (Min. Max)		
	Stomach	102 (48 172)	
	Duodonum	102 (40,175)	
		102.4 (04.0,158.8)	
	Jejunum I	126 (92,181)	
	Jejunum II	126 (92,181)	
	Illeum I	113.3 (80.4,157.5)	
	Illeum II	100.5 (71.4,139.7)	
	Illeum III	84 (59.6,116.7)	
	Illeum IV	67.4 (58,79)	
	Colon	13 (7,20)	
	Stomach CV	27.5	
	Small Intestine CV	15.1	
	Colon CV	13	
	Sodium (Na ⁺) Mean (Min. Max)		
	Stomach	68 (19,122)	
	Duodenum	118 4 (89 6 155 1)	
	leiunum l	142 (111 165)	
		142(111,105) 1/2(111,165)	
		142(111,103) 1262(10741710)	
		130.5 (107.4,171.6)	
		130.5 (102.8,164.6)	
		128.9 (101.5,162.5)	
	lileum IV	127.2 (112,138)	
	Colon	30 (6,93)	
	Stomach CV	42.6	
	Small Intestine CV	9.2	
	Colon CV	42	
	Potassium (K ⁺) Mean (Min, Max)		
	Stomach	13.4 (8.4,19.3)	
	Duodenum	11.2 (3.4,32.1)	
	Jejunum l	5.4 (1.7,11.6)	
	Jejunum II	5.4 (1.7,11.6)	
	Illeum I	6.1 (4.6,8)	
	Illeum II	6.7 (5,8.8)	
	Illeum III	6.3 (4.7,8,3)	
	Illeum IV	5.9 (5.3,6.5)	
	Colon	77 (40,108)	
	Stomach CV	22.4	
	Small Intestine CV	38.9	
	Colon CV	11	
	Calcium (Ca ²⁺) Mean (Min, Max)		
	Stomach	0.6 (0.3,1.2)	
	Duodenum	0.5 (0.1,1.3)	
	Jejunum I	0.5 (0.1, 1.3)	
	Jejunum II	0.5 (0.1, 1.3)	
	Illeum I	0.5 (0.1, 1.3)	
	Illeum II	0.5 (0.1, 1.3)	
	Illeum III	0.5 (0.1, 1.3)	
	Illeum IV	0.5 (0.1, 1.3)	





	Colon	20 (7.85)	
	Stomach CV	33.3	
	Small Intestine CV	60	
	Colon CV	34	
		54	
Luminal Bile Salts (mM)	CMC Fasted		In-house meta-
	Stomach	1	analysis based on
	Duodenum	1	nublished data
		1	including (Poroz do
		1	Including (Ferez de
		1	
			(Schindibeck et al.,
			1987).
	lleum IV	1	
	Colon	1	
	[Bile] Fasted Mean (CV %)		
	Stomach	0.34 (134)	
	Duodenum	3.31 (97)	
	Jejunum I	2.3 (100)	
	Jejunum II	3.55 (42)	
	lleum I	1.25 (30)	
	lleum II	1.25 (30)	
	lleum III	1.25 (30)	
	Ileum IV	1.25 (30)	
	Colon	0.12 (104)	
	CMC Fed		
	Stomach	1	
	Duodenum	1	
	Jejunum I	1	
	Jejunum II	1	
	lleum I	1	
	Ileum II	1	
	Ileum III	1	
	Ileum IV	1	
	Colon	1	
	[Bile] Fed Mean (CV %)		
	Stomach	0.34 (216.7)	
	Duodenum	8.74 (79)	
	Jeiunum I	10.03 (73)	
	Jejunum II	4,79 (66)	
	lleum I	5.86 (84)	
	lleum II	8.61 (88)	
	lleum III	8.06 (65)	
	lleum IV	5 96 (65)	
	Colon	0 59 (70)	
		(. •)	
GI Morphology	Channel Depth (µm) Mean (CV %)		In-house meta-
Villi	Duodenum	522.78 (32.72)	analysis based on
	Jejunum I	448.81 (21.82)	published data
	Jejunum II	448.81 (21.82)	including
	lleum I	289.94 (49.37)	(Trbojevic-
	lleum II	289.94 (49.37)	Stankovic et al.
	Ileum III	289.94 (49.37)	2010).
	Ileum IV	289.94 (49.37)	,-





	Channel Width (µm) Mean (CV %) Duodenum Jejunum I Jejunum II Ileum I Ileum II Ileum III Ileum IV Thickness (µm) Mean (CV %) Duodenum	28.03 (28.69) 22.44 (31.68) 22.44 (31.68) 56.19 (30) 56.19 (30) 56.19 (30) 56.19 (30) 56.19 (30)	
	Jejunum I Jejunum II Jejunum I	137.7 (14.42) 137.7 (14.42) 127 (20)	
	lleum II	127 (30)	
	lleum III	127 (30)	
	lleum IV	127 (30)	
	Apply Villus Accessible Surface Area	Active	Default
Plicae Circulares	Fold Expansion		
	Duodenum	1 (0)	In-house meta-
	Jejunum I	1.97 (24.54)	analysis based on
	Jejunum II	1.38 (20.19)	published data
	lleum l	1.1 (9.15)	from (Wilson,
	lleum II	1.1 (9.15)	1967).
	lleum III	1.08 (16.07)	
	lieum IV	1.04 (12.4)	
	Colon	1(0)	
Paracellular	Pore Radius ²		
	Duodenum	8.6 (0)	(Sugano, 2009).
	Jejunum I	8.6 (0)	(00800) =000).
	Jejunum II	8.6 (0)	
	Ileum I	8.6 (0)	
	lleum II	8.6 (0)	
	lleum III	8.6 (0)	
	lleum IV	8.6 (0)	
	Colon	8.6 (0)	
	Paracellular Scalar	0.00039	
	Pore Electric Gradient Potential		
	Drop (mV)	-64.145	
Luminal Boundary	Unstirred Layer Thickness (µm) Mean (CV %)		
	Duodenum	170 (22.35)	(Atuma et al.,
	Jejunum I	123 (3)	2001).
	Jejunum II	123 (3)	
	lleum I	480 (10)	
	lleum II	480 (10)	
	lleum III	480 (10)	
	lleum IV	480 (10)	
	Colon	830 (13)	
		1	1





	Unstirred Layer pH Mean (CV %)		
	Duodenum	6.5 (0.5)	
	Jejunum l	6.5 (0.5)	
	Jejunum II	6.5 (0.5)	
	lleum I	6.5 (0.5)	
	lleum II	6.5 (0.5)	
	lleum III	6.5 (0.5)	
	lleum IV	65 (05)	
	Colon	65 (05)	
	Earce gut unstirred boundary laver	inactive	Default
	nH to equal bulk lumen nH	Indelive	Delault
	pri to equal buik lumen pri		
Viscosity	Apparent Viscosity (cB) Easted		
viscosity	Apparent viscosity (CF) Fasted		In house analysis
	Stemach	2 (71)	hasad an nublished
	Stomach	3(71)	date from
	Duodenum	3 (71)	data from
	Jejunum I	3 (71)	(Pedersen et al.,
	Jejunum II	3 (71)	2013).
	lleum I	3 (71)	
	lleum II	3 (71)	
	lleum III	3 (71)	
	lleum IV	3 (71)	
	Colon	3 (71)	
	Apparent Viscosity (cP) Fed		
	Mean (CV %)		In-house analysis
	Stomach	232 (32)	based on published
	Duodenum	65 (27)	data from (Radwan
	Jejunum I	33 (36)	et al., 2012).
	Jejunum II	12 (14)	
	lleum I	9 (2)	
	lleum II	3 (71)	
	Ileum III	3 (71)	
	lleum IV	3 (71)	
	Colon	3 (71)	
		- ()	
Luminal Fluid Volume	Initial volume of stomach fluid (mL)		
Fluid Volume Dynamics (FVD)	Fasted Mean (CV %)	50 (30)	In-house analysis
Model	Fed Mean (CV %)	1000 (30)	based on published
	User Defined Intestinal Baseline	()	data from (ICRP.
	Fluid Volumes- Fasted Mean (CV %)	inactive	2002) & (Schiller et
	Duodenum	34 35	al 2005)
		21 1	uii, 2005).
		21.1	
		12.6	
		12.0	
		12.0	
		12.0	
		12.6	
	Total Jej I to lie IV	92.6 (37)	
	Colon	13 (4.4)	
	Fed Mean (CV %)		
	Duodenum	34.35	
	Jejunum I	21.1	
	Jejunum II	21.1	
	lleum I	12.6	
	lleum II	12.6	





	lleum III	12.6	
	lleum IV	12.6	
		02 6 (27)	
		92.0 (57)	
	Colon	13 (4.4)	
Advanced Fluid Volume	Basal (Steady State) Fluid Volumes		In-house meta-
Dynamics (aEVD) Model	(ml) Moon (CV %)		analysis based on
	(IIIL) Mean (CV 78)	24.26 (07)	allalysis based oli
Baseline volumes	Stomach	31.36 (97)	published data
	Small Intestine	85.8 (65)	including (Schiller
	Colon	11.92 (90)	et al., 2005).
	Recal Distribution of Water Within		
	Basal Distribution of Water Within		
	Small Intestine- % of Total Volume	40.55	
	Duodenum	10.55	In-nouse analysis
	Jejunum I	15.55	based on published
	Jejunum II	22.6	data from (Mudie
	lleum I	13.53	et al., 2014) &
	lleum II	13.53	(Schiller et al.,
	lleum III	12.12	2005).
	lleum IV	12.12	
	Volume in mL		
	Duodenum	9.0519	
	Jejunum I	13.3419	
	Jejunum II	19.3908	
	lleum I	11.6087	
	lleum II	11.6087	
	lleum III	10.399	
	Ileum IV	10.399	
Secretions	Stomach (Fasted Mean)-		In-house analysis
Fluid Secretion Rates	Saliva Secretion Rate (mL/h)	33.3229	based on published
	Gastric Juice Secretion Rate (mL/h)	82.82524	data including
	Stomach High Fat Fed/Fed/Low Fat		(Richardson and
	Fed Secretion Rates-		Feldman, 1986).
	Time Dependent Saliva Secretion		
	Rsaliva fasted (mL/h) Mean	33.3229	
	T_{et} (h) Mean (CV %)	0.335 (30)	
	Realize max (ml /h) Mean (CV %)	199 36 (52)	
	$T_{\rm ex}$ (h) Mean (CV %)	2.4 (16)	
	Slope (ml /h/h)	/95 6331	
	K (1/b)	0 8662704	
	Time Dependent Gastric Secretion	0.0002734	
	Reastric fasted (mL/h) Mean	82.82525	
	T_{gmax} (h) Mean (CV %)	0.63 (26)	
	Bractric max (ml /h) Mean (CV/%)	209 67 (57)	
	T_{res} (h) Mean (CV %)	3 2 (14 28)	
	Slope (ml /h/h)	201 3/09	
		0.361/02	
	NS (+/11) Duodonum Socration Potos (ml /h)	0.301402	In house analysis
	Duouenum secretion Rates (mL/N)	26.28 (66)	m-nouse analysis
	Pancreatic Juice Mean (CV %)		based on published
	Bile Mean (CV %)	29.2/10.051 (30)	data including
	Brunner's Fasted/Fed Mean (CV %)	5.21 (30)	(Malagelada et al.,
	Other Secretion (TOS * f _{surface,duo})	4.728084	1979) & (Gullo et
			al., 1988). Bile
			secretion rate





	Time Dependent Pancreatic		depends on the
	Secretion (High Eat Fed/Fed/Low Eat	26.28 (66)	enterohenatic
	End)	0.48 (30)	recirculation model
		0.46 (50)	
	Rpancreatic, fasted (IIIL/II) Medii (CV %)	78.18 (42)	selected.
	$I_{p,max}$ (n) IVIEAN (CV %)	3.38 (30)	
	Rpancreatic, max (mL/h) Mean (CV %)	108.125	
	T _{ps} (h) Mean (CV %)	0.375933	
	Slope (mL/h/h)	Defined in liver tab	
	K _s (1/h)		
	Time Dependent Bile Secretion	79.17 (30)	
	Rest of SI Secretion Rates (mL/h)	74.44191	In-house meta-
	Fasted Mean (CV %)		analysis based on
	Total Other Secretion (TOS)	79.17 (30)	published data
	Other Secretion (TOS * (1-f _{surface,duo}))	74.44191	including (ICRP,
	Fed Mean (CV %)		2002).
	Total Other Secretion (TOS)		,
	Other Secretion (TOS $*$ (1-f _{surface dup}))	5.42 (30)	
	Colonic Secretion Rates (ml /h)	5 42 (30)	
	Easted Mean (CV %)	3112 (30)	
	Fed Mean (CV %)		Values are back-
		1/ 100//11 8605	calculated from
Water Absorption Pate	Moon	2 0 2 7 2 4	factod residence
Constants (h-1)	Duadanum	0.200695	times secretions
constants (n)		0.560065	unies, secretions
		1.92378	
		1.01863	volumes. Duodenai
	lieum I	1.36233	water absorption
	lieum II	1.13/13	rate depends on
	lleum III	2.116475	what bile salt
	Ileum IV		model is selected.
	Colon		
		50 (20)	luminal contant for
		50 (30)	Luminal content for
Luminal Content Weight	Fasted (grams) Mean (CV %)	34 (30)	stomach to lieum
	Stomacn	23 (30)	are assumed to be
	Duodenum	23 (30)	the baseline fluid
	Jejunum I	14 (30)	volume for a
	Jejunum II	14 (30)	population
	lleum l	14 (30)	representative
	lleum II	14 (30)	corrected using a
	lleum III	133.29 (62.2)	density of 1g/ml
	lleum IV		(see reference
	Colon	1000 (30)	above).
	Fed (grams) Mean (CV %)	34 (30)	For colon: In-house
	Stomach	23 (30)	meta-analysis
	Duodenum	23 (30)	based on published
	Jejunum I	14 (30)	data including
	Jejunum II	14 (30)	(Cummings, 2011)
	lleum I	14 (30)	
	lleum II	14 (30)	
	lleum III	133.29 (62.2)	
	lleum IV		
	Colon		
<u> </u>	1		· · · · · · · · · · · · · · · · · · ·

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)
	KPAIR	0.037	(Rodgers and
	KP1pp	0.068	Rowland 2006)
	Tissue volume fold scalar	1	110001010, 2000)
	IW nH ² -	-	
		7	(Coffey and De
	Subcellular	5	
	Membrane Potential (m)/)-	5	(Boos and Boron
		_/11	1021)
	Subcollular	10	(1301)
	Vo (fraction tissue volume)	10	(Vali Dyke, 1988)
	ve (fraction tissue volume)	0.001925	
Pono	Relative Valume of Mat Tissue (%)		
воне	Relative volume of wet fissue (%)-	0.0	In house analysis
		9.8	In-nouse analysis
		34.1	based on (Poulin
		7.4	anu men, 2002).
	NP Sub-selluler	0.11	
		0	(Dedeens stal
	AP (mg/g)	0.67	(Rodgers et al.,
	Binding Proteins-		2005)
	KPALB	0.1	(Rodgers and
		0.05	Rowland, 2006)
	lissue 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 (%)-		In have enablish
	EW	9.2	In-nouse 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
	KPLPP	0.041	Rowland, 2006)
	Tissue volume fold scalar	1	
	IW pH ² -		(Snen et al.,
	Local	7.12	2004)
	Subcellular	5	(Cottey 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)
lleast	Polotivo Volumo of Mot Tissue (%)		
Heart	EW/	21.2	In-house analysis
		J1.J	hased on (Poulin
	NI	44.5	and Theil 2002)
		1.15	
	Subcellular	1.00	
	$\Delta P (mg/g)$	3 07	
	Binding Proteins-	5.07	
		0 157	(Rodgers and
	K PL DD	0.157	Rowland, 2006)
	Tissue volume fold scalar	1	
	IW nH ² -	-	
	Local	7	(Coffey and De
	Subcellular	5	Duve, 1968)
	Membrane Potential (mV)-	5	(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	
	KPLPP	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)-		(Coffey and De
	Local	-70	Duve, 1968)
			(Roos and Boron,
	Subcellular	10	1981)
	Ve (fraction tissue volume)	0.001925	, (Van Dvke. 1988)
	- (,		(- ,,
Liver	Relative Volume of Wet Tissue (%)-		
	FW/	16.5	
		58.6	In-house analysis
	NU	3 / 8	hased on (Poulin
	ND	2 52	and Theil 2002)
	Subcollular	1	anu men, 2002).
		т т оо	(Logan at al
	AP (mg/g)	5.09	(Logan et al.,
	Binding Proteins-	0.000	2013)
	KPALB	0.086	
		0.161	(Rodgers and
	lissue volume fold scalar IW pH ² -	1	Rowland, 2006)
	Local	7	
	Subcellular	5	(Coffey and De
	Membrane Potential (mV)-	5	Duve 1968)
		_/11	(Roos and Boron
	Subcellular	10	1981)
	Vo (fraction tissue volume)	0 001275	(1/20 D)/(20 1088)
		0.001375	(Van Dyke, 1988)
Lung	Relative Volume of Wet Tissue (%)-		
	EW	34.8	
	IW	46.3	In-house analysis
	NL	0.3	based on (Poulin
	NP	0.9	and Theil, 2002).
	Subcellular	1	
	AP (mg/g)	0.5	(Logan et al.,
	Binding Proteins-		2013)
	KPAIR	0.212	/
	KP1pp	0.168	(Rodgers and
	Tissue volume fold scalar	1	Rowland 2006)
	IW pH ² -	-	
	local	67	
		0.7	(Effros and
	Subcellular	5	Chinard 1969)
	Membrane Potential (m\/)-	5	(Coffey and De
		-/11	
		71	(Roos and Boron
	Subcollular	10	1001)
	Va (fraction tissue valume)	10	$(1/20 D) (k_0 1099)$
		0.0050985	(Vali Dyke, 1988)
Muscle	Relative Volume of Wet Tissue (%)-		
	EW	9.1	
	IW	66.9	In-house analysis
	NL	2.38	based on
	NP	0.72	published data
	Subcellular	0	including (Poulin
	AP (mg/g)	2.49	and Theil, 2002)
			& (Bergstrom et
	Binding Proteins-		al., 1974).





	KP _{ALB}	0.034	
	KPLPP	0.059	(Rodgers and
	Tissue volume fold scalar	1	Rowland, 2006)
	IW pH ² -	-	
	local	7	
	Subcollular	5	(Coffey and De
	Mombrane Detential (m)()	5	
	wembrane Potential (mv)-		Duve, 1900)
		-41	(Roos and Boron,
	Subcellular	10	1981)
	Ve (fraction tissue volume)	0.001375	(Van Dyke, 1988)
Pancreas	Relative Volume of Wet Tissue (%)-		
	EW	12	
	IW	66.4	(Rodgers and
	NL	4.1	Rowland, 2006)
	NP	0.93	
	Subcellular	0	
	AP (mg/g)	1.67	
	Binding Proteins-		
	KPAIB	0.06	
	KPIPP	0.06	(Kawai et al.,
	Tissue volume fold scalar	1	1994)
	$IW pH^2$ -	-	
	local	7	
	Subcellular	5	(Coffey and De
	Mombrano Potontial (m)()	5	
		41	(Poos and Poron
	LOCAI Such as Nuclear	-41	
		10	(1901)
	Ve (fraction tissue volume)	0.001375	(Van Dyke, 1988)
ch in	Deletive Melvine - findet Tierve (94)		
Skin	Relative volume of wet lissue (%)-		
	EW	62.3	
	IW	9.47	In-nouse analysis
	NL	2.84	based on (Poulin
	NP	1.11	and Theil, 2002).
	Subcellular	0	
	AP (mg/g)	1.32	
			(Rodgers et al.,
	Binding Proteins-		2005)
	KP _{ALB}	0.277	
	KPLPP	0.096	(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)	0.00275	(Van Dyke. 1988)
		0.00275	
Snleen	Relative Volume of Wet Tissue (%)-		
Spicen	FW/	20.8	
		57.0	In-house analysis
		2.01	hased on (Poulin
		2.01	and Thoil 2002)
	NP	1.98	anu men, 2002).





AP (mg/g) Binding Proteins- KPAia 2.81 (Rodgers et al., 2005) KPAia 0.097 2005) KPaia 0.207 (Rodgers and Rowland, 2006) IW pH ²⁻ Local 7 5 Local 7 0.207 Subcellular 7 0.207 Membrane Potential (mV)- Local 41 (Roos and Boron, 1981) Subcellular 0.001375 (Van Dyke, 1988) Ve (fraction tissue volume) 0.001375 (Van Dyke, 1988) Plasma Relative Volume of Wet Tissue (%)- EW 94.5 In-house analysis NL 0.35 based on (Poulin NP 0.23 and Theil, 2002). AP (mg/g) 0.04 1 (Rodgers et al., 2005) 2005) KW 0.11 (Boon et al., 1W pH ²⁻ Local (Rodgers et al., 2005) 2005) KW 0.23 in house analysis based on 2005) 2005) KW 0.17 published data 0.17 published data 0.44 including (Bolmann et al., 1979), (Rodgers 41, 2002). VP (mg/g) 0.23 1 1979), (Rodger		Subcellular	0	
Binding Proteins- KPALB(Rodgers et al., (Rodgers and Rowland, 2006)KPALB0.0972005)KPALB0.207(Rodgers and Rowland, 2006)Wy PH*- Local1Rowland, 2006)Local7SubcellularSubcellular5(Coffey and De Duve, 1968)Local41(Roos and Boron, SubcellularVe (fraction tissue volume)0.001375(Van Dyke, 1988)PlasmaRelative Volume of Wet Tissue (%)- EW94.5EW94.5In-house analysis based on (Poulin NPNL0.35based on (Poulin NPNP0.23and Theil, 2002).AP (mg/g)0.04(Rodgers et al., (Boon et al., 100)Tissue volume fold scalar1(Rodgers et al., (Rodgers et al., 2005)RBCRelative Volume of Wet Tissue (%)- EW0In-house analysis based on (Poulin NPNP0.23and Theil, 2002). AP (mg/g)0.04(Rodgers et al., 2005)RBCRelative Volume of Wet Tissue (%)- EW0In-house analysis based on 0NP0.29published data including Tissue volume fold scalar1(Rodgers et al., 2005)Wy PH*- Local0.29published data including Tissue volume fold scalar1(Boon et al., 1979), (Rodgers (Rodgers (Rodgers (Boon et al., 1979), (Rodgers (Rodgers (Rodgers et al., 2005) & (Boon et al., 1979), (Rodgers (Rodgers (Rodgers11969)Local7.22et al., 2005) & (AP (mg/g)	2.81	
KPAB KPup0.097 0.2072005) (Rodgers and Rowland, 2006)KPAB KPup0.207(Rodgers and Rowland, 2006)Tissue volume fold scalar IW pH²- Local75Local7(Coffey and De Duve, 1968)Membrane Potential (mV)- Local-41(Roos and Boron, 1981)Ve (fraction tissue volume)0.001375(Van Dyke, 1988)PlasmaRelative Volume of Wet Tissue (%)- EW94.5In-house analysis based on (Poulin NPNP0.23and Theil, 2002).AP (mg/g)0.041Tissue volume fold scalar IW pH²- Local1(Boon et al., 1969)RBCRelative Volume of Wet Tissue (%)- EW66.6In-house analysis based on (Poulin 1969)RBCRelative Volume of Wet Tissue (%)- EW0In-house analysis based on (Poulin 1969)NP0.23and Theil, 2002).AP (mg/g)0.44including including 11NP0.29published data including 11NP0.29published data including 11NP0.29published data including 11NP0.29published data including 11NP0.29published data including 11NP0.29published data including 11NP0.291969)NP0.291969)NP0.211969)NP0.2210NP0.2311User defined Lua Script (See		Binding Proteins-		(Rodgers et al
NADSCOOTLOOTRPup0.207(Rodgers and Rowland, 2006)ITissue volume fold scalar1Rowland, 2006)IW pH2-1Rowland, 2006)Local75Subcellular5(Coffey and De Duve, 1968)Local-41(Roos and Boron, SubcellularVe (fraction tissue volume)0.001375(Van Dyke, 1988)PlasmaRelative Volume of Wet Tissue (%)- EW94.5In-house analysis based on (Poulin and Theil, 2002).NP0.23and Theil, 2002).NP0.044(Boon et al., 1969)IWy H7- Local1(Boon et al., 1969)Local7.4(Rodgers et al., 2005)RBCRelative Volume of Wet Tissue (%)- EW0Relative Volume of Wet Tissue (%)- EW0.044In-house analysis based on (Poulin and Theil, 2002).(Rodgers et al., 2005)RBCRelative Volume of Wet Tissue (%)- EW0NP0.23published data including (Rodgers et al., 2005)NU0.17based on Dased on DYPNP0.29published data including (Bolmann et al., 1079), (Rodgers tet al., 2005) & (Boon et al., 1979), (Rodgers tet al., 2005) & (Boon e			0.097	2005)
NumberDecomposition(Notigets and General Science)Tissue volume fold scalar1Rowland, 2006)IW pH2-71Local71Subcellular101981)Ve (fraction tissue volume)0.001375(Van Dyke, 1988)Ve (fraction tissue volume)0.001375In-house analysisbased on (Poulin0.223and Theil, 2002).AP (mg/g)0.04(Boon et al.,NP0.23and Theil, 2002).AP (mg/g)0.04(Rodgers et al.,Local7.4(Rodgers et al.,RBCRelative Volume of Wet Tissue (%)-(Rodgers et al.,EW0.23and Theil, 2002).AP (mg/g)0.04(Rodgers et al.,Local7.4(Rodgers et al.,W pH2-0(Rodgers et al.,Local7.29published dataIn-house analysis0.17based on (PoulinNP0.29published dataNP0.29published dataIncludingTissue volume fold scalar1IW pH2-0.17based onLocal7.22et al., 2005) & (Boon et al.,1979) (Kodgers101979) (KodgersLocal7.22et al., 2005) & (Boon et al.,1969)101969)1969)Define Cardiac OutputLua ScriptUser defined Lua Script (See section S).Cardiac Output Scalar11		KPLDD	0.007	(Rodgers and
Insular out scalar1Noward, 2000)IW pH2- Local7(Coffey and De Duve, 1968)Subcellular5(Coffey and De Duve, 1968)Iocal-41(Roos and Boron, SubcellularVe (fraction tissue volume)0.001375(Van Dyke, 1988)PlasmaRelative Volume of Wet Tissue (%)- EW94.5IW0In-house analysis based on (Poulin NPNL0.355based on (Poulin NPNP0.23and Theil, 2002).AP (mg/g)0.04Tissue volume fold scalar1IW pH2- Local7.4IW pH2- Local2005)EW0IW pH2- Local1NE0IW pH2- Local1INV NL0.17Bedive Volume of Wet Tissue (%)- EW2005)EW0IW pH2- Local1INV NL0.17Bedive Volume of Wet Tissue (%)- EW2005)EW0NL0.17Define Cardiac OutputTissue volume fold scalar INVLocal7.22EW0.44Including Tissue volume fold scalar INVNL0.17Define Cardiac OutputLua ScriptLocalScript (See section S). Cardiac Output ScalarLocalScript (See section S). Cardiac Output ScalarLocalScript (See section S).Site of the scalar Site of the scalarRBCLocal Rembrane Potential (mV)-		Tissue volume fold scalar	1	(Nougers and Rowland 2006)
Iw µr - Local77Local7(Coffey and De Duve, 1968)Membrane Potential (mV)- Local41(Roos and Boron, 			T	Rowianu, 2000)
Lucal Subcellular/ Membrane Potential (mV)- Local/ - 			7	
SubcellularSColley and De (Ros and Boron, 1983) (Ros and Boron, 1981) (Van Dyke, 1988)PlasmaRelative Volume of Wet Tissue (%)- EW94.5In-house analysis based on (Poulin NLNL0.35based on (Poulin NPNL0.004In-house analysis based on (Poulin NPNP0.23and Theil, 2002). AP (mg/g)AP (mg/g)0.04In-house analysis based on (Poulin NPLocal7.4(Rodgers et al., 1969) LocalRBCRelative Volume of Wet Tissue (%)- Local7.4EW0In-house analysis based on Poulin 1969) LocalNV0.04In-house analysis based on Poulin 1969) LocalRBCRelative Volume of Wet Tissue (%)- EW0EW0In-house analysis based on published data including (Boilmann et al., 1979), (Rodgers et al., 2005) & (Boolmann et al., 1979), (Rodgers et al., 2005) & (Boolmann et al., 1979), (Rodgers et al., 2005) & (Boolmann et al., 1969)Define Cardiac OutputLua ScriptUser defined Lua Script (See section S). Cardiac Output Scalar		Lucal		(Coffee and De
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Cardiac Output Scalar5).1			Script (See section	
Cardiac Output Scalar 1			5).	
		Cardiac Output Scalar	1	
Male/Female			Male/Female	
Tissue blood flow rates (% ofAdipose5/8.5(ICRP, 2002).	Tissue blood flow rates (% of	Adipose	5/8.5	(ICRP, 2002).
cardiac output) Bone 5/5	cardiac output)	Bone	5/5	
Brain 12/12		Brain	12/12	
Stomach & Oesophagus 1/1		Stomach & Oesophagus	1/1	
Small Intestine 10/11		Small Intestine	10/11	
Villi 6/6		Villi	6/6	
Large Intestine 4/5		Large Intestine	4/5	
Heart 4/5		Heart	4/5	
Kidney 19/17		Kidney	19/17	
Liver (Arterial) 6.5/6.5		Liver (Arterial)	6.5/6.5	
Liver (Portal) 19/21.5		Liver (Portal)	19/21.5	
Lung 100/100		Lung	100/100	





	Muselo	17/12		
	Demorran	1//12		
	Pancreas			
	Skin	5/5		
	Spleen	2/3		
	Cervix	NA/0.15		
	Vagina	NA/0.24		
	Additional Organ	0.65/0.65		
	SC Site	0.016/0.016		
		01020,01020		
Lymph Flow Pate (% total	Adinose	12.8	(Gill et al. 2016)	
Lymph flow	Adipose	12.0	(Gill et al., 2010).	
iymph now)	Bone	0		
	Brain	1.05		
	Stomach & Oesophagus	12		
	Heart	1		
	Kidney	8.5		
	Liver (Arterial)	33		
	Lung	3		
	Muscle	16		
	Pancreas	03		
	Fallcreas Clein	0.5		
	SKIII	7.5		
	Spleen	1		
	Additional Organ	0		
	SC Site	0.039		
Lymph Flow Bate (non ren)	Adinose	0 0/5/908		
	Rono	0.0454508		
(L/II)	Bolle	0 00272167		
	Brain	0.003/310/		
	Stomach & Oesophagus	0.0426476		
	Heart	0.00355397		
	Kidney	0.0302087		
	Liver (Arterial)	0.117281		
	Lung	0.0106619		
	Muscle	0.0568635		
	Pancreas	0.00106619		
	Skin	0.025944		
	Skin	0.023344		
	Spieen	0.00355397		
	Additional Organ	0		
	SC Site	0.000138605		
Time-dependent Small	High Fat Fed/Fed/Low Fat Fed			
Intestine Blood Flow	Omax Mean (CV %)	4 (20)	(Rose et al	
		4 (20)	(1030 61 al.,	
red/rasted ratio		0.093147 (30)	2017).	
	kQ (1/h) Mean (CV %)	1.25 (30)		
	Cap on Portal Vein Blood Flow			
	Fed/Fasted Ratio	10		
	BLOOD			
Blood Composition	Male Mean (CV %)	43 (6.5)	(ICRP, 2002).	
Haematocrit (%)	Female Mean (CV %)	38 (7.1)		
Alpha-1-acid-glyconrotein	Male Mean (CV %)	0 793 (23)	In-house meta-	
	Eemale Mean (CV %)	0 715 (24)	analysis based on	
(6/ -/		0.7 13 (24)	nublished date	





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



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Simcyp

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.

160 А В 140 140 120 120 100 100 Weight (kg) Weight (kg) 80 80 60 60 40 40 20 20 10 100 10 Ag Age (vears)

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

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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) aacid 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

Howgate EM, Rowland Yeo K, Proctor NJ, Tucker GT, Rostami-Hodjegan A. 2006. Prediction of in vivo drug clearance from in vitro data. L: Impact of inter-individual variability. Xenobiotica 36: 473-497. 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.

Johnson TN, Zhou D, Bui KH. 2014. Development of physiologically-based pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents. *Biopharmaceutics & Drug Disposition* 35(6), 341-352.

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.





4. References

- AL-JAHDARI, W. S., YAMAMOTO, K., HIRAOKA, H., NAKAMURA, K., GOTO, F. & HORIUCHI, R. 2006. Prediction of total propofol clearance based on enzyme activities in microsomes from human kidney and liver. *Eur J Clin Pharmacol*, 62, 527-33.
- ALEMAN, C., ANNEREAU, J. P., LIANG, X. J., CARDARELLI, C. O., TAYLOR, B., YIN, J. J., ASZALOS, A.
 & GOTTESMAN, M. M. 2003. P-glycoprotein, expressed in multidrug resistant cells, is not responsible for alterations in membrane fluidity or membrane potential. *Cancer Res*, 63, 3084-91.

ATUMA, C., STRUGALA, V., ALLEN, A. & HOLM, L. 2001. The adherent gastrointestinal mucus gel layer: thickness and physical state in vivo. *Am J Physiol Gastrointest Liver Physiol*, 280, G922-9.

BAKER, M. 2014. Kinetic determinants of hepatic uptake. PhD, University of Sheffield.

BARTER, Z. E. 2006. *Determination of hepatic scaling factors and their inter-individual variability for use in the prediction of human metabolic clearance.* PhD, University of Sheffield.

- BARTER, Z. E., BAYLISS, M. K., BEAUNE, P. H., BOOBIS, A. R., CARLILE, D. J., EDWARDS, R. J., HOUSTON, J. B., LAKE, B. G., LIPSCOMB, J. C., PELKONEN, O. R., TUCKER, G. T. & ROSTAMI-HODJEGAN, A. 2007. Scaling factors for the extrapolation of in vivo metabolic drug clearance from in vitro data: reaching a consensus on values of human microsomal protein and hepatocellularity per gram of liver. *Curr Drug Metab*, 8, 33-45.
- BARTER, Z. E., CHOWDRY, J. E., HARLOW, J. R., SNAWDER, J. E., LIPSCOMB, J. C. & ROSTAMI-HODJEGAN, A. 2008. Covariation of human microsomal protein per gram of liver with age: absence of influence of operator and sample storage may justify interlaboratory data pooling. *Drug Metab Dispos*, 36, 2405-9.
- BARTER, Z. E., PERRETT, H. F., YEO, K. R., ALLORGE, D., LENNARD, M. S. & ROSTAMI-HODJEGAN, A. 2010. Determination of a quantitative relationship between hepatic CYP3A5*1/*3 and CYP3A4 expression for use in the prediction of metabolic clearance in virtual populations. *Biopharm Drug Dispos*, 31, 516-32.
- BERGSTROM, J., FURST, P., NOREE, L. O. & VINNARS, E. 1974. Intracellular free amino acid concentration in human muscle tissue. *J Appl Physiol*, 36, 693-7.
- BLAIN, P. G., MUCKLOW, J. C., RAWLINS, M. D., ROBERTS, D. F., ROUTLEDGE, P. A. & SHAND, D. G. 1985. Determinants of plasma alpha 1-acid glycoprotein (AAG) concentrations in health. *Br J Clin Pharmacol*, 20, 500-2.
- BLOUCH, K., DEEN, W. M., FAUVEL, J. P., BIALEK, J., DERBY, G. & MYERS, B. D. 1997. Molecular configuration and glomerular size selectivity in healthy and nephrotic humans. *Am J Physiol*, 273, F430-7.
- BOLLMANN, G., JAGER, B. & FREITAG, G. 1979. In vitro effects of contrast media on the water content of human erythrocytes. *Acta Radiol Diagn (Stockh),* 20, 681-7.
- BOON, J., BROEKHUYSE, R. M., VAN MUNSTER, P. & SCHRETLEN, E. 1969. Abnormal pattern of the phospholipids of plasma and erythrocytes in four children with obstructive jaundice with abnormal spontaneous hemolysis. *Clin Chim Acta*, 23, 453-61.
- BURK, O., TEGUDE, H., KOCH, I., HUSTERT, E., WOLBOLD, R., GLAESER, H., KLEIN, K., FROMM, M. F., NUESSLER, A. K., NEUHAUS, P., ZANGER, U. M., EICHELBAUM, M. & WOJNOWSKI, L. 2002. Molecular mechanisms of polymorphic CYP3A7 expression in adult human liver and intestine. *J Biol Chem*, 277, 24280-8.
- CECCHIN, E., INNOCENTI, F., D'ANDREA, M., CORONA, G., DE MATTIA, E., BIASON, P., BUONADONNA, A. & TOFFOLI, G. 2009. Predictive role of the UGT1A1, UGT1A7, and UGT1A9 genetic variants and their haplotypes on the outcome of metastatic colorectal cancer patients treated with fluorouracil, leucovorin, and irinotecan. *J Clin Oncol*, 27, 2457-65.
- COCHET, A., PIGEONNAT, S., KHOURY, B., VRIGNEAUD, J. M., TOUZERY, C., BERRIOLO-RIEDINGER, A., DYGAI-COCHET, I., TOUBEAU, M., HUMBERT, O., COUDERT, B., FUMOLEAU, P., ARNOULD, L. & BRUNOTTE, F. 2012. Evaluation of breast tumor blood flow with dynamic first-pass 18F-FDG PET/CT: comparison with angiogenesis markers and prognostic factors. *J Nucl Med*, 53, 512-20.
- COCKCROFT, D. W. & GAULT, M. H. 1976. Prediction of creatinine clearance from serum creatinine. *Nephron,* 16, 31-41.

CERTARA.O

- COFFEY, J. W. & DE DUVE, C. 1968. Digestive activity of lysosomes. I. The digestion of proteins by extracts of rat liver lysosomes. *J Biol Chem*, 243, 3255-63.
- COLLER, J. K., KREBSFAENGER, N., KLEIN, K., ENDRIZZI, K., WOLBOLD, R., LANG, T., NUSSLER, A., NEUHAUS, P., ZANGER, U. M., EICHELBAUM, M. & MURDTER, T. E. 2002. The influence of CYP2B6, CYP2C9 and CYP2D6 genotypes on the formation of the potent antioestrogen Z-4-hydroxy-tamoxifen in human liver. *Br J Clin Pharmacol*, 54, 157-67.
- CRETTOL, S., DEGLON, J. J., BESSON, J., CROQUETTE-KROKKAR, M., GOTHUEY, I., HAMMIG, R., MONNAT, M., HUTTEMANN, H., BAUMANN, P. & EAP, C. B. 2005. Methadone enantiomer plasma levels, CYP2B6, CYP2C19, and CYP2C9 genotypes, and response to treatment. *Clin Pharmacol Ther*, 78, 593-604.
- CROWE, P. T. & MARSH, M. N. 1993. Morphometric analysis of small intestinal mucosa. IV. Determining cell volumes. *Virchows Arch A Pathol Anat Histopathol*, 422, 459-66.
- CUBITT, H. E., YEO, K. R., HOWGATE, E. M., ROSTAMI-HODJEGAN, A. & BARTER, Z. E. 2011. Sources of interindividual variability in IVIVE of clearance: an investigation into the prediction of benzodiazepine clearance using a mechanistic population-based pharmacokinetic model. *Xenobiotica*, 41, 623-38.
- CUMMINGS, J. H. 2011. Effects of dietary fiber on fecal weight and composition. *In:* SPILLER, G. A. (ed.) *CRC handbook of dietary fiber in human nutrition.* CRC Press.
- DANOFF, T. M., CAMPBELL, D. A., MCCARTHY, L. C., LEWIS, K. F., REPASCH, M. H., SAUNDERS, A. M., SPURR, N. K., PURVIS, I. J., ROSES, A. D. & XU, C. F. 2004. A Gilbert's syndrome UGT1A1 variant confers susceptibility to tranilast-induced hyperbilirubinemia. *Pharmacogenomics J*, 4, 49-53.
- DARWICH, A. S., BURT, H. J. & ROSTAMI-HODJEGAN, A. 2019. The nested enzyme-within-enterocyte (NEWE) turnover model for predicting dynamic drug and disease effects on the gut wall. *Eur J Pharm Sci*, 131, 195-207.
- DE WAZIERS, I., CUGNENC, P. H., BERGER, A., LEROUX, J. P. & BEAUNE, P. H. 1991. Drug-metabolizing enzyme expression in human normal, peritumoral and tumoral colorectal tissue samples. *Carcinogenesis*, 12, 905-9.
- DEGEN, L., MATZINGER, D., DREWE, J., NISSLE, S., MAECKE, H., LENGSFELD, H., HADVARY, P. & BEGLINGER, C. 2006. Role of free fatty acids in regulating gastric emptying and gallbladder contraction. *Digestion*, 74, 131-9.
- DIAKIDOU, A., VERTZONI, M., GOUMAS, K., SODERLIND, E., ABRAHAMSSON, B., DRESSMAN, J. & REPPAS, C. 2009. Characterization of the contents of ascending colon to which drugs are exposed after oral administration to healthy adults. *Pharm Res,* 26, 2141-51.
- DONNELLY, L. A., DONEY, A. S., TAVENDALE, R., LANG, C. C., PEARSON, E. R., COLHOUN, H. M., MCCARTHY, M. I., HATTERSLEY, A. T., MORRIS, A. D. & PALMER, C. N. 2011. Common nonsynonymous substitutions in SLCO1B1 predispose to statin intolerance in routinely treated individuals with type 2 diabetes: a go-DARTS study. *Clin Pharmacol Ther*, 89, 210-6.
- DROZDZIK, M., BUSCH, D., LAPCZUK, J., MULLER, J., OSTROWSKI, M., KURZAWSKI, M. & OSWALD, S. 2018. Protein Abundance of Clinically Relevant Drug-Metabolizing Enzymes in the Human Liver and Intestine: A Comparative Analysis in Paired Tissue Specimens. *Clin Pharmacol Ther*, 104, 515-524.
- DU BOIS, D. & DU BOIS, E. F. 1916. A Formula to Estimate the Approximate Surface Area if Height and Weight Be Known. *Archives of Internal Medicine*, 17, 863-871.
- DUDLEY, A. J. & BROWN, C. D. 1995. pH-dependent transport of procainamide in cultured renal epithelial monolayers of OK cells: consistent with nonionic diffusion. *Br J Pharmacol*, 116, 1685-91.
- EFFROS, R. M. & CHINARD, F. P. 1969. The in vivo pH of the extravascular space of the lung. *J Clin Invest,* 48, 1983-96.
- ELLENBOGEN, S., JENKINS, S. A., GRIME, J. S., CRITCHLEY, M., MACKIE, C. R. & BAXTER, J. N. 1988. Preduodenal mechanisms in initiating gallbladder emptying in man. *Br J Surg*, 75, 940-5.
- EMI, Y., OMURA, S., IKUSHIRO, S. & IYANAGI, T. 2002. Accelerated degradation of mislocalized UDPglucuronosyltransferase family 1 (UGT1) proteins in Gunn rat hepatocytes. *Arch Biochem Biophys*, 405, 163-9.



- ENGIN, K., LEEPER, D. B., CATER, J. R., THISTLETHWAITE, A. J., TUPCHONG, L. & MCFARLANE, J. D. 1995. Extracellular pH distribution in human tumours. *Int J Hyperthermia*, 11, 211-6.
- FADDA, H. M., MERCHANT, H. A., ARAFAT, B. T. & BASIT, A. W. 2009. Physiological bicarbonate buffers: stabilisation and use as dissolution media for modified release systems. *Int J Pharm*, 382, 56-60.
- FALLINGBORG, J., CHRISTENSEN, L. A., INGEMAN-NIELSEN, M., JACOBSEN, B. A., ABILDGAARD, K. & RASMUSSEN, H. H. 1989. pH-profile and regional transit times of the normal gut measured by a radiotelemetry device. *Aliment Pharmacol Ther*, **3**, 605-13.
- GERVOT, L., CARRIERE, V., COSTET, P., CUGNENC, P. H., BERGER, A., BEAUNE, P. H. & DE WAZIERS, I. 1996. CYP3A5 is the major cytochrome P450 3A expressed in human colon and colonic cell lines. *Environ Toxicol Pharmacol*, 2, 381-8.
- GIBBS, J. P., YANG, J. S. & SLATTERY, J. T. 1998. Comparison of human liver and small intestinal glutathione S-transferase-catalyzed busulfan conjugation in vitro. *Drug Metab Dispos*, 26, 52-5.
- GILL, K. L., GARDNER, I., LI, L. & JAMEI, M. 2016. A Bottom-Up Whole-Body Physiologically Based Pharmacokinetic Model to Mechanistically Predict Tissue Distribution and the Rate of Subcutaneous Absorption of Therapeutic Proteins. *AAPS J*, 18, 156-70.
- GRAFF, J., BRINCH, K. & MADSEN, J. L. 2001. Gastrointestinal mean transit times in young and middleaged healthy subjects. *Clin Physiol*, 21, 253-9.
- GREENBLATT, D. J., VON MOLTKE, L. L., HARMATZ, J. S., CHEN, G., WEEMHOFF, J. L., JEN, C., KELLEY, C. J., LEDUC, B. W. & ZINNY, M. A. 2003. Time course of recovery of cytochrome p450 3A function after single doses of grapefruit juice. *Clin Pharmacol Ther*, 74, 121-9.
- GRIMM, M., SCHOLZ, E., KOZIOLEK, M., KUHN, J. P. & WEITSCHIES, W. 2017. Gastric Water Emptying under Fed State Clinical Trial Conditions Is as Fast as under Fasted Conditions. *Mol Pharm*, 14, 4262-4271.
- GULLO, L., PRIORI, P., PEZZILLI, R., BILIOTTI, G., MATTIOLI, G. & BARBARA, L. 1988. Pancreatic secretory response to ordinary meals: studies with pure pancreatic juice. *Gastroenterology*, 94, 428-33.
- GUTZEIT, A., PATAK, M. A., VON WEYMARN, C., GRAF, N., DOERT, A., WILLEMSE, E., BINKERT, C. A. & FROEHLICH, J. M. 2010. Feasibility of small bowel flow rate measurement with MRI. *J Magn Reson Imaging*, 32, 345-51.
- HABERL, M., ANWALD, B., KLEIN, K., WEIL, R., FUSS, C., GEPDIREMEN, A., ZANGER, U. M., MEYER, U. A. & WOJNOWSKI, L. 2005. Three haplotypes associated with CYP2A6 phenotypes in Caucasians. *Pharmacogenet Genomics*, 15, 609-24.
- HAINING, R. L., HUNTER, A. P., SADEQUE, A. J., PHILPOT, R. M. & RETTIE, A. E. 1997. Baculovirusmediated expression and purification of human FMO3: catalytic, immunochemical, and structural characterization. *Drug Metab Dispos*, 25, 790-7.
- HARBOURT, D. E., FALLON, J. K., ITO, S., BABA, T., RITTER, J. K., GLISH, G. L. & SMITH, P. C. 2012. Quantification of human uridine-diphosphate glucuronosyl transferase 1A isoforms in liver, intestine, and kidney using nanobore liquid chromatography-tandem mass spectrometry. *Anal Chem*, 84, 98-105.
- HARWOOD, M. D., ZHANG, M., PATHAK, S. M. & NEUHOFF, S. 2019. The Regional-Specific Relative and Absolute Expression of Gut Transporters in Adult Caucasians: A Meta-Analysis. *Drug Metab Dispos*, 47, 854-864.
- HEINEMANN, A., WISCHHUSEN, F., PUSCHEL, K. & ROGIERS, X. 1999. Standard liver volume in the Caucasian population. *Liver Transpl Surg*, **5**, 366-8.
- HOFMANN, M. H., BLIEVERNICHT, J. K., KLEIN, K., SAUSSELE, T., SCHAEFFELER, E., SCHWAB, M. & ZANGER, U. M. 2008. Aberrant splicing caused by single nucleotide polymorphism c.516G>T [Q172H], a marker of CYP2B6*6, is responsible for decreased expression and activity of CYP2B6 in liver. *J Pharmacol Exp Ther*, 325, 284-92.
- HOY, W. E., DOUGLAS-DENTON, R. N., HUGHSON, M. D., CASS, A., JOHNSON, K. & BERTRAM, J. F. 2003. A stereological study of glomerular number and volume: preliminary findings in a multiracial study of kidneys at autopsy. *Kidney Int Suppl*, S31-7.
- HULIN, I. 1997. Pathophysiology of kidneys and urinary system. Pathophysiology. Bratislava: SAP.



- ICRP 1975. Report on the Task Group on Reference Man. INTERNATIONAL COMMISSION ON RADIOLOGICAL PROTECTION Publication 23. Pergamon Press.
- ICRP 1994. Human Respiratory Tract Model for Radiological Protection. International Commission on Radiological Protection Publication 66. Elsevier.
- ICRP 2002. Basic Anatomical and Physiological Data for Use in Radiological Protection: Reference Values. International Commission on Radiological Protection Publication 89. Pergamon Press.
- JOHNSON, T. N., TUCKER, G. T., TANNER, M. S. & ROSTAMI-HODJEGAN, A. 2005. Changes in liver volume from birth to adulthood: a meta-analysis. *Liver Transpl*, 11, 1481-93.
- KAWAI, R., LEMAIRE, M., STEIMER, J. L., BRUELISAUER, A., NIEDERBERGER, W. & ROWLAND, M. 1994. Physiologically based pharmacokinetic study on a cyclosporin derivative, SDZ IMM 125. J Pharmacokinet Biopharm, 22, 327-65.
- KOBAYASHI, D., IEIRI, I., HIROTA, T., TAKANE, H., MAEGAWA, S., KIGAWA, J., SUZUKI, H., NANBA, E., OSHIMURA, M., TERAKAWA, N., OTSUBO, K., MINE, K. & SUGIYAMA, Y. 2005. Functional assessment of ABCG2 (BCRP) gene polymorphisms to protein expression in human placenta. Drug Metab Dispos, 33, 94-101.
- KOZIOLEK, M., GRIMM, M., BECKER, D., IORDANOV, V., ZOU, H., SHIMIZU, J., WANKE, C., GARBACZ, G. & WEITSCHIES, W. 2015. Investigation of pH and Temperature Profiles in the GI Tract of Fasted Human Subjects Using the Intellicap((R)) System. J Pharm Sci, 104, 2855-63.
- KRAG, E. & PHILLIPS, S. F. 1974. Active and passive bile acid absorption in man. Perfusion studies of the ileum and jejunum. J Clin Invest, 53, 1686-94.
- KRAUSE, R. J., LASH, L. H. & ELFARRA, A. A. 2003. Human kidney flavin-containing monooxygenases and their potential roles in cysteine s-conjugate metabolism and nephrotoxicity. J Pharmacol Exp Ther, 304, 185-91.
- KROMBACH, F., MUNZING, S., ALLMELING, A. M., GERLACH, J. T., BEHR, J. & DORGER, M. 1997. Cell size of alveolar macrophages: an interspecies comparison. Environ Health Perspect, 105 Suppl 5, 1261-3.
- LANOIX, J. P., LENAERTS, A. J. & NUERMBERGER, E. L. 2015. Heterogeneous disease progression and treatment response in a C3HeB/FeJ mouse model of tuberculosis. *Dis Model Mech*, 8, 603-10.
- LEVEY, A. S., GREENE, T., KUSEK, J. W. & BECK, G. J. 2000. A simplified equation to predict glomerular filtration rate from serum creatinine. Journal of the American Society of Nephrology, 11, 155A.
- LOGAN, R., KONG, A. & KRISE, J. P. 2013. Evaluating the roles of autophagy and lysosomal trafficking defects in intracellular distribution-based drug-drug interactions involving lysosomes. J Pharm Sci, 102, 4173-80.
- LU, G., NEUHOFF, S., JOHNSON, T. N., ROSTAMI-HODJEGAN, A. & JAMEI, M. 2016. Development of a permeability-limited model of the human brain and cerebrospinal fluid (CSF) to integrate known physiological and biological knowledge: Estimating time varying CSF drug concentrations and their variability using in vitro data. Drug Metab Pharmacokinet, 31, 224-33.
- LU, G., WEDAGEDERA, J., SMALL, B. G., ALMOND, L., ROMERO, K., HERMANN, D., HANNA, D., JAMEI, M. & GARDNER, I. 2015. Development of a Multicompartment Permeability-Limited Lung PBPK Model and Its Application in Predicting Pulmonary Pharmacokinetics of Antituberculosis Drugs. CPT Pharmacometrics Syst Pharmacol, 4, 605-13.
- LUIKING, Y. C., VAN DER REIJDEN, A. C., VAN BERGE HENEGOUWEN, G. P. & AKKERMANS, L. M. 1998. Migrating motor complex cycle duration is determined by gastric or duodenal origin of phase III. Am J Physiol, 275, G1246-51.
- MALAGELADA, J. R., GO, V. L. & SUMMERSKILL, W. H. 1979. Different gastric, pancreatic, and biliary responses to solid-liquid or homogenized meals. Dig Dis Sci, 24, 101-10.
- MANABE, N., CAMILLERI, M., RAO, A., WONG, B. S., BURTON, D., BUSCIGLIO, I., ZINSMEISTER, A. R. & HARUMA, K. 2010. Effect of daikenchuto (TU-100) on gastrointestinal and colonic transit in humans. Am J Physiol Gastrointest Liver Physiol, 298, G970-5.
- MEKHJIAN, H. S., PHILLIPS, S. F. & HOFMANN, A. F. 1979. Colonic absorption of unconjugated bile acids: perfusion studies in man. Dig Dis Sci, 24, 545-50.
- MUDIE, D. M., MURRAY, K., HOAD, C. L., PRITCHARD, S. E., GARNETT, M. C., AMIDON, G. L., GOWLAND, P. A., SPILLER, R. C., AMIDON, G. E. & MARCIANI, L. 2014. Quantification of gastrointestinal liquid volumes and distribution following a 240 mL dose of water in the fasted state. Mol Pharm, 11, 3039-47.



- NEUHOFF, S., GAOHUA, L., BURT, H., JAMEI, M., LI, L., TUCKER, G. & ROSTAMI-HODJEGAN, A. 2013. Accounting for Transporters in renal clearance: Towards a mechanistic kidney model (Mech KiM). In: SUGIYAMA, Y. & STEFFANSEN, B. (eds.) Transporters in Drug Development. New York: Springer.
- NG, T. C., MAJORS, A. W., VIJAYAKUMAR, S., BALDWIN, N. J., THOMAS, F. J., KOUMOUNDOUROS, I., TAYLOR, M. E., GRUNDFEST, S. F., MEANEY, T. F., TUBBS, R. R. & ET AL. 1989. Human neoplasm pH and response to radiation therapy: P-31 MR spectroscopy studies in situ. Radiology, 170, 875-8.
- OHLSON, M., SORENSSON, J. & HARALDSSON, B. 2001. A gel-membrane model of glomerular charge and size selectivity in series. Am J Physiol Renal Physiol, 280, F396-405.
- OHNISHI, A. & EMI, Y. 2003. Rapid proteasomal degradation of translocation-deficient UDPglucuronosyltransferase 1A1 proteins in patients with Crigler-Najjar type II. Biochem Biophys Res Commun, 310, 735-41.
- OLSSON, B., BONDESSON, E., BORGSTRÖM, L., EDSBÄCKER, S., EIREFELT, S., EKELUND, K., GUSTAVSSON, L. & HEGELUND-MYRBÄCK, T. 2011. Pulmonary Drug Metabolism, Clearance, and Absorption. In: SMYTH, H. & HICKEY, A. (eds.) Controlled Pulmonary Drug Delivery. Springer.
- PAINE, M. F., HART, H. L., LUDINGTON, S. S., HAINING, R. L., RETTIE, A. E. & ZELDIN, D. C. 2006. The human intestinal cytochrome P450 "pie". Drug Metab Dispos, 34, 880-6.
- PAINE, M. F., KHALIGHI, M., FISHER, J. M., SHEN, D. D., KUNZE, K. L., MARSH, C. L., PERKINS, J. D. & THUMMEL, K. E. 1997. Characterization of interintestinal and intraintestinal variations in human CYP3A-dependent metabolism. J Pharmacol Exp Ther, 283, 1552-62.
- PALASCIANO, G., SERIO, G., PORTINCASA, P., PALMIERI, V., FANELLI, M., VELARDI, A., CALO' GABRIELI, B. & VINCIGUERRA, V. 1992. Gallbladder volume in adults, and relationship to age, sex, body mass index, and gallstones: a sonographic population study. Am J Gastroenterol, 87, 493-7.
- PARK, S. J., CHOI, W. W., KWON, O. S., CHUNG, J. H., EUN, H. C., EARM, Y. E. & KIM, S. J. 2008. Acidic pH-activated Cl Current and Intracellular Ca Response in Human Keratinocytes. Korean J Physiol Pharmacol, 12, 177-83.
- PEDERSEN, P. B., VILMANN, P., BAR-SHALOM, D., MULLERTZ, A. & BALDURSDOTTIR, S. 2013. Characterization of fasted human gastric fluid for relevant rheological parameters and gastric lipase activities. Eur J Pharm Biopharm, 85, 958-65.
- PEREZ DE LA CRUZ MORENO, M., OTH, M., DEFERME, S., LAMMERT, F., TACK, J., DRESSMAN, J. & AUGUSTIJNS, P. 2006. Characterization of fasted-state human intestinal fluids collected from duodenum and jejunum. J Pharm Pharmacol, 58, 1079-89.
- PETERKIN, V. C., BAUMAN, J. N., GOOSEN, T. C., MENNING, L., MAN, M. Z., PAULAUSKIS, J. D., WILLIAMS, J. A. & MYRAND, S. P. 2007. Limited influence of UGT1A1*28 and no effect of UGT2B7*2 polymorphisms on UGT1A1 or UGT2B7 activities and protein expression in human liver microsomes. Br J Clin Pharmacol, 64, 458-68.
- PIENAAR, E., CILFONE, N. A., LIN, P. L., DARTOIS, V., MATTILA, J. T., BUTLER, J. R., FLYNN, J. L., KIRSCHNER, D. E. & LINDERMAN, J. J. 2015. A computational tool integrating host immunity with antibiotic dynamics to study tuberculosis treatment. J Theor Biol, 367, 166-179.
- PORTINCASA, P., DI CIAULA, A., BALDASSARRE, G., PALMIERI, V., GENTILE, A., CIMMINO, A. & PALASCIANO, G. 1994. Gallbladder motor function in gallstone patients: sonographic and in vitro studies on the role of gallstones, smooth muscle function and gallbladder wall inflammation. J Hepatol, 21, 430-40.
- POULIN, P., CHEN, Y. H., DING, X., GOULD, S. E., HOP, C. E., MESSICK, K., OEH, J. & LIEDERER, B. M. 2015. Prediction of drug distribution in subcutaneous xenografts of human tumor cell lines and healthy tissues in mouse: application of the tissue composition-based model to antineoplastic drugs. J Pharm Sci, 104, 1508-21.
- POULIN, P. & THEIL, F. P. 2002. Prediction of pharmacokinetics prior to in vivo studies. 1. Mechanismbased prediction of volume of distribution. J Pharm Sci, 91, 129-56.
- PRICE, P. S., CONOLLY, R. B., CHAISSON, C. F., GROSS, E. A., YOUNG, J. S., MATHIS, E. T. & TEDDER, D. R. 2003. Modeling interindividual variation in physiological factors used in PBPK models of humans. Crit Rev Toxicol, 33, 469-503.

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RACHUMALLU, R., HARWOOD, M., BURT, H. & NEUHOFF, S. 2020. Protein Abundance of Hepatic Drug Transporters in Healthy Caucasians to support IVIVE and PBPK: A Meta-analysis. *AAPS Workshop on Drug Transporters in ADME: From the Bench to the Bedside.* McLean, Virginia.

- RADWAN, A., AMIDON, G. L. & LANGGUTH, P. 2012. Mechanistic investigation of food effect on disintegration and dissolution of BCS class III compound solid formulations: the importance of viscosity. *Biopharm Drug Dispos*, 33, 403-16.
- REED, R. K. & WIIG, H. 1983. Interstitial albumin mass and transcapillary extravasation rate of albumin in DMBA-induced rat mammary tumours. *Scand J Clin Lab Invest*, 43, 503-12.
- RICHARDSON, C. T. & FELDMAN, M. 1986. Salivary response to food in humans and its effect on gastric acid secretion. *Am J Physiol*, 250, G85-91.
- RIETHORST, D., MOLS, R., DUCHATEAU, G., TACK, J., BROUWERS, J. & AUGUSTIJNS, P. 2016. Characterization of Human Duodenal Fluids in Fasted and Fed State Conditions. *J Pharm Sci*, 105, 673-681.
- RODGERS, T., LEAHY, D. & ROWLAND, M. 2005. Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases. *J Pharm Sci*, 94, 1259-76.
- RODGERS, T. & ROWLAND, M. 2006. Physiologically based pharmacokinetic modelling 2: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. *J Pharm Sci*, 95, 1238-57.
- ROOS, A. & BORON, W. F. 1981. Intracellular pH. *Physiol Rev*, 61, 296-434.
- ROSE, R. H., TURNER, D. B., NEUHOFF, S. & JAMEI, M. 2017. Incorporation of the Time-Varying Postprandial Increase in Splanchnic Blood Flow into a PBPK Model to Predict the Effect of Food on the Pharmacokinetics of Orally Administered High-Extraction Drugs. *AAPS J*, 19, 1205-1217.
- ROSS, M. K., BORAZJANI, A., WANG, R., CROW, J. A. & XIE, S. 2012. Examination of the carboxylesterase phenotype in human liver. *Arch Biochem Biophys*, 522, 44-56.
- ROWLAND-YEO, K., ROSTAMI-HODJEGAN, A. & TUCKER, G. T. 2004. Abundance of cytochromes P450 in human liver: a meta-analysis. *British Journal of Pharmacology*, 57, 687-688.
- SCHILLER, C., FROHLICH, C. P., GIESSMANN, T., SIEGMUND, W., MONNIKES, H., HOSTEN, N. & WEITSCHIES, W. 2005. Intestinal fluid volumes and transit of dosage forms as assessed by magnetic resonance imaging. *Aliment Pharmacol Ther*, 22, 971-9.
- SCHINDLBECK, N. E., HEINRICH, C., STELLAARD, F., PAUMGARTNER, G. & MULLER-LISSNER, S. A. 1987. Healthy controls have as much bile reflux as gastric ulcer patients. *Gut*, 28, 1577-83.
- SCHMIDT, M. M. & WITTRUP, K. D. 2009. A modeling analysis of the effects of molecular size and binding affinity on tumor targeting. *Mol Cancer Ther*, 8, 2861-71.
- SCHMIDT, T., PFEIFFER, A., HACKELSBERGER, N., WIDMER, R., MEISEL, C. & KAESS, H. 1996. Effect of intestinal resection on human small bowel motility. *Gut*, 38, 859-63.
- SCHNEIDER, F., GRIMM, M., KOZIOLEK, M., MODESS, C., DOKTER, A., ROUSTOM, T., SIEGMUND, W.
 & WEITSCHIES, W. 2016. Resolving the physiological conditions in bioavailability and bioequivalence studies: Comparison of fasted and fed state. *Eur J Pharm Biopharm*, 108, 214-219.
- SHAFFER, E. A., MCORMOND, P. & DUGGAN, H. 1980. Quantitative cholescintigraphy: assessment of gallbladder filling and emptying and duodenogastric reflux. *Gastroenterology*, 79, 899-906.
- SHEN, D. D., ARTRU, A. A. & ADKISON, K. K. 2004. Principles and applicability of CSF sampling for the assessment of CNS drug delivery and pharmacodynamics. *Adv Drug Deliv Rev*, 56, 1825-57.
- SIEGEL, J. A., URBAIN, J. L., ADLER, L. P., CHARKES, N. D., MAURER, A. H., KREVSKY, B., KNIGHT, L. C., FISHER, R. S. & MALMUD, L. S. 1988. Biphasic nature of gastric emptying. *Gut*, 29, 85-9.
- SIMEONI, M., MAGNI, P., CAMMIA, C., DE NICOLAO, G., CROCI, V., PESENTI, E., GERMANI, M., POGGESI, I. & ROCCHETTI, M. 2004. Predictive pharmacokinetic-pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. *Cancer Res,* 64, 1094-101.
- SKANDALAKIS, J. E., SKANDALAKIS, L. J. & SKANDALAKIS, P. N. 2007. Anatomy of the lymphatics. *Surg Oncol Clin N Am*, 16, 1-16.
- SPIERINGS, E., HENDRIKS, M., ABSI, L., CANOSSI, A., CHHAYA, S., CROWLEY, J., DOLSTRA, H., ELIAOU, J. F., ELLIS, T., ENCZMANN, J., FASANO, M. E., GERVAIS, T., GORODEZKY, C., KIRCHER, B., LAURIN, D., LEFFELL, M. S., LOISEAU, P., MALKKI, M., MARKIEWICZ, M., MARTINETTI, M., MARUYA, E., MEHRA, N., OGUZ, F., OUDSHOORN, M., PEREIRA, N., RANI,



R., SERGEANT, R., THOMSON, J., TRAN, T. H., TURPEINEN, H., YANG, K. L., ZUNEC, R., CARRINGTON, M., DE KNIJFF, P. & GOULMY, E. 2007. Phenotype frequencies of autosomal minor histocompatibility antigens display significant differences among populations. *PLoS Genet*, **3**, e103.

- STOLK, M. F., VAN ERPECUM, K. J., SMOUT, A. J., AKKERMANS, L. M., JANSEN, J. B., LAMERS, C. B., PEETERS, T. L. & VANBERGE-HENEGOUWEN, G. P. 1993. Motor cycles with phase III in antrum are associated with high motilin levels and prolonged gallbladder emptying. *Am J Physiol*, 264, G596-600.
- SUGANO, K. 2009. Theoretical investigation of passive intestinal membrane permeability using Monte Carlo method to generate drug-like molecule population. *Int J Pharm*, 373, 55-61.
- SWANSON, C., MELLSTROM, D., LORENTZON, M., VANDENPUT, L., JAKOBSSON, J., RANE, A., KARLSSON, M., LJUNGGREN, O., SMITH, U., ERIKSSON, A. L., BELANGER, A., LABRIE, F. & OHLSSON, C. 2007. The uridine diphosphate glucuronosyltransferase 2B15 D85Y and 2B17 deletion polymorphisms predict the glucuronidation pattern of androgens and fat mass in men. *J Clin Endocrinol Metab*, 92, 4878-82.
- TAMMINGA, W. J., WEMER, J., OOSTERHUIS, B., WEILING, J., WILFFERT, B., DE LEIJ, L. F., DE ZEEUW, R. A. & JONKMAN, J. H. 1999. CYP2D6 and CYP2C19 activity in a large population of Dutch healthy volunteers: indications for oral contraceptive-related gender differences. *Eur J Clin Pharmacol*, 55, 177-84.
- TARKIAINEN, E. K., BACKMAN, J. T., NEUVONEN, M., NEUVONEN, P. J., SCHWAB, M. & NIEMI, M. 2012. Carboxylesterase 1 polymorphism impairs oseltamivir bioactivation in humans. *Clin Pharmacol Ther*, 92, 68-71.
- TRBOJEVIC-STANKOVIC, J. B., MILICEVIC, N. M., MILOSEVIC, D. P., DESPOTOVIC, N., DAVIDOVIC, M., ERCEG, P., BOJIC, B., BOJIC, D., SVORCAN, P., PROTIC, M., DAPCEVIC, B., MILJKOVIC, M. D. & MILICEVIC, Z. 2010. Morphometric study of healthy jejunal and ileal mucosa in adult and aged subjects. *Histol Histopathol*, 25, 153-8.
- VAN BERGE HENEGOUWEN, G. P. & HOFMANN, A. F. 1978. Nocturnal gallbladder storage and emptying in gallstone patients and healthy subjects. *Gastroenterology*, 75, 879-85.
- VAN DYKE, R. W. 1988. Proton pump-generated electrochemical gradients in rat liver multivesicular bodies. Quantitation and effects of chloride. *J Biol Chem*, 263, 2603-11.
- VANDAL, O. H., NATHAN, C. F. & EHRT, S. 2009. Acid resistance in Mycobacterium tuberculosis. *J* Bacteriol, 191, 4714-21.
- VILLENEUVE, L., GIRARD, H., FORTIER, L. C., GAGNE, J. F. & GUILLEMETTE, C. 2003. Novel functional polymorphisms in the UGT1A7 and UGT1A9 glucuronidating enzymes in Caucasian and African-American subjects and their impact on the metabolism of 7-ethyl-10-hydroxycamptothecin and flavopiridol anticancer drugs. *J Pharmacol Exp Ther*, 307, 117-28.
- WAGNER, P. D., LARAVUSO, R. B., UHL, R. R. & WEST, J. B. 1974. Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100 per cent O2. *J Clin Invest*, 54, 54-68.
- WANG, X., CHEN, J., XU, S., NI, C., FANG, Z. & HONG, M. 2019. Amino-terminal region of human organic anion transporting polypeptide 1B1 dictates transporter stability and substrate interaction. *Toxicol Appl Pharmacol*, 378, 114642.
- WEST, J. B. 1962. Regional differences in gas exchange in the lung of erect man. *J Appl Physiol*, 17, 893-8.
- WILSON, C. G., O'MAHONY, B., CONNOLLY, S. M., CANTARINI, M. V., FARMER, M. R., DICKINSON, P. A., SMITH, R. P. & SWAISLAND, H. C. 2009. Do gastrointestinal transit parameters influence the pharmacokinetics of gefitinib? *Int J Pharm*, 376, 7-12.

WILSON, J. P. 1967. Surface area of the small intestine in man. Gut, 8, 618-21.

- XYDA, A., HABERLAND, U., KLOTZ, E., BOCK, H. C., JUNG, K., KNAUTH, M., SCHRAMM, R., PSYCHOGIOS, M. N., ERB, G. & SCHRAMM, P. 2011. Brain volume perfusion CT performed with 128-detector row CT system in patients with cerebral gliomas: a feasibility study. *Eur Radiol*, 21, 1811-9.
- YANG, J., LIAO, M., SHOU, M., JAMEI, M., YEO, K. R., TUCKER, G. T. & ROSTAMI-HODJEGAN, A. 2008. Cytochrome p450 turnover: regulation of synthesis and degradation, methods for determining rates, and implications for the prediction of drug interactions. *Curr Drug Metab*, 9, 384-94.



- YASAR, U., LUNDGREN, S., ELIASSON, E., BENNET, A., WIMAN, B., DE FAIRE, U. & RANE, A. 2002. Linkage between the CYP2C8 and CYP2C9 genetic polymorphisms. *Biochem Biophys Res Commun*, 299, 25-8.
- ZEEBEE, R. E. 2011. On the molecular diffusion coefficients of dissolved , and and their dependence on isotopic mass. *Geochimica et Cosmochimica Acta*, 75, 2483-2498.
- ZHU, H. J. & MARKOWITZ, J. S. 2009. Activation of the antiviral prodrug oseltamivir is impaired by two newly identified carboxylesterase 1 variants. *Drug Metab Dispos*, 37, 264-7.
- ZIESSMAN, H. A., CHANDER, A., CLARKE, J. O., RAMOS, A. & WAHL, R. L. 2009. The added diagnostic value of liquid gastric emptying compared with solid emptying alone. *J Nucl Med*, 50, 726-31.

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</pre>
```

