

Supplementary Table S1. Literature reports and pharmacokinetic parameters of metformin given intravenously in different species

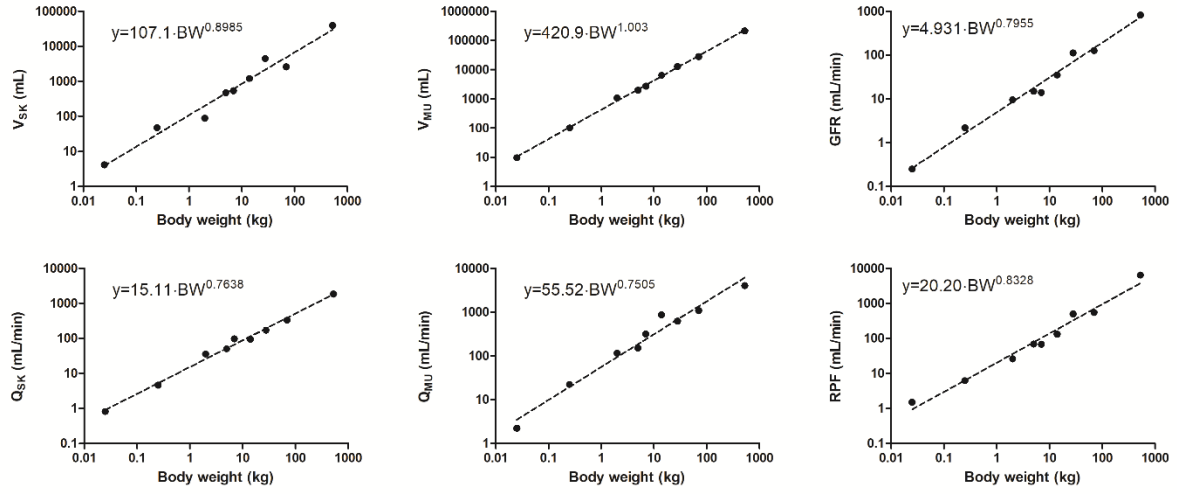
Reference	Species	Strain	Sex	Dosing route	Dose (mg/kg)	Assay	CL (mL/min/kg)	CL_R (mL/min/kg)	V_{SS} (mL/kg)
Tsuda et al (2009) [26]	Mouse	C57BL/6	M	IV	5	HPLC-UV	40.7	37.2	994
Higgins et al (2012) [27]*	Mouse	FVB	M	IV	5	LC-MS/MS	81.7	40.0	1840
Nakamichi et al (2013) [28]	Mouse	C57BL/6J	M	IV(+IF)	6 (+0.12 mg/min/kg)	HPLC-UV	60.7	60.3	-
Chen et al (2015) [29]	Mouse	C57BL/6J	M	IV	50	LSC	18.6	-	1480
Shirasaka et al (2016) [30]	Mouse	FVB	M	IV	8	LSC	12.7	-	1740
Kakemi et al (1983) [31]	Rat	Wistar	M	IV	50	GC-MS	42.8**	-	1920**
					100	GC-MS	14.5**	-	1020**
					200	GC-MS	7.73**	-	880**
Choi et al (2006) [32]*	Rat	Sprague-Dawley	M	IV	50	HPLC-UV	26.4	19.5	693
					100	HPLC-UV	24.5	18.7	586
					200	HPLC-UV	23.6	17.8	586
Choi and Lee (2006) [33]	Rat	Sprague-Dawley	M	IV	100	HPLC-UV	17.2-23.0	10.5-13.4	566-844
Choi et al (2007) [34]	Rat	Sprague-Dawley	M	IV	100	HPLC-UV	20.2	11.7	797
Choi et al (2007) [35]	Rat	Sprague-Dawley	M	IV	100	HPLC-UV	21.7	13.6	444
Choi et al (2007) [36]	Rat	Sprague-Dawley	M	IV	30 μ mol/mL/kg	HPLC-UV	19.0	-	426

Maeda et al (2007) [37]	Rat	Wistar	M	IV	1	LSC	12.3	-	764
Lee et al (2008) [38]	Rat	Sprague-Dawley	M	IV	100	HPLC-UV	19.6	11.7	655
Choi et al (2008) [39]	Rat	Sprague-Dawley	M	IV	100	HPLC-UV	20.3-22.6	11.7-12.4	651-826
Choi et al (2008) [40]	Rat	Sprague-Dawley	M	IV	100	HPLC-UV	16.8	9.46	539
Jin et al (2008) [41]	Rat	Sprague-Dawley	M	IV	5	HPLC-UV	21.4	17.6	766
Cho et al (2009) [42]	Rat	Sprague-Dawley	M	IV	100	HPLC-UV	14.6	10.9	307
Lee et al (2010) [43]	Rat	Sprague-Dawley	M	IV	100	HPLC-UV	22.3	6.67	755
Choi et al (2010) [44]	Rat	Sprague-Dawley	M	IV	100	HPLC-UV	14.7	11.6	383
Choi and Lee (2012) [45]	Rat	Sprague-Dawley	M	IV	100	HPLC-UV	21.3	14.9	764
Lee et al (2013) [46]	Rat	Sprague-Dawley	M	IV	50	HPLC-UV	33.8	25.8	929
Kwon et al (2015) [47]	Rat	Sprague-Dawley	M	IV	2	LC-MS/MS	25.9	-	867
Ma et al (2016) [48]	Rat	Wistar	M	IV	25	HPLC-UV	8	28.6-74.2%	3250
			F	IV	25	HPLC-UV	6	26.7-57.6%	3530
Gabr et al (2017) [49]	Rat	Sprague-Dawley	M	IV	30	LC-MS	29.5	27.2	2320
Ma et al (2018) [50]	Rat	Wistar	M	IV	25	HPLC-UV	23.3	70.3%**	3050
Yang et al (2018) [51]	Rat	Wistar	M	IV	25	LC-MS/MS	9.07	7.05	1040

Nishizawa et al (2019) [52]	Rat	Wistar	M	IV	30	LC-MS/MS	41.2	23.0	1320
Han and Choi (2020) [53]	Rat	Sprague-Dawley	M	IV	30	HPLC-UV	24.2	16.1	349
Bouriche et al (2020) [54]*	Rabbit	New Zealand	F	IV	5	HPLC-UV	2.05	-	413
Michels et al (1999) [55]*	Cat	Domestic shorthair	-	IV	25	HPLC-UV	2.5	2.17	550
Shen et al (2016) [56]*	Monkey	Cynomolgus	M	IV	3.9	LC-MS/MS	11.2	10.7	980
Morse et al (2017) [57]	Monkey	Cynomolgus	M	IV	2.5	LC-MS/MS	8.06**	86%	353**
Patel et al (2017) [58]	Minipig	Yucatan	M	IV	0.5	LC-MS/MS	10.1	-	-
		Hanford*	M	IV	0.5	LC-MS/MS	9.7	-	2260
		Sinclair	M	IV	0.5	LC-MS/MS	8.7	-	991
		Gottingen	M	IV	0.5	LC-MS/MS	19.6	-	695
Johnston et al (2017) [59]*	Dog	Mixed	-	IV	24.8	FIA-MS/MS	24.1	-	10100
Sirtori et al (1978) [60]*	Man	Healthy	4 M 1 F	IV	926 mg	GC-MS	6.13	4.65	432**
Pentikäinen et al (1979) [61]*	Man	Healthy	1 M 2 F	IV	500 mg	LSC	7.61	7.52	856**
Tucker et al (1981) [62]*	Man	Healthy	M	IV	250 mg	GC-EC	10.1	7.83	511**
Hustace et al (2009) [63]*	Horse	-	-	IV	6 g	HPLC-UV	10.8	-	2250**

* Dataset used for minimal physiologically-based pharmacokinetic model fitting across 9 species

** Calculated from digitized data



Supplementary Figure S1. Physiological and anatomical information (i.e., V_{SK} , V_{MU} , Q_{SK} , Q_{MU} , RPF , and GFR) collected from different sources (Supplementary Table S2) showed an allometric relationship among 9 species [i.e., mouse (0.025 kg), rat (0.25 kg), rabbit (2 kg), cat (5 kg), monkey (7 kg), minipig (14 kg), dog (28 kg), man (70 kg), and horse (530 kg)]

Supplementary Table S2. Summary of physiological input variables for meta-analysis of metformin pharmacokinetics in various species

	Mouse	Rat	Rabbit	Cat	Monkey	Minipig	Dog	Man	Horse
<i>BW</i> (kg)	0.025	0.25	2	5	7	14	28	70	530
<i>V_B</i> (mL)	1.64	15.3	120	300	420	875	2520	5200 ^a	39800
<i>V_{SK}</i> (mL)	4.13	47.5	88 ^a	469 ^b	540 ^c	1200 ^d	4480	2600	39200
<i>V_{MU}</i> (mL)	9.6	101	1080 ^a	1980 ^b	2750 ^c	6390	12800	28000	213000
<i>Q_{CO}</i> (mL/min)	14.0	80.0	395	786	1010	1700	2860	5690	26000
<i>Q_{SK}</i> (mL/min)	0.813	4.64	35.6 ^e	50.4 ^b	96.4 ^c	94.8 ^d	172	330	1840 ^f
<i>Q_{MU}</i> (mL/min)	2.23	22.2	116 ^a	151 ^b	315 ^c	863 ^d	621	1090	4040 ^f
<i>GFR</i> (mL/min)	0.25	2.18	9.6	15 ^g	14	35 ^d	112	126	820 ^h
<i>RPF</i> (mL/min)	1.50 ⁱ	6.20	26.1 ^e	69.2 ^b	67.3 ^c	131 ^d	500 ^j	547	6400 ^k
Gut radius (<i>R</i>) (cm)	0.135 ^l	0.2	0.246 ^m	0.35 ⁿ	0.6	1 ^d	1.25 ^d	2.5	3 ^o
<i>V_{Lumen}</i> (mL)	0.4	6.18	74.5	145 ^p	894	754	1000	330	15500 ^p
<i>T_{SI}</i> (min)	96.2 ^q	103 ^r	80 ^s	144 ^t	180	210	111	238	240 ^u

V_{SK}, *V_{MU}*, *Q_{SK}*, *Q_{MU}*, *RPF*, and *Q_{CO}* ($= 0.235 \cdot BW^{0.75}$) from Brown et al (1997) [1], *V_B* from Wolfensohn & Lloyd (2003) [2], *GFR* from Lin (1995) [3], and gut radius from Kararli (1995) [4], unless otherwise noted

^aDavies & Morris (1993) [5]; ^bLindstedt & Schaeffer (2002) [6]; ^cValues adopted in Simcyp V19 (Simcyp Ltd. Sheffield, UK) [7];

^dSuenderhauf & Parrott (2013) [8]; ^eSweeny et al (2009) [9]; ^fStaddon et al (1984) [10]; ^gVon Hendy-Willson & Pressler (2011) [11]; ^hWalsh and Royal (1992) [12]; ⁱThuesen et al (2014) [13]; ^jWesolowski et al (2019) [14]; ^kHoldstock et al (1998) [15]; ^lFerraris et al (1989) [16]; ^mMerchant et al (2011) [17]; ⁿBettini et al (2003) [18]; ^oClauss et al (2003) [19]

V_{Lumen} as the sum of fluid volume in stomach and small intestine, obtained from Hatton et al (2015) [20]; ^pcat and horse values were estimated by the interpolation and extrapolation from allometric relationship between *V_{Lumen}* and *BW* in the 7 species ($V_{Lumen} = 28.9 \cdot BW^{1.00}$, $R^2=0.88$)

T_{SI} is the small intestinal transit time obtained from Hatton et al (2015) [20]; ^qMyagmarjalbuu et al (2013) [21]; ^rQuini et al (2012) [22]; ^sDavies and Davies (2003) [23], considering jejunum and ileum; ^tChandler et al (1997) [24]; ^uSteinmann et al (2020) [25]

Supplementary Table S3. Literature information collected for tissue distribution and blood partitioning of metformin

Species	Tissue	Value	Sex	Comments	Source
K_p					
Mouse	Liver	4.47	M	C_t/C_p (0.5 hr)	Wilcock and Bailey (1994) [64]
		4.95	M	C_t/C_p (1 hr)	Wilcock and Bailey (1994) [64]
		4.86	M	C_t/C_p (2 hr)	Wilcock and Bailey (1994) [64]
		7.10	M	C_t/C_p (4 hr)	Wilcock and Bailey (1994) [64]
		1.72	M	AUC_t/AUC_p (0-8 hr)	Lee et al (2014) [65]
		1.82	F	AUC_t/AUC_p (0-8 hr)	Lee et al (2014) [65]
		3.35	M	C_t/C_p (at day 7)	Chaudhari et al (2020) [66]
		3.69	F	C_t/C_p (at day 7)	Chaudhari et al (2020) [66]
		2.52	M	C_t/C_p (at day 30)	Chaudhari et al (2020) [66]
		3.90	F	C_t/C_p (at day 30)	Chaudhari et al (2020) [66]
		4.20	M	Median (10-300 mg/kg, 1.5-2.5 hr)	Higgins et al (2012) [27]*
		2.30	M	$C_{t,ss}/C_{p,ss}$	Ito et al (2012) [67]
		1.81	M	C_t/C_p (at day 98)	Chae et al (2019) [68]
		1.88	M	C_t/C_p (at 24 hr)	Toyama et al (2012) [69]*
		2.13	M	$C_{t,ss}/C_{p,ss}$	Nakamichi et al (2013) [28]*
		4.83	F	C_t/C_p (at 10 min)	Wang et al (2002) [70]*
	Brain	0.184	M	C_t/C_p (at day 7)	Chaudhari et al (2020) [66]
		0.257	F	C_t/C_p (at day 7)	Chaudhari et al (2020) [66]
		0.174	M	C_t/C_p (at day 30)	Chaudhari et al (2020) [66]
		0.237	F	C_t/C_p (at day 30)	Chaudhari et al (2020) [66]
		0.0354	M	$C_{t,ss}/C_{p,ss}$	Nakamichi et al (2013) [28]*
	Kidney	3.35	M	AUC_t/AUC_p (0-8 hr)	Lee et al (2014) [65]
		3.55	F	AUC_t/AUC_p (0-8 hr)	Lee et al (2014) [65]

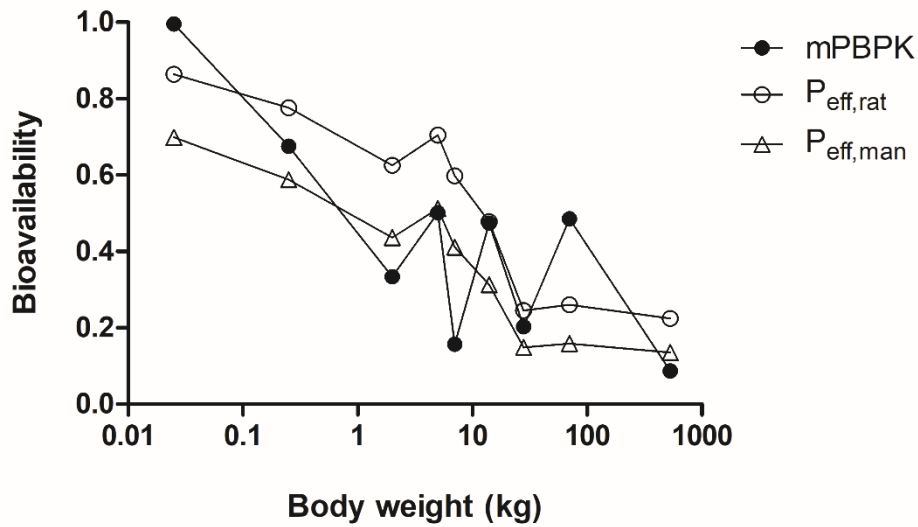
	5.30	M	C_t/C_p (at day 7)	Chaudhari et al (2020) [66]
	6.64	F	C_t/C_p (at day 7)	Chaudhari et al (2020) [66]
	4.90	M	C_t/C_p (at day 30)	Chaudhari et al (2020) [66]
	6.44	F	C_t/C_p (at day 30)	Chaudhari et al (2020) [66]
	11.8	M	Median (10-300 mg/kg, 1.5-2.5 hr)	Higgins et al (2012) [27]*
	5.00	M	$C_{t,ss}/C_{p,ss}$	Ito et al (2012) [67]
	16.0	M	C_t/C_p (at day 98)	Chae et al (2019) [68]
	7.84	M	C_t/C_p (at 24 hr)	Toyama et al (2012) [69]*
	13.6	M	$C_{t,ss}/C_{p,ss}$	Nakamichi et al (2013) [28]*
	20.5	F	C_t/C_p (at 10 min)	Wang et al (2002) [70]*
Muscle	0.537	M	AUC_t/AUC_p (0-8 hr)	Lee et al (2014) [65]
	0.582	F	AUC_t/AUC_p (0-8 hr)	Lee et al (2014) [65]
	1.38	M	C_t/C_p (at day 7)	Chaudhari et al (2020) [66]
	2.06	F	C_t/C_p (at day 7)	Chaudhari et al (2020) [66]
	1.00	M	C_t/C_p (at day 30)	Chaudhari et al (2020) [66]
	1.59	F	C_t/C_p (at day 30)	Chaudhari et al (2020) [66]
	0.771	M	C_t/C_p (at 24 hr)	Toyama et al (2012) [69]*
	0.359	M	$C_{t,ss}/C_{p,ss}$	Nakamichi et al (2013) [28]*
Heart	0.599	M	AUC_t/AUC_p (0-8 hr)	Lee et al (2014) [65]
	0.712	F	AUC_t/AUC_p (0-8 hr)	Lee et al (2014) [65]
	0.519	M	$C_{t,ss}/C_{p,ss}$	Nakamichi et al (2013) [28]*
Adipose	0.471	M	$C_{t,ss}/C_{p,ss}$	Nakamichi et al (2013) [28]*
Stomach	5.25	M	C_t/C_p (at 0.5 hr)	Wilcock and Bailey (1994) [64]
	4.67	M	C_t/C_p (at 1 hr)	Wilcock and Bailey (1994) [64]
	6.57	M	C_t/C_p (at 2 hr)	Wilcock and Bailey (1994) [64]
	9.03	M	C_t/C_p (at 4 hr)	Wilcock and Bailey (1994) [64]

Rat	Small intestine	13.7-15.3	M	C_t/C_p (at 0.5 hr)	Wilcock and Bailey (1994) [64]
		14.6-21.1	M	C_t/C_p (at 1 hr)	Wilcock and Bailey (1994) [64]
		9.57-21.3	M	C_t/C_p (at 2 hr)	Wilcock and Bailey (1994) [64]
		12.3-17.7	M	C_t/C_p (at 4 hr)	Wilcock and Bailey (1994) [64]
		4.42	M	$C_{t,ss}/C_{p,ss}$	Nakamichi et al (2013) [28]*
		0.837	F	C_t/C_p (at 10 min)	Wang et al (2002) [70]*
	Colon	4.52	M	C_t/C_p (at 0.5 hr)	Wilcock and Bailey (1994) [64]
		6.17	M	C_t/C_p (at 1 hr)	Wilcock and Bailey (1994) [64]
		6.29	M	C_t/C_p (at 2 hr)	Wilcock and Bailey (1994) [64]
		13.9	M	C_t/C_p (at 4 hr)	Wilcock and Bailey (1994) [64]
	Salivary gland	2.60	M	AUC_t/AUC_p (0-8 hr)	Lee et al (2014) [65]
		3.45	F	AUC_t/AUC_p (0-8 hr)	Lee et al (2014) [65]
	Liver	2.91	M	C_t/C_p (at 2 hr)	Ma et al (2016) [71]*
		3.40	M	C_t/C_p (at 2 hr of day 7)	Ma et al (2016) [71]*
		3.04-3.47	M	C_t/C_p (at 1 hr)	You et al (2018) [72]
		3.09-3.53	M	C_t/C_p (at 3 hr)	You et al (2018) [72]
		0.368-0.502	M	C_t/C_p (at 12 hr)	You et al (2018) [72]
		6.83	M	C_t/C_p (at 2 hr)	Maeda et al (2007) [37]
		0.773	M	C_t/C_p (at 0.5 hr)	Han and Choi [53]
		2.43	M	C_t/C_p (at 1 hr)	Han and Choi [53]
Rat		3.81	M	C_t/C_p (at 3 hr)	Han and Choi [53]
		3.50	M	C_t/C_p (at 6 hr)	Han and Choi [53]
		0.491	M	C_t/C_p (at 24 hr), diabetic rats	Wu et al (2019) [73]*
	Kidney	5.15	M	C_t/C_p (at 2 hr)	Ma et al (2016) [71]*
		5.84	M	C_t/C_p (at 2 hr of day 7)	Ma et al (2016) [71]*
		16.6	M	C_t/C_p (at 4 hr)	Nishizawa et al (2019) [52]

		4.16-5.92	M	C_t/C_p (at 1 hr)	You et al (2018) [72]
		4.86-5.64	M	C_t/C_p (at 3 hr)	You et al (2018) [72]
		0.604-0.861	M	C_t/C_p (at 12 hr)	You et al (2018) [72]
		24.9	M	C_t/C_p (at 2 hr)	Maeda et al (2007) [37]
		0.128	M	C_t/C_p (at 0.5 hr)	Han and Choi [53]
		3.39	M	C_t/C_p (at 1 hr)	Han and Choi [53]
		4.92	M	C_t/C_p (at 3 hr)	Han and Choi [53]
		5.92	M	C_t/C_p (at 6 hr)	Han and Choi [53]
		0.923	M	C_t/C_p (at 24 hr), diabetic rats	Wu et al (2019) [73]*
	Brain	0.2	M	C_t/C_p (at 1 hr)	Łabuzek et al (2010) [74]
		0.69	M	C_t/C_p (at 4 hr)	Łabuzek et al (2010) [74]
		0.99	M	C_t/C_p (at 6 hr)	Łabuzek et al (2010) [74]
		0.64	M	C_t/C_p (at 12 hr)	Łabuzek et al (2010) [74]
		1.48	M	C_t/C_p (at 24 hr)	Łabuzek et al (2010) [74]
	Heart	0.761	M	C_t/C_p (at 24 hr), diabetic rats	Wu et al (2019) [73]*
	Spleen	0.956	M	C_t/C_p (at 2 hr)	Maeda et al (2007) [37]
	Gut	4.63	M	C_t/C_p (at 2 hr)	Maeda et al (2007) [37]
		1.00	M	C_t/C_p (at 24 hr), diabetic rats	Wu et al (2019) [73]*
	Muscle	0.455	M	C_t/C_p (at 2 hr)	Ma et al (2016) [71]*
		0.738	M	C_t/C_p (at 2 hr of day 7)	Ma et al (2016) [71]*
		0.640	M	C_t/C_p (at 24 hr), diabetic rats	Wu et al (2019) [73]*
Monkey	Liver	15	M	Fitted (equivalent to AUC_t/AUC_p)	Morse et al (2017) [57]
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<i>f_{d,tissue}</i>					
Mouse	Kidney	0.0953	M	Kidney slice	Ito et al (2012) [67]
Rat	Liver	0.231		In vitro hepatocytes	Umehara et al (2007) [75]
		0.345	M	In vivo	Kimura et al (2005) [76]*
		0.236	F	In vivo	Kimura et al (2005) [76]*
		0.261	M	In vivo	Jin et al (2009) [41]
		0.0172		In vitro hepatocytes	Liao et al (2019) [77]
	Kidney	0.443	M	In vivo	Kimura et al (2005) [76]*
		0.334	F	In vivo	Kimura et al (2005) [76]*
		0.00806	M	Kidney slice	Ma et al (2016) [71]*

		0.262	M	In vivo	Jin et al (2009) [41]
		0.996	M	Kidney slice	Umehara et al (2008) [78]
Monkey	Liver	0.0428		In vitro hepatocytes	Liao et al (2019) [77]
		0.0722	M	In vitro hepatocytes	Liao et al (2019) [77]
		0.0342	F	In vitro hepatocytes	Liao et al (2019) [77]
Dog	Liver	0.0250		In vitro hepatocytes	Liao et al (2019) [77]
Man	Liver	0.0269		In vitro hepatocytes	Umehara et al (2007) [75]
		0.0285		In vitro hepatocytes	Liao et al (2019) [77]
		0.0185	M	In vitro hepatocytes	Liao et al (2019) [77]
		0.0370	F	In vitro hepatocytes	Liao et al (2019) [77]
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f_u					
Rat	Plasma	0.849		Equilibrium dialysis (10 µg/mL)	Choi et al (2006) [32]
		0.874		Equilibrium dialysis (5 µg/mL)	Choi and Lee (2012) [45]
		0.897		Equilibrium dialysis (0.1 – 200 µg/mL)	Choi et al (2010) [44]
Dog	Plasma	0.93		Centrifugal filtration (0.05 – 10 mM)	Garrett et al (1972) [79]
		0.83-0.951		Equilibrium dialysis (0.05 – 10 mM)	Garrett et al (1972) [79]
	Blood	0.92		Centrifugal filtration (0.05 – 10 mM)	Garrett et al (1972) [79]
Man	Plasma	1		Equilibrium dialysis (0.05 – 5 µg/mL)	Sirtori et al (1978) [60]
		1		Equilibrium dialysis (0.05 – 50 µg/mL)	Pentikäinen et al (1979) [61]
		1		Equilibrium dialysis (0.1 – 10 µg/mL)	Tucker et al (1981) [62]
		0.899		Centrifugal filtration (0.05 – 10 mM)	Garrett et al (1972) [79]
		0.75-0.98		Equilibrium dialysis (0.05 – 10 mM)	Garrett et al (1972) [79]
	Blood	0.932		Centrifugal filtration (0.05 – 10 mM)	Garrett et al (1972) [79]
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R_b					
Rat		0.76-0.98		In vitro (0.1 – 10 µg/mL, 72 hr)	Xie et al (2015) [80]
		0.98-1.37		In vitro (0.1 – 10 µg/mL, 168 hr)	Xie et al (2015) [80]
Man		0.83-1.23		In vitro (0.1 – 10 µg/mL, 168 hr)	Xie et al (2015) [80]

*Calculated from digitized data



Supplementary Figure S2. ACAT model-based estimation of bioavailability using $F_a = 1 - (1 + 2P_{eff}T_{SI}/7R)^{-7}$ (7-enteric compartments), assuming that the effective intestinal permeability (P_{eff}) of the 9 species is the same with that of rat ($P_{eff, rat}$), and that of man ($P_{eff, man}$) predicted from Caco-2 cell permeability, which were compared with bioavailability determined from our mPBPK modeling (1-enteric compartment as a cylinder).

Supplementary Table S4. Calculation of the steady-state volume of distribution (V_{SS}) using *in vivo* tissue K_p values based on the equation $V_{SS} = V_B + \sum V_{T,i}K_{p,i}$ [81]. Tissue K_p values were assumed to be muscle K_p (1.03 for mouse and 0.597 for rat) if unavailable in Table 6.

Tissue	Mouse (0.025 kg)			Tissue	Rat (0.25 kg)		
	V_T (mL)	K_p	$V_T \cdot K_p$ (mL)		V_T (mL)	K_p	$V_T \cdot K_p$ (mL)
Adipose	1.88	0.471	0.885	Adipose	16.7	0.597	9.97
Bone	1.51	1.03	1.56	Bone	15.7	0.597	9.37
Brain	0.45	0.213	0.0959	Brain	1.24	0.8	0.992
Gut	2.56	11.3	28.9	Gut	6.19	4.63	28.7
Heart	0.12	0.610	0.0732	Heart	1.05	0.597	0.627
Kidney	0.34	8.74	2.97	Kidney	2.19	4.04	8.85
Liver	1.19	3.47	4.13	Liver	8.57	3.07	26.3
Lung	0.15	1.03	0.155	Lung	1.24	0.597	0.740
Muscle	9.5	1.03	9.79	Muscle	116	0.597	69.3
Skin	3.07	1.03	3.16	Skin	39.4	0.597	23.5
Spleen	0.11	1.03	0.113	Spleen	0.57	0.956	0.545
Blood (V_B)	1.64			Blood (V_B)	15.3		
$V_{SS,mouse}$ (mL/kg)			2140	$V_{SS,rat}$ (mL/kg)			777

^a V_T obtained from Simcyp V19

Supplementary Table S5. Model fitting results using a tri-exponential function [$C_p(t) = C_1e^{-\lambda_1t} + C_2e^{-\lambda_2t} + C_3e^{-\lambda_3t}$] for metformin PK in various species (CV% obtained by fitting). It is noted that five parameters (C_1 , λ_1 , C_2 , λ_2 , and λ_3) were optimized while C_3 values were estimated as a secondary parameter ($C_3 = C_0 - C_1 - C_2$; $C_0 = Dose/V_B$)

Species (body weight, kg)	Source	C_0 ($\mu\text{g/mL}$)	C_1 ($\mu\text{g/mL}$)	λ_1 (min^{-1})	C_2 ($\mu\text{g/mL}$)	λ_2 (min^{-1})	C_3 ($\mu\text{g/mL}$)	λ_3 (min^{-1})	CL_D (mL/min) ^a	Q_{CO} (mL/min) ^b	CL (mL/min/kg) ^c	V_{SS} (mL/kg) ^c
Mouse (0.025)	Higgins et al (2012) [27]	76.2	69.1 (3.18)	2.49 (324)	6.52 (32.9)	0.197 (22.0)	0.601 (18.3)	0.0219 (12.0)	2.32 (455)	14.0	56.7 (97.4)	918 (189)
Rat (0.25)	Choi et al (2006) [32]	817	789 (0.404)	0.647 (5.56)	27.3 (11.5)	0.0414 (6.94)	1.01 (15.1)	0.00543 (8.21)	3.52 (10.7)	80.0	24.2 (3.25)	611 (6.79)
		1630	1550 (0.459)	0.572 (4.39)	80.6 (8.77)	0.0524 (4.54)	1.85 (8.78)	0.00547 (4.99)	2.90 (8.65)		21.8 (2.50)	456 (4.99)
		3270	2990 (1.49)	0.863 (19.7)	277 (16.0)	0.0494 (7.54)	3.85 (19.7)	0.00600 (8.49)	6.99 (29.7)		20.6 (6.90)	477 (12.2)
Rabbit (2)	Bouriche et al (2020) [54]	83.3	56.8 (6.48)	0.336 (17.5)	17.9 (18.7)	0.0389 (21.6)	8.63 (9.21)	0.00475 (5.63)	24.5 (15.4)	395	2.05 (1.87)	330 (3.72)
Cat (5)	Michels et al (1999) [55]	417	355 (1.31)	0.127 (7.88)	59.5 (7.58)	0.0114 (5.28)	2.17 (13.7)	0.00123 (11.3)	20.2 (11.0)	786	2.55 (2.43)	501 (8.43)
Monkey (7)	Shen et al (2016) [56]	65.0	62.6 (0.726)	0.210 (9.20)	2.35 (19.2)	0.0201 (11.5)	0.0422 (27.9)	0.00138 (9.61)	23.9 (19.9)	1010	8.75 (5.39)	576 (13.0)
Minipig (14)	Patel et al (2017) [58]	8.0	7.24 (2.15)	0.752 (21.2)	0.744 (20.8)	0.0250 (14.7)	0.0176 (21.8)	0.00122 (16.5)	468 (25.5)	1700	9.29 (7.69)	2240 (19.7)
Dog (28)	Johnston et al (2017) [59]	275	266 (0.175)	0.201 (4.66)	8.96 (5.15)	0.0123 (3.03)	0.217 (6.24)	0.00105 (4.47)	183 (8.33)	2860	10.9 (2.56)	1270 (5.65)
Man (70)	Tucker et al (1981) [62]	48.1	43.1 (1.47)	0.164 (6.91)	4.56 (13.0)	0.0175 (9.43)	0.404 (19.9)	0.00395 (8.68)	373 (11.1)	5690	5.71 (2.64)	387 (5.02)
	Pentikäinen et al (1979) [61]	96.1	79.7 (0.725)	0.930 (19.4)	13.5 (4.05)	0.0325 (4.21)	2.91 (4.10)	0.00658 (1.48)	3500 (21.5)		7.57 (1.62)	643 (3.00)
	Sirtori et al (1978) [60]	178	136 (7.01)	0.513 (36.4)	34.5 (25.8)	0.0391 (25.6)	7.40 (25.3)	0.00768 (9.25)	1640 (39.6)		6.27 (4.96)	441 (8.22)
Horse (530)	Hustace et al (2009) [63]	150	125 (4.32)	0.208 (28.0)	25.2 (21.5)	0.0297 (8.87)	0.119 (fixed)	0.000599 (fixed)	3460 (44.5)	26000	6.86 (8.54)	1510 (16.7)

^a $CL_D = Dose \left(\frac{\sum C_i \lambda_i}{C_0^2} - \frac{1}{AUC} \right)$ estimated as a secondary parameter

^b Q_{CO} obtained from Supplementary Table S1

^c CL and V_{SS} estimated as a secondary parameter where $CL = \frac{Dose}{AUC}$ and $V_{SS} = \frac{Dose \cdot AUMC}{AUC^2}$

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