Lin and Chiu:

Development of a Physiologically Based Gut Absorption Model for Probabilistic Prediction of Environmental Chemical Bioavailability

Supplementary Data

Content of supplementary materials

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1 Probabilistic environmental compartmental absorption and transit (PECAT) model

Our PECAT model was adapted from the PBPK absorption model by Hsieh et al. (2021). The equations listed as follow, with the parameters in Tables S5 and S6, define the current PECAT model. In addition to the same equations included in the PECAT model code, some additional equations for unit conversions or numerical stability, i.e., truncating small values at 10^{-10} and preventing the values being negative while simulating, are provided here.

1.1. Primary differential equations

Under the assumption of environmental chemicals being exposed in dissolved form, the dissolution and precipitation processes of chemicals and the compartments of undissolved chemical in gut lumen were firstly removed. For oral uptake, the amount of dissolved chemical (A_{Input}) enters the stomach lumen and undergoes absorption, transport, and transit to the following segment of the GI tract. The differential equation for the amount of dissolved chemical in the intestinal lumen (A_{Lumen}) for segments *i*, including stomach, duodenum, jejunum, cecum, and colon, are:

$$\frac{dA_{Lumen_i}}{dt} = A_{Input} - K_{t_i} \cdot C_{Lumen_i} - K_{a_i}\left(C_{Lumen_i} - K_{E/Ae} \cdot C_{uEpith_i}\right) + \frac{V_{max,eff\ i} \cdot C_{uEpith_i}}{K_{m,eff} + C_{uEpith_i}} - \frac{V_{max,inf\ i} \cdot C_{Lumen_i}}{K_{m,inf} + C_{Lumen_i}} \quad (1)$$

where A_{Input} is the amount of chemical oral administration; C_{Lumen_i} is chemical concentration in the lumen of segment *i* (A_{Lumen_i} divided by luminal volume [V_{Lumen_i}]); C_{uEpith_i} is unbound chemical concentration in the epithelium of segment *i*; $K_{E/Ae}$ is the excretion over absorption rate constant ratios between lumen and epithelium; $V_{max,eff\ i}$ and $V_{max,inf\ i}$ are the maximum rate of active efflux and influx transport of segment *i*, respectively; $K_{m,eff}$ and $K_{m,inf}$ are the Michaelis-Menten constants of active efflux and influx transport, respectively.

Additionally, C_{uEpith_i} is calculated as:

$$C_{uEpith_i} = f_{u_i} \cdot C_{Epith_i} \quad (2)$$

where f_{u_i} is the fraction unbound in segment *i*, and C_{Epith_i} is the chemical concentration in the epithelium of segment *i* (chemical amount in intestinal epithelium *i* [A_{Epith_i}] divided by epithelium volume [V_{Epith_i}]).
Note that the intestinal transit rate in segment *i*, K_{t_i}, is given by V_{Lumen_i} and transit half-lives in segment *i*, $t_{1/2_i}$:

$$K_{t_i} = log2 \cdot V_{Lumen_i} \cdot t_{1/2_i} \quad (3)$$

Also, the equation for the absorption rate in segment *i*, K_{a_i}, is based on permeability (P_{eff} or P_{app}) and surface area of segment *i*, SA_i:

$$K_{t_i} = Permeability \cdot SA_i \quad (4)$$

When the dissolved chemical is transited to the colon lumen, the chemical is subsequently excreted in the feces. The amount of dissolved chemical in the feces is given by:

$$\frac{dA_{Feces}}{dt} = K_{t_{Colon}} \cdot C_{Lumen_{Colon}} \quad (5)$$

The differential equation for the amount in the epithelium (A_{Epith_i}), as middle layer between lumen and wall tissue, is the sum of passive absorption from lumen and wall, bidirectional active transport flux from lumen and intestinal metabolism:

$$\frac{dA_{Epith_i}}{dt} = K_{a_i}\left(C_{Lumen_i} - K_{E/Ae} \cdot C_{uEpith_i}\right) - K_{a_i}\left(C_{uEpith_i} - K_{E/At} \cdot C_{uWall_i}\right) + \frac{V_{max,inf\ i} \cdot C_{Lumen_i}}{K_{m,inf} + C_{Lumen_i}} - \frac{V_{max,eff\ i} \cdot C_{uEpith_i}}{K_{m,eff} + C_{uEpith_i}} - \frac{V_{max,met\ i} \cdot C_{uEpith_i}}{K_{m,met} \cdot f_{u,vitro_i} + C_{uEpith_i}} \quad (6)$$

where C_{uWall_i} is unbound chemical concentration in the intestinal wall tissue of segment *i*; $K_{E/At}$ is the excretion over absorption rate constant ratios between epithelium and wall tissue; $V_{max,met\ i}$ is the maximum metabolism rate of epithelium *i*; $K_{m,met}$ is the Michaelis-Menten constant of intestinal metabolism; $f_{u,vitro_i}$ is the fraction of unbound chemical in the *in vitro* cell assay corresponding to the epithelium *i*.

Being similar to C_{uEpith_i}, C_{uWall_i} is calculated as:

$$C_{uWall_i} = f_{u_i} \cdot C_{Wall_i} \tag{7}$$

where C_{Wall_i} is the chemical concentration in the intestinal wall tissue *i* (chemical amount in intestinal wall tissue *i* [A_{Wall_i}] divided by volume of wall tissue *i* [V_{Wall_i}]).

After chemical transported from lumen to epithelium, the intestinal wall tissue *i* absorbs chemicals from the epithelium and is interconnected with the liver through blood vessels. The differential equation for A_{Wall_i} is therefore given by:

$$\frac{dA_{Wall_i}}{dt} = K_{a_i}\left(C_{uEpith_i} - K_{E/At} \cdot C_{uWall_i}\right) + Q_{GI_i}\left(C_{Input} - Cv_{Wall_i}\right) \tag{8}$$

where C_{Input} is the concentration in the gut artery which inputs into gut wall tissue; Q_{GI_i} is the blood flow of gut segment *i*; Cv_{Wall_i} is the chemical concentration in venous blood leaving wall tissue *i*.
Cv_{Wall_i} is calculated as:

$$Cv_{Wall_i} = \frac{C_{uWall_i}}{K_{puu_i} \cdot f_{uBlood}} \tag{9}$$

$$f_{uBlood} = \frac{f_{uPlasma}}{Ratio_{BP}} \tag{10}$$

where K_{puu_i} is the partition coefficient of gut segment *i*; f_{uBlood} and f_{uPlasm} are the fraction of unbound chemical in blood and plasma, respectively, and $Ratio_{BP}$ is the ratio of blood over plasma concentration.

Through the portal vein, the absorbed chemical is distributed to liver, and the differential equation for the amount in liver (A_{Liver}) is:

$$\frac{dA_{Liver}}{dt} = \sum_{i \in S} Q_{GI_i} \cdot Cv_{Wall_i} + Q_{Liver} \cdot C_{Blood} - (Q_{Liver} + Q_{Portal}) \cdot Cv_{Liver} + \frac{V_{max,inf_{Liver}} \cdot Cv_{uLiver}}{K_{m,inf} + Cv_{uLiver}} - \frac{V_{max,eff_{Liver}} \cdot C_{uLiver}}{K_{m,eff} + C_{uLiver}} - \frac{V_{max,met_{Liver}} \cdot C_{uLiver}}{K_{m,met} \cdot f_{u,vitro_{Liver}} + C_{uLiver}},$$

$$S = \{\text{stomach, duodenum, jejunum, ileum, cecum, colon}\} \tag{11}$$

where Q_{Liver} is the blood flow into liver; Q_{Portal} is the blood flow of portal vein and equal to the sum of Q_{GI_i}; C_{Blood} is the chemical concentration in the blood compartment; Cv_{Liver} and Cv_{uLiver} are the total and unbound chemical concentrations in venous blood leaving from liver, respectively; C_{uLiver} is the unbound chemical concentration in liver; $V_{max,eff_{Liver}}$ and $V_{max,inf_{Liver}}$ are the maximum rate of active efflux and influx transport of liver, respectively; $V_{max,met_{Liver}}$ is the maximum metabolism rate of liver; $f_{u,vitro_{Liver}}$ is the fraction of unbound chemical in the *in vitro* cell assay used to investigate the hepatic metabolism.

C_{uLiver}, Cv_{Liver} and Cv_{uLiver} are computed as follows:

$$C_{uLiver} = f_{uLiver} \cdot C_{Liver} \tag{12}$$

$$Cv_{Liver} = \frac{C_{uLiver}}{K_{puu_{Liver}} \cdot f_{uBlood}} \tag{13}$$

$$Cv_{uLiver} = \frac{C_{uLiver}}{K_{puu_{Liver}}} \tag{14}$$

where C_{Liver} is the chemical concentration in liver (A_{Liver} divided by volume of liver [V_{Liver}]); f_{uLiver} is the fraction of unbound chemical in liver; $K_{puu_{Liver}}$ is the partition coefficient of liver.

The other main adaption of our PECAT model is to replace the two-compartment model (central and peripheral compartments) with a classic PBPK model. Therefore, the original peripheral compartment was changed to two compartments: kidney and body (merged rest of body). The differential equation for the amount of chemical in kidney (A_{Kidney}) is based on the blood circulation, renal metabolism, and clearance:

$$\frac{dA_{Kidney}}{dt} = Q_{Kidney} \cdot \left(C_{Blood} - Cv_{Kidney}\right) - \frac{V_{max,met_{Kidney}} \cdot C_{uKidney}}{K_{m,met} \cdot f_{u,vitro_{Kidney}} + C_{uKidney}} - C_{Plasma} \cdot CL_{Kidney} \tag{15}$$

where Q_{Kidney} is the blood flow into kidney; Cv_{Kidney} is the chemical concentration in venous blood leaving from kidney; $C_{uKidney}$ is the unbound chemical concentration in kidney; $V_{max,met_{Kidney}}$ is the maximum metabolism rate of kidney; $f_{u,vitro_{Kidney}}$ is the fraction of unbound chemical in the *in vitro* cell assay used to investigate the renal metabolism; C_{Plasma} is the chemical concentration in plasma.

CL_{Kidney} is the clearance of kidney and its computation was referred to in Sakolish et al. (2020):

$$CL_{Kidney} = Q_{Kidney}\left(f_{uBlood} \cdot \frac{GFR}{Q_{Kidney}} + \left(1 - f_{uBlood} \cdot \frac{GFR}{Q_{Kidney}}\right) \cdot E_{TS}\right) \cdot (1 - f_{reabs}) \tag{16}$$

where *GFR* is the glomerular filtration rate; E_{TS} is the extraction ratio for tubular secretion; f_{reabs} is the fraction of renal reabsorption.

$C_{uKidney}$ and Cv_{Kidney} are computed as follows:

$$C_{uKidney} = f_{uKidney} \cdot C_{Kidney} \tag{17}$$

$$Cv_{Kidney} = \frac{C_{uKidney}}{K_{puu_{Kidney}} \cdot f_{uBlood}} \tag{18}$$

where C_{Kidney} is the chemical concentration in kidney (A_{Kidney} divided by volume of kidney [V_{Kidney}]); $f_{uKidney}$ is the fraction of unbound chemical in kidney; $K_{puu_{Kidney}}$ is the partition coefficient of kidney.

The differential equation for the amount of chemical in the rest of body (A_{Body}), i.e., excluding blood, liver, kidney and gut, is:

$$\frac{dA_{Body}}{dt} = Q_{Body} \cdot \left(C_{Body} - Cv_{Body}\right) \tag{19}$$

where Q_{Body} is the blood flow into the rest of the organs; Cv_{Body} is the chemical concentration in venous blood leaving from the rest of the organs, and calculated as:

$$Cv_{Body} = \frac{f_{uBody} \cdot C_{Body}}{K_{puu_{Body}} \cdot f_{uBlood}} \tag{20}$$

where C_{Body} is the chemical concentration in the rest of the body (A_{Body} divided by volume of the rest of body [V_{Body}]); f_{uBody} is the fraction of unbound chemical in the rest of the body; $K_{puu_{Body}}$ is the partition coefficient of the rest of body.

Finally, the differential equation for the amount of chemical in blood (A_{Blood}) is similar to the original central compartment in the ACAT model compartment, given by:

$$\frac{dA_{Blood}}{dt} = (Q_{Liver} + Q_{Portal}) \cdot Cv_{Liver} + Q_{Kidney} \cdot Cv_{Kidney} + Q_{Body} \cdot Cv_{Body} - C_{Body}\left(Q_{Liver} + Q_{Portal} + Q_{Kidney} + Q_{Body}\right) + \frac{V_{max,eff_{Liver}} \cdot C_{uLiver}}{K_{m,eff} + C_{uLiver}} - \frac{V_{max,inf_{Liver}} \cdot Cv_{uLiver}}{K_{m,inf} + Cv_{uLiver}} \tag{21}$$

1.2. Miscellaneous equations

Miscellaneous equations, including calculating the fraction of chemical absorbed by gut (F_{abs}) and mass balance checking, are compiled in this section. The notion of calculating F_{abs} is that the total input minus the amount of chemical left in gut lumen and feces, is given by:

$$F_{abs} = 1 - \left(\frac{A_{Lumen} + A_{Feces}}{A_{Total}}\right) \times 100\% \tag{22}$$

The equations used to check mass balance are listed as follows:

$$A_{Lumen} = \sum_{i \in S} A_{Lumen_i} \tag{23}$$

$$A_{Epith} = \sum_{i \in S} A_{Epith_i} \tag{24}$$

$$A_{Wall} = \sum_{i \in S} A_{Wall_i} \tag{25}$$

$$A_{met} = \sum_{i \in S} A_{met_i} \tag{26}$$

$$A_{elim_{gut}} = A_{met} + A_{Feces} \tag{27}$$

$$A_{elim_{total}} = A_{elim_{gut}} + A_{elim_{Liver}} + A_{elim_{Kidney}} + A_{Urine} \tag{28}$$

$$A_{Organ} = A_{Lumen} + A_{Epith} + A_{Wall} + A_{Liver} + A_{Kidney} + A_{Blood} + A_{Body} \tag{29}$$

$$A_{Total} = A_{Organ} + A_{elim_{total}} \tag{30}$$

2 Sensitivity analysis: effect of the chemical-related parameters on the prediction of F_{abs}

Monte Carlo (MC) algorithm with setting distributions for chemical-related parameters was applied as a sensitivity analysis to evaluate the effect of these parameters on the prediction of F_{abs}. The evaluated chemical-related parameters included the ratio of blood over plasma concentration ($Ratio_{BP}$), fraction of unbound chemical in various organs (f_u), fraction of unbound chemical in various *in vitro* cell assays ($f_{u,\ in\ vitro}$), partition coefficient of various organs (K_{upp}), and the maximum metabolism rate of liver ($V_{max,met_{Liver}}$). The distributions of these evaluated parameters were assumed to be uniform distributions with ranges mainly referred to in published databases. As for the f_u and $f_{u,\ in\ vitro}$, Ryu et al. (2020) provided a list for fraction unbound of 24 drugs in 5 organs, and we extracted the minimal and maximal values among this list as the uniform range for f_u and $f_{u,\ in\ vitro}$ in different organs. A similar process of distribution parametrization was also applied on the $Ratio_{BP}$, K_{upp} and $V_{max,met_{Liver}}$, referred to in the databases in R package *httk* (*v.2.1.0*; Pearce et al., 2017) and published by Utsey et al. (2020) and Bu (2006), respectively. The simulated scenario for predicting F_{abs} was under continuous exposure for 10,000 hours, as well as simulating in the ranging from 10^{-8} to 10^{-2} cm/s of permeability. The sensitivity analysis was performed by visually comparing the F_{abs} generated by MC algorithm with the results by basic simulation with baseline values in Tables S5 and S6. The MC algorithm with 10,000 iterations was executed by GNU MCSim v6.1.0 (version 6.1.0) in the R environment. The visual comparison is presented in Figure S1. The solid line is the result from basic simulation with pointed baseline values of chemical-related parameters, and the dashed line represents the result of median from executing MC algorithm with setting parameter distributions. The overlap of two simulated curves demonstrated that the uncertainties of chemical-related parameters have negligible effects on the prediction of F_{abs}.

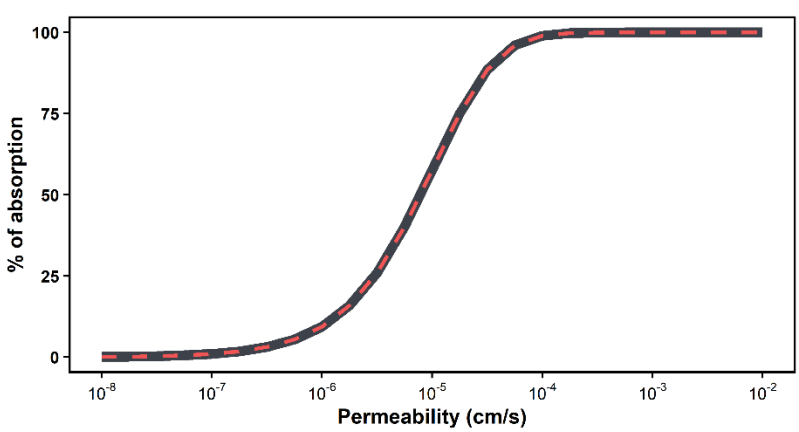
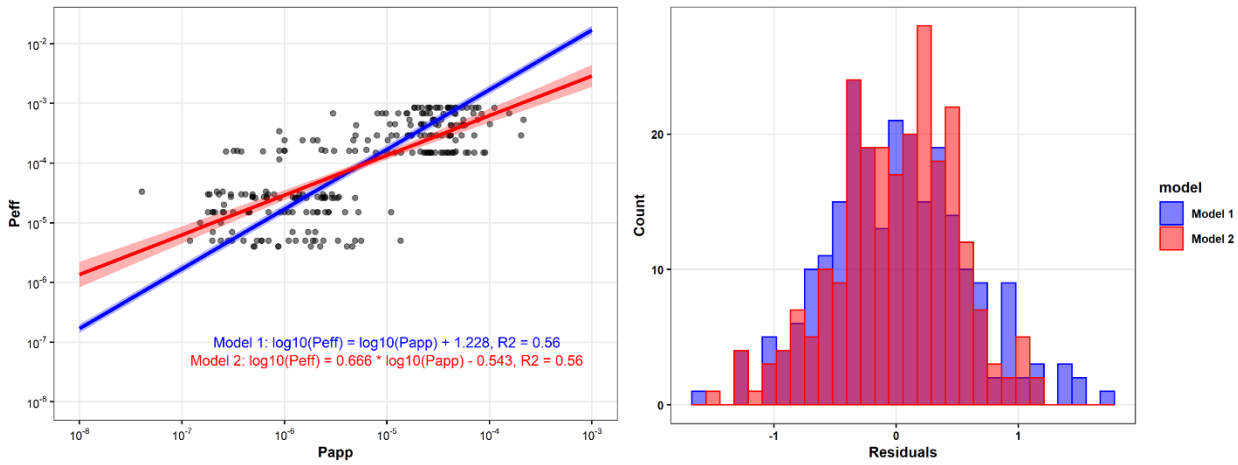


Fig. S1: Comparisons of simulated results from the basic simulation with pointed baseline values of chemical-related parameters (solid line) and the result of median from executing MC algorithm with parameter distributions (dashed line)

3 Discussion

3.1. Scaling methodology comparison: regression model vs. ratio method

Construction of a regression model has been a common scaling method and has also been applied to estimation of *in vivo* gut permeability by using Caco-2 permeability data as scaler (Sun et al., 2002). In our study, we tried to construct empirical distributions of scaling ratios for converting *in vitro* to *in vivo* permeability and gut segment-specific permeability. To check whether the scaling ratio method could be an alternative, we used two kinds of simple linear regression model with fitting slope (being equivalent to the regression model used in Sun et al. (2002)) and fixing slope of 1 (being equivalent to the ratio method). This comparison was applied to the relationships of *in vitro* and *in vivo* permeability and gut segment-specific permeability, and the results are presented in Figures S2, S3 and S4. Note that the data of gut segment-specific permeability has outliers; therefore, we demonstrated results of regression models with and without outliers (Fig. S3), and, in the following discussion, we only consider the results without outliers. These regression results showed that the determined coefficients are the same, and most 95% CIs of fitted slope included 1, which means that both models have no significant differences.



	Intercept (95%CI)	Slope (95%CI)	R^2
Model 1 (with fixing slope of 1)	1.228*** (1.155, 1.301)	1	0.56
Model 2 (with fitting slope)	-0.543** (-0.946, -0.141)	0.666*** (0.591, 0.741)	0.56

Fig. S2: Regression models describing the relationship between *in vitro* P_{app} and *in vivo* P_{eff} (left panel); histogram (right panel) showing the residuals between observed and predicted P_{eff}; table summarizing the fitting parameters * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

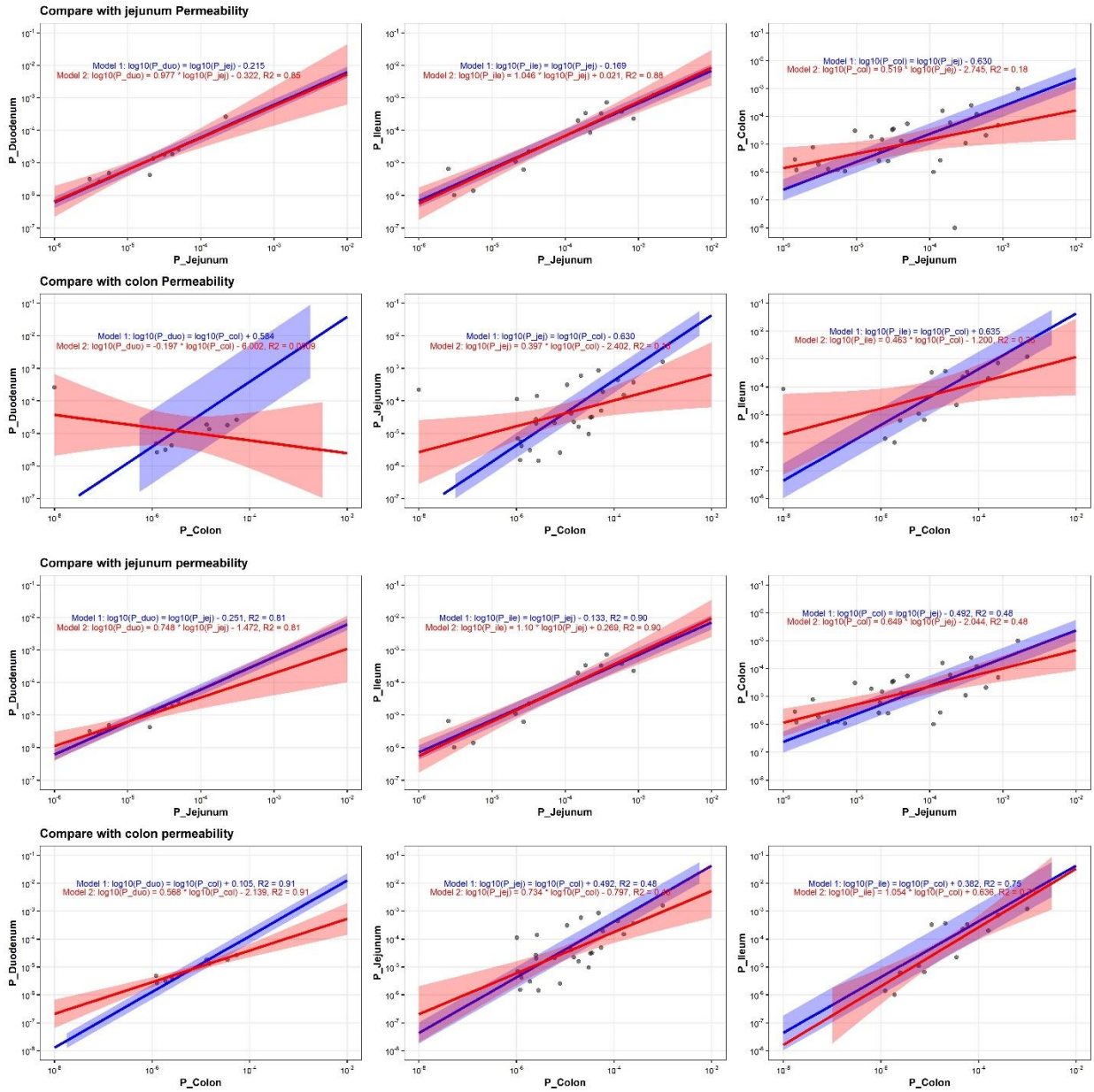
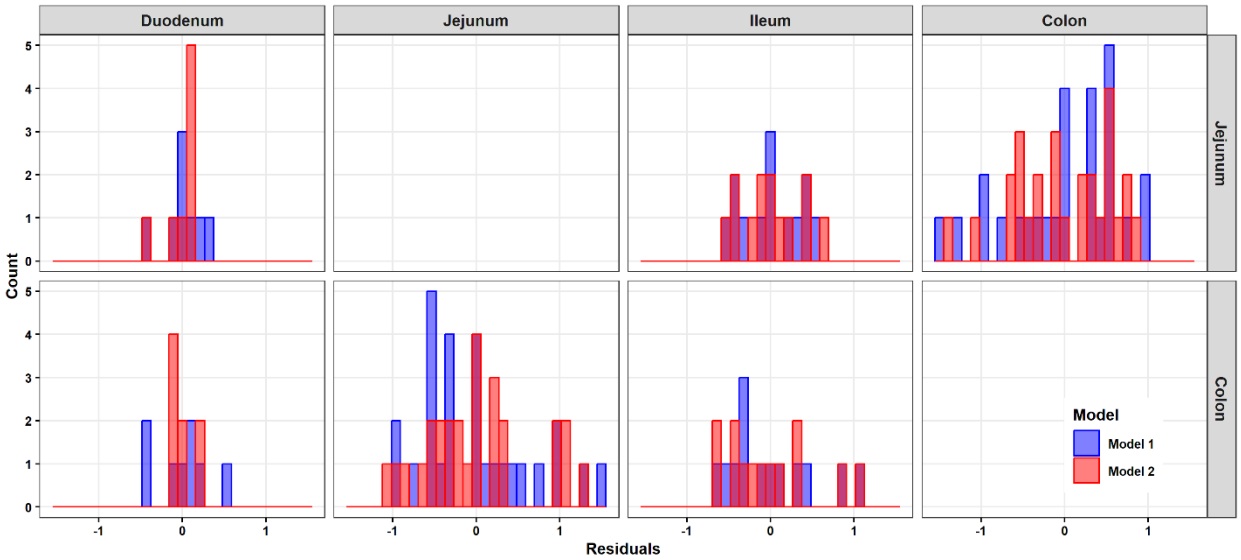


Fig. S3: Regression models describing the relationship among different segment-specific permeabilities (A) with outliers and (B) without outliers

The blue lines represent the linear regression model with fixing slope of 1 (Model 1); the red lines represent the simple linear regression model with fitting slope (Model 2).



Gut segment	Model	Intercept (95%CI)	Slope (95%CI)	R^2
Compare with jejunum				
Duodenum	**Model 1**	-0.251 (-0.426, -0.077)	1.000	0.81
	Model 2	-1.472** (-3.201, 0.257)	0.748** (0.392, 1.104)	0.81
Ileum	**Model 1**	-0.133* (-0.265, 0.001)	1.000	0.90
	Model 2	0.269 (-0.408, 0.947)	1.100*** (0.935, 1.265)	0.90
Colon	**Model 1**	-0.492*** (-0.755, -0.230)	1.000	0.48
	Model 2	-2.044** (-3.301, -0.788)	0.649*** (0.370, 0.928)	0.48
Compare with colon				
Duodenum	**Model 1**	0.105 (-0.155, 0.364)	1.000	0.91
	Model 2	-2.139** (-3.055, -1.224)	0.568*** (0.393, 0.743)	0.91
Jejunum	**Model 1**	0.492*** (0.230, 0.755)	1.000	0.48
	Model 2	-0.797 (-2.376, 0.781)	0.738*** (0.421, 1.055)	0.48
Ileum	**Model 1**	0.382* (0.058, 0.706)	1.000	0.75
	Model 2	0.636 (-1.287, 2.559)	1.054*** (0.648, 1.460)	0.75

Fig. S4: Residual histogram between observed and predicted segment-specific permeabilities, using model constructed without outliers

The blue bars represent the linear regression model with fixing slope of 1 (Model 1); the red bars represent the simple linear regression model with fitting slope (Model 2). The table summarizes the fitting parameters without outliers. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

3.2. Effects of adding transporter inhibitors and different pH value in the *in vitro* testing environment on IVIVC factors

In order to confirm that the various sources of Caco-2 permeability data have negligible effects on the distributions of IVIVC factors, we compiled the detailed information on the pH setting and presence of transporter inhibitors in Tables S2 and S4 and construct the distributions of IVIVC factors based on different conditions. Kolmogorov-Smirnov (KS) test was used to compare the discrepancy of two distributions. For the presence of transporter inhibitors, we found that most Caco-2 permeability testing did not consider the presence of transporter inhibitors, and only one literature clearly stated that the permeability data was measured with adding efflux transporter inhibitors (n = 10). We compare the distributions: one considers all IVIVC factors, the other only considers the IVIVC factors derived from Caco-2 permeability data without transporter inhibitors. Figure S5 shows that there is no significant difference between the two distributions (*p*-value of KS test = 1).

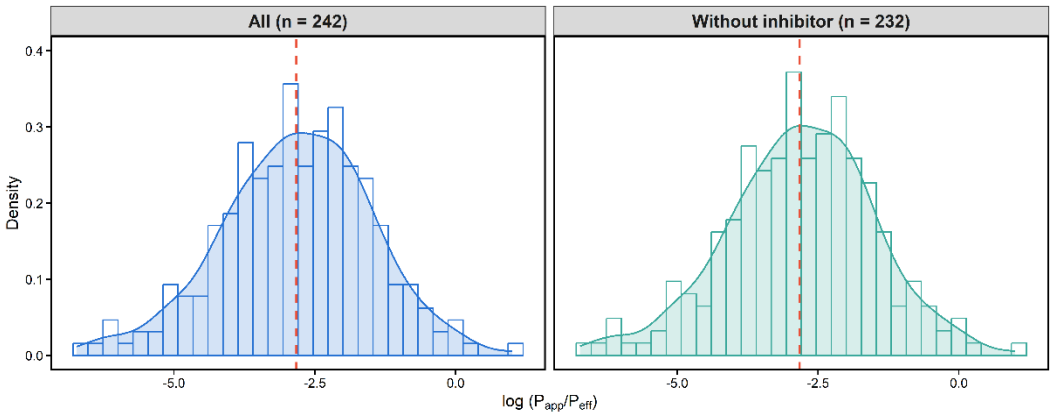


Fig. S5: Density plots of IVIVC factors considering all ratios (Log Mean ± Log SD: -2.827 ± 1.326; Geometric Mean ± Geometric SD: 0.059 ± 3.766) and ratios without transporter inhibitors (-2.824 ± 1.317; 0.059 ± 3.730)

As for the pH value of the *in vitro* testing environment, the common pH condition of permeability data included: (I) different pH settings in the apical and basolateral chambers, (II) only using physiological pH value (pH 7.4 or using Hank's balanced salt solution), and (III) in a range of pH values due to considering different permeability databases at the same time. Note that, since there are only two *in vitro* P_{app} measured in pH 6.8 and some values (n = 20) did not clearly mention their experimental pH value, we did not classify these into any groups. Based on the above-mentioned condition, we classified the pH setting into three groups (Groups I – III) to individually compare to overall distribution. The *p*-values of the KS test comparing overall distribution with Groups I to III are 0.607, 0.376 and 0.095, respectively. Figure S6 and *p*-values demonstrate that there are also no significant differences between overall and each group distributions.

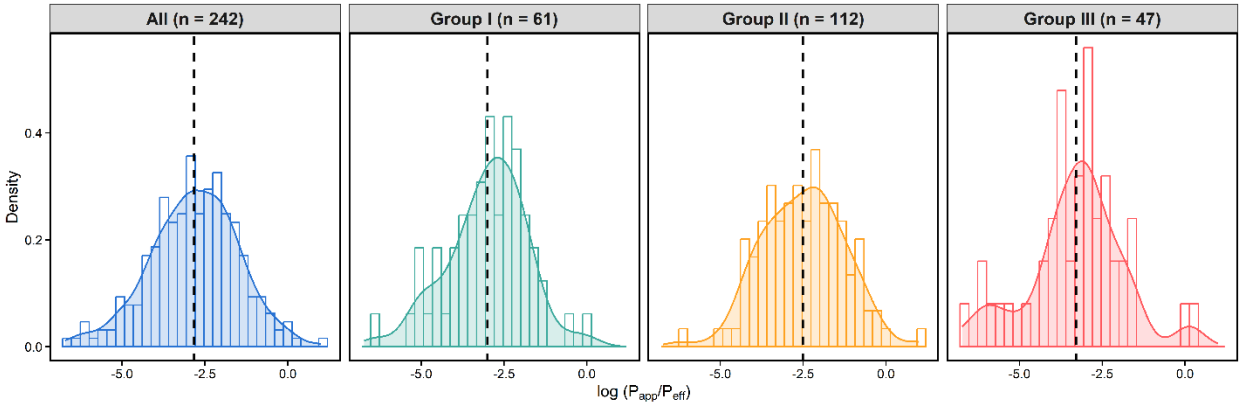


Fig. S6: Density plots of IVIVC factors considering overall ratios and ratios under specific pH setting groups (Log Mean ± Log SD: Group I, -3.004 ± 1.195; Group II, -2.508 ± 1.221; Group III, -3.286 ± 1.436 / Geometric Mean ± Geometric SD: Group I, 0.050 ± 3.303; Group II, 0.081 ± 3.392; Group III, 0.037 ± 4.204)

4 Supplementary Tables

Tab. S1: Raw data of gut segment-specific permeability (×10^{-6} cm/s)

Chemicals	Gut segment				Data type	Reference
	Duodenum	Jejunum	Ileum	Colon		
Acetobutolol		11.00			*Ex vivo* P_{app}	Dahlgren et al., 2015
Antipyrine	26.30	49.70		54.60	*Ex vivo* P_{app}	Dahlgren et al., 2015
Atenolol	2.61	4.11		1.27	*Ex vivo* P_{app}	Dahlgren et al., 2015
Bevirimat		590.00	370.00	21.00	*In vivo* P_{eff}	Sjögren et al., 2015
Budesonide		190.00	340.00	59.00	*In vivo* P_{eff}	Sjögren et al., 2015
Candesartan		3.60			*Ex vivo* P_{app}	Dahlgren et al., 2015
Carvedilol		2.60			*Ex vivo* P_{app}	Dahlgren et al., 2015
Cetirizine		19.10			*Ex vivo* P_{app}	Dahlgren et al., 2015
Cimetidine		3.74			*Ex vivo* P_{app}	Dahlgren et al., 2015
Cimetidine		10.70			*Ex vivo* P_{app}	Dahlgren et al., 2015
Ciprofloxacin		15.70			*Ex vivo* P_{app}	Dahlgren et al., 2015
Creatinine	4.24	20.20		2.55	*Ex vivo* P_{app}	Dahlgren et al., 2015
Diazepam		89.00			*Ex vivo* P_{app}	Dahlgren et al., 2015
Diclofenac		8.55			*Ex vivo* P_{app}	Dahlgren et al., 2015
Digoxin		1.44		2.83	*Ex vivo* P_{app}	Dahlgren et al., 2015
Diltiazem				23.60	*Ex vivo* P_{app}	Dahlgren et al., 2015
Fenofibric acid		860.00	230.00	48.00	*In vivo* P_{eff}	Sjögren et al., 2015
Fexofenadine		27.00	6.20	2.50	*In vivo* P_{eff}	Sjögren et al., 2015
Fexofenadine				0.22	*Ex vivo* P_{app}	Dahlgren et al., 2015
Glucose		113.00		1.02	*Ex vivo* P_{app}	Dahlgren et al., 2015
Hydrocortisone	13.50	22.30		15.00	*Ex vivo* P_{app}	Dahlgren et al., 2015
Indomethacine		48.20			*Ex vivo* P_{app}	Dahlgren et al., 2015
Ipsapirone		31.00		33.00	*In vivo* P_{eff}	Sjögren et al., 2015
Lisdexamfetamine		310.00	330.00	11.00	*In vivo* P_{eff}	Sjögren et al., 2015
l-Leucine		140.00		2.63	*Ex vivo* P_{app}	Dahlgren et al., 2015
Lumiracoxib		370.00	720.00	250.00	*In vivo* P_{eff}	Sjögren et al., 2015
Mannitol	4.85	5.56	1.39	1.22	*Ex vivo* P_{app}	Dahlgren et al., 2015
Melagatran		1.51		1.20	*Ex vivo* P_{app}	Dahlgren et al., 2015
Metoprolol		150.00	200.00	160.00	*In vivo* P_{eff}	Sjögren et al., 2015
Metoprolol		15.90		18.80	*Ex vivo* P_{app}	Dahlgren et al., 2015
Metoprolol		17.80			*Ex vivo* P_{app}	Dahlgren et al., 2015
Midazolam		38.00			*Ex vivo* P_{app}	Dahlgren et al., 2015
Nifedipine		440.00		120.00	*In vivo* P_{eff}	Sjögren et al., 2015
Oseltamivir		4.64			*Ex vivo* P_{app}	Dahlgren et al., 2015
Oxprenolol		9.50		30.40	*Ex vivo* P_{app}	Dahlgren et al., 2015
Pindolol		35.80			*Ex vivo* P_{app}	Dahlgren et al., 2015
Propranolol	18.00	31.90	22.40	35.40	*Ex vivo* P_{app}	Dahlgren et al., 2015
Quinidine		3.36			*Ex vivo* P_{app}	Dahlgren et al., 2015
Ranitidine				0.62	*Ex vivo* P_{app}	Dahlgren et al., 2015
Ranitidine		5.50			*Ex vivo* P_{app}	Dahlgren et al., 2015
Ranitidine (capsule)		21.00	11.00	6.00	*In vivo* P_{eff}	Sjögren et al., 2015
Ranitidine (tube)		39.00			*In vivo* P_{eff}	Sjögren et al., 2015
Rivastigmine		1600.00	1200.00	1000.00	*In vivo* P_{eff}	Sjögren et al., 2015
Ropivacaine		2.54	6.55	7.79	*Ex vivo* P_{app}	Dahlgren et al., 2015
Rosuvastatin		6.95		1.07	*Ex vivo* P_{app}	Dahlgren et al., 2015
Salicylic acid	18.40	41.10		13.30	*Ex vivo* P_{app}	Dahlgren et al., 2015
Sulphasalazine		0.90			*Ex vivo* P_{app}	Dahlgren et al., 2015
Sulphasalazine		0.09			*Ex vivo* P_{app}	Dahlgren et al., 2015
Sumatriptan		170.00			*In vivo* P_{eff}	Sjögren et al., 2015
Testosterone		68.00			*Ex vivo* P_{app}	Dahlgren et al., 2015
Theophylline			92.00		*In vivo* P_{eff}	Sjögren et al., 2015
Verapamil		36.00			*Ex vivo* P_{app}	Dahlgren et al., 2015
Vinblastine		1.31			*Ex vivo* P_{app}	Dahlgren et al., 2015
Ximelagatran	3.15	3.03	1.01	1.90	*Ex vivo* P_{app}	Dahlgren et al., 2015

Tab. S2: Raw data of human fraction absorption (%), *in vivo* effective and *in vitro* apparent permeability (×10^{-6} cm/s) for drugs and environmental chemicals presented in Figure 5

Chemical	*In vivo* P_{eff}	*In vitro* P_{app}	Fa	BDDCS[a]	pH value	Inhibitor	Reference
Environmental chemicals							
2,4-D		4.2	85	IV[#]	AP: pH 6.5 / BL: pH 7.4[b]	w/o	Punt et al., 2022; Chedik et al., 2017
Bisphenol A		15.95	95	II	AP: pH 6.5 / BL: pH 7.4	w/o	Punt et al., 2022; Thayer et al., 2015
Coumarin		76.98	100	II[#]	AP: pH 6.5 / BL: pH 7.4	w/o	Punt et al., 2022; Chiou and Buehler, 2002
Imazalil		30.6	80	II	AP: pH 6.5 / BL: pH 7.4	w/o	Punt et al., 2022; Tebby et al., 2020
Malathion		11.8	73.8	II	AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011; Bouchard et al., 2003
Ochratoxin A		0.99	85.5	II	AP: pH 6.5 / BL: pH 7.4	w/o	Punt et al., 2022; Dietrich et al., 2015
Parathion		25.93	86	II	AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011; Morgan et al., 1977
Pentachlorophenol		60.1	86	II	AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011; Chedik et al., 2017
Warfarin		35.48	93	II	–	–	Mansouri et al., 2018; Chedik et al., 2017
Drugs							
Acetaminophen		31.05	100	I	AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
Acetylsalicylic acid		2.4	100	I	pH 7.4	w/o	Artursson and Karlsson, 1991
		37.94	100		AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
Alprenonol		40.5	93	N.C.	pH 7.4	w/o	Artursson and Karlsson, 1991
Amiloride	160		90	III	–	–	Varma et al., 2012
		3.05	58		AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
		0.32	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		4.9	–		pH 7.1-7.5	w/o	O'Hagan and Kell, 2015
		4.29	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		0.347	–		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010
Amoxicillin	30		60	III	–	–	Lennernäs, 2007
		0.18	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		0.79	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		0.19	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
Antipyrine	560		97	I	–	–	Varma et al., 2012
	500		100		–	–	Lennernäs, 2007
		29.1	97		pH 7.4	w/o	Bock et al., 2004
		76.71	100		AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
		28.18	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		28.2	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		16.6	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		55.7	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
Atenolol	15		50	III	–	–	Varma et al., 2012
		0.2	50		pH 7.4	w/o	Artursson and Karlsson, 1991
		0.26	55		pH 7.4	w/o	Bock et al., 2004
		0.92	50		AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
		0.32	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		0.2	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		1.2	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		0.7	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		2.7	–		Ranging from 6.5 to 7.4	w/o	O'Hagan and Kell, 2015
		1.09	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		5.27	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		0.25	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		11.04	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		0.44	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		0.18	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		3.9	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		2.1	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		0.45	–		pH 7.4	w/o	O'Hagan and Kell, 2015

Chemical	*In vivo* P_{eff}	*In vitro* P_{app}	Fa	BDDCS[a]	pH value	Inhibitor	Reference
		2.1	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		1.9	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		2.7	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		1.64	–		pH 7.4	w/o	O'Hagan and Kell, 2015
AVP		0.14	0	N.C.	pH 7.4	w/o	Artursson and Karlsson, 1991
Caffeine		13.5	100	I	pH 7.4	w/o	Bock et al., 2004
		44.29	100		AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
Carbamazepine	430		100	II	–	–	Varma et al., 2012
		31.8	70		pH 7.4	w/o	Bock et al., 2004
		5.01	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		47.6	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		55.3	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		53.6	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		57.9	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		41.75	–		pH 7.4	w/o	O'Hagan and Kell, 2015
Cephalexin	156		95	III	–	–	Lennernäs, 2007
		0.27	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		21.21	–		pH 7.4	w/o	O'Hagan and Kell, 2015
Chlorothiazide		1.69	13	IV	AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
Chlorpheniramine		6	80	I	pH 6.8	w/o	Lentz et al., 2000
Cimetidine	26		68	III	–	–	Varma et al., 2012
		1.29	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		2.9	–		pH 7.1-7.5	w/o	O'Hagan and Kell, 2015
		1.32	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		0.9	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		3.06	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		2.3	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		2.5	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		3.3	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		1.64	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		1.4	–		Not mentioned	w/o	O'Hagan and Kell, 2015
		2.4	–		Not mentioned	w/ efflux	O'Hagan and Kell, 2015
Citalopram		14	90	II	pH 7.4	w/o	Bock et al., 2004
Clonidine		9.75	75	I	pH 7.4	w/o	Bock et al., 2004
Corticosterone		54.5	100	N.C.	pH 7.4	w/o	Artursson and Karlsson, 1991
Coumarin		141	100	N.C.	pH 6.8	w/o	Lentz et al., 2000
Cyclosporine	161		95	II	–	–	Lennernäs, 2007
		0.89	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		1	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		1	–		Not mentioned	w/o	O'Hagan and Kell, 2015
		2.5	–		Not mentioned	w/ efflux	O'Hagan and Kell, 2015
dDAVP		0.13	1	–	pH 7.4	w/o	Artursson and Karlsson, 1991
Desipramine	450		100	I	–	–	Varma et al., 2012
		101.17	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		22.91	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		30	–		pH 7.1-7.5	w/o	O'Hagan and Kell, 2015
		12	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		21.6	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
Desipramine HCl	450		100	I	–	–	Lennernäs, 2007
Dexamethasone		12.5	100	I	pH 7.4	w/o	Artursson and Karlsson, 1991
Digoxin		0.38	81	III	pH 7.4	w/o	Bock et al., 2004
Diltiazem HCl		42.4	99	I	pH 6.8	w/o	Lentz et al., 2000
Disopyramide		4.24	85.3	III	pH 6.8	w/o	Lentz et al., 2000

Chemical	*In vivo* P_{eff}	*In vitro* P_{app}	Fa	BDDCS[a]	pH value	Inhibitor	Reference
Enalapril maleate	157		65	I	–	–	Lennernäs, 2007
		0.617	–		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010
Enalaprilat	20		8	III	–	–	Lennernäs, 2007
		0.257	–		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010
Famotidine		2.98	45	III	AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
Felodipine		22.7	100	II	pH 7.4	w/o	Artursson and Karlsson, 1991
Fexofenadine	7		30	III	–	–	Varma et al., 2012
		2	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		0.2	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		1.2	–		Not mentioned	w/o	O'Hagan and Kell, 2015
		1.7	–		Not mentioned	w/ efflux	O'Hagan and Kell, 2015
		0.309	–		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010
FITC-Dextran		0.21	0	N.C.	AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
Fluvastatin	240		100	I	–	–	Varma et al., 2012
		46.77	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		10.2	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		1.9	–		Not mentioned	w/o	O'Hagan and Kell, 2015
		1	–		Not mentioned	w/ efflux	O'Hagan and Kell, 2015
		2.1	–		Not mentioned	w/o	O'Hagan and Kell, 2015
		4.7	–		Not mentioned	w/ efflux	O'Hagan and Kell, 2015
		1.5	–		Not mentioned	w/o	O'Hagan and Kell, 2015
		6.5	–		Not mentioned	w/ efflux	O'Hagan and Kell, 2015
Fluvastatin sodium	240		95	I	–	–	Lennernäs, 2007
Furosemide	5		50	IV	–	–	Lennernäs, 2007
		3.33	61		pH 6.8	w/o	Lentz et al., 2000
		0.2	61		pH 7.4	w/o	Bock et al., 2004
		0.54	60		AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
		0.31	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		0.12	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		2	–		pH 7.1-7.5	w/o	O'Hagan and Kell, 2015
		0.28	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		0.4	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		5.6	–		Ranging from 6.5 to 7.4	w/o	O'Hagan and Kell, 2015
		2.4	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		4.9	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		1.29	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		0.7	–		Not mentioned	w/o	O'Hagan and Kell, 2015
		1.1	–		Not mentioned	w/ efflux	O'Hagan and Kell, 2015
		0.6	–		Not mentioned	w/o	O'Hagan and Kell, 2015
		1.6	–		Not mentioned	w/ efflux	O'Hagan and Kell, 2015
		0.6	–		Not mentioned	w/o	O'Hagan and Kell, 2015
		1.9	–		Not mentioned	w/ efflux	O'Hagan and Kell, 2015
Hydrochlorothiazide	4		55	III	–	–	Varma et al., 2012
		2.24	70		AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
		0.87	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		0.51	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		4.07	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		0.5	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		4.6	–		Ranging from 6.5 to 7.4	w/o	O'Hagan and Kell, 2015
		1.81	–		pH 7.4	w/o	O'Hagan and Kell, 2015
Hydrocortisone		21.5	89	I	pH 7.4	w/o	Artursson and Karlsson, 1991
Ibuprofen		60.13	100	II	AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
Indomethacin		38.4	100	II	pH 6.8	w/o	Lentz et al., 2000

Chemical	*In vivo* P_{eff}	*In vitro* P_{app}	Fa	BDDCS[a]	pH value	Inhibitor	Reference
Inogatran	3		7	N.C.	–	–	Lennernäs, 2007
Isotretinoin	99		90	II	–	–	Lennernäs, 2007
Ketoprofen	850		92	II	–	–	Varma et al., 2012
		18.6	92		pH 7.4	w/o	Bock et al., 2004
		26.47	100		AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
		20.1	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		25	–		pH 7.1-7.5	w/o	O'Hagan and Kell, 2015
		46.77	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		67.9	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		39.5	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		39.2	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		41.3	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		18.49	–		pH 7.4	w/o	O'Hagan and Kell, 2015
Labetalol		14.96	90	I	AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
Levodopa	340		100	I	–	–	Varma et al., 2012
Lisinopril	33		35	III	–	–	Varma et al., 2012
		0.22	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		0.25	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		0.66	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		0.0407	–		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010
Lisuride		61.1	100	N.C.	pH 6.8	w/o	Lentz et al., 2000
Losartan	115		90	II	–	–	Varma et al., 2012
Mannitol		0.18	16	III	pH 7.4	w/o	Artursson and Karlsson, 1991
		0.18	16		pH 7.4	w/o	Bock et al., 2004
Methyldopa	10		60	III	–	–	Lennernäs, 2007
	10		43		–	–	Varma et al., 2012
		0.15	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		0.24	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
Metoprolol	150		98	I	–	–	Varma et al., 2012
		40	94.5		pH 6.8	w/o	Lentz et al., 2000
		27	95		pH 7.4	w/o	Artursson and Karlsson, 1991
		22.9	95		pH 7.4	w/o	Bock et al., 2004
		37.33	95		AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
		25.7	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		23.7	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		12	–		pH 7.1-7.5	w/o	O'Hagan and Kell, 2015
		29.51	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		10.1	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		27	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		87.57	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		58.82	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		71.13	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		45.49	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		42.85	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		7.77	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		24.71	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		43.69	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		35.09	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		62.17	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		33.7	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		27	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		39.2	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		17.74	–		pH 7.4	w/o	O'Hagan and Kell, 2015

Chemical	*In vivo* P_{eff}	*In vitro* P_{app}	Fa	BDDCS[a]	pH value	Inhibitor	Reference
Nadolol		0.62	35	III	AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
Naproxen	850		100	II	–	–	Varma et al., 2012
		25.8	99		pH 7.4	w/o	Bock et al., 2004
		60.06	100		AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
		74.13	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		39.5	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		30	–		pH 7.1-7.5	w/o	O'Hagan and Kell, 2015
		46.77	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		112	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		54.2	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		31.07	–		pH 7.4	w/o	O'Hagan and Kell, 2015
Nicardipine		19.8	100	I	pH 6.8	w/o	Lentz et al., 2000
Olsalazine		0.11	2	I	pH 7.4	w/o	Artursson and Karlsson, 1991
PEG		0.05	0	N.C.	pH 7.4	w/o	Artursson and Karlsson, 1991
PEG400		0.45	10	N.C.	pH 7.4	w/o	Bock et al., 2004
PEG4000		5	0	N.C.	pH 7.4	w/o	Bock et al., 2004
PEG900		0.24	10	N.C.	pH 7.4	w/o	Bock et al., 2004
Phenytoin		15.13	90	II	AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
Pindolol		21.64	95	I	AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
Piroxicam	665		100	II	–	–	Lennernäs, 2007; Varma et al., 2012
		35.48	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		83.8	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		46.8	–		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010
Practolol		0.9	100	IV	pH 7.1-7.5	w/o	Artursson and Karlsson, 1991
Propranolol	291		99	I	AP: pH 6.5 / BL: pH 7.4	w/o	Varma et al., 2012
		41.9	90		AP: pH 6.5 / BL: pH 7.4	w/o	Artursson and Karlsson, 1991
		34.2	99		Ranging from 6.5 to 7.4	w/o	Bock et al., 2004
		30.76	100		pH 7.4	w/o	Volpe et al., 2007
		26.3	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		41.9	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		17.5	–		pH 7.1-7.5	w/o	O'Hagan and Kell, 2015
		39.81	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		12.4	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		16	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		27.5	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		8	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		16	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		53.6	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		4.94	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		40.9	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		21.29	–		pH 7.4	w/o	O'Hagan and Kell, 2015
Ranitidine	27		55	III	–	–	Varma et al., 2012
		0.67	50		AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
		0.49	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		0.49	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		0.63	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		0.3	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		3.4	–		Ranging from 6.5 to 7.4	w/o	O'Hagan and Kell, 2015
		2.1	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		1.2	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		2.51	–		pH 7.4	w/o	O'Hagan and Kell, 2015
Salicylicylic acid		11.9	100	I	pH 7.4	w/o	Artursson and Karlsson, 1991
Sulfasalazine		2.93	13	II	AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007

Chemical	*In vivo* P_{eff}	*In vitro* P_{app}	Fa	BDDCS[a]	pH value	Inhibitor	Reference
		0.13	13		pH 7.4	w/o	Artursson and Karlsson, 1991
Terbutaline	30		65	III	–	–	Lennernäs, 1998
		0.38	73		pH 7.4	w/o	Artursson and Karlsson, 1991
		0.42	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		1.5	–		pH 7.1-7.5	w/o	O'Hagan and Kell, 2015
		0.3	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		1.4	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		2.38	–		pH 7.4	w/o	O'Hagan and Kell, 2015
Testosterone		51.8	100	II	pH 7.4	w/o	Artursson and Karlsson, 1991
Theophylline		61	96	I	pH 6.8	w/o	Lentz et al., 2000
		50.9	100		AP: pH 6.8 / BL: pH 7.4	w/o	Volpe et al., 2007
Valacyclovir	166		90	N.C.	–	–	Lennernäs, 2007
		6.31	–		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010
Verapamil	680		100	II	–	–	Varma et al., 2012
		24.2	100		pH 7.4	w/o	Bock et al., 2004
		155.63	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		26.3	–		Ranging from 6.5 to 7.5	w/o	O'Hagan and Kell, 2015
		15.8	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		9.8	–		pH 7.1-7.5	w/o	O'Hagan and Kell, 2015
		45.71	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		12.9	–		AP: pH 6.5 / BL: pH 7.4	w/o	O'Hagan and Kell, 2015
		22	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		69.4	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		22.68	–		pH 7.4	w/o	O'Hagan and Kell, 2015
		9	–		Not mentioned	w/o	O'Hagan and Kell, 2015
		8.1	–		Not mentioned	w/ efflux	O'Hagan and Kell, 2015
		24.2	–		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010
Warfarin		38.3	98	II	pH 7.4	w/o	Artursson and Karlsson, 1991

[a] The Biopharmaceutics Drug Disposition Classification System (BDDCS) is referred to in Benet et al. (2011), Bocci et al. (2022), and Hosey et al. (2016) for drug classification. The classification of environmental chemicals is based on the criteria of drug classification (Benet et al. 2011; Wu and Benet, 2005), and the detailed information is summarized in Table S3. N.C., not classified.

[b] AP, apical buffer; BL, basolateral buffer

AVP, arginine-vasopressin; dDAVP, 1-deamino-8-D-arginine-vasopressin; PEG, polyethylene glycol

Tab. S3: Summary of BDDCS assignment for environmental chemicals

Chemical	LogKow (LogP)	Upper 95%-tile of exposure (mg kg^{-1} day^{-1})	Estimated highest dose strength (mg mL^{-1})[a]	Minimal solubility (mg mL^{-1})[a]	Reference	Dose number[a]	BDDCS[d]
2,4-D	2.81	1.43×10^{-4}	4.00×10^{-5}	3.36×10^{-7}	EPA CompTox Chemical Dashboard[b]	119.20	IV[#]
Bisphenol A	3.32	2.04×10^{-2}	5.71×10^{-3}	1.20×10^{-7}	EPA CompTox Chemical Dashboard	47656.59	II
Coumarin	1.39	0.24	6.72×10^{-2}	1.88×10^{-6}	EPA CompTox Chemical Dashboard	35655.73	II[#]
Imazalil	3.82	4.91×10^{-4}	1.37×10^{-4}	1.80×10^{-7}	EPA CompTox Chemical Dashboard	763.34	II
Malathion	2.36	1.01×10^{-5}	2.83×10^{-6}	1.43×10^{-7}	EPA CompTox Chemical Dashboard	19.77	II
Ochratoxin A	4.74	1.27×10^{-5}	3.56×10^{-6}	9.85×10^{-10}*	EPA CompTox Chemical Dashboard; EFSA Panel on CONTAM et al., 2020[c]	3609.16	II
Parathion	3.83	3.53×10^{-7}	9.88×10^{-8}	1.11×10^{-8}	EPA CompTox Chemical Dashboard	8.93	II
Pentachlorophenol	5.12	6.81×10^{-8}	1.91×10^{-8}	1.40×10^{-8}	EPA CompTox Chemical Dashboard	1.36	II
Warfarin	2.70	2.26×10^{-4}	6.33×10^{-5}	5.61×10^{-9}	EPA CompTox Chemical Dashboard	11276.52	II

[a] Solubility in the BDDCS is classified by dose number, which is calculated by the highest dose strength (HDS) of the drug in the pH range between 1 to 7.5 being soluble in 250 mL of water at 37°C divided by minimal solubility ($\text{dose number} = \frac{HDS\,(mg)/250(mL)}{MInimal\ Solubility\ (mg/mL)}$; Benet et al. 2011; Hosey et al., 2016). The HDS of environmental chemicals is estimated by using the upper 95%-tile of ExpoCast-predicted exposure from EPA CompTox Chemical Dashboard × 70 (assumed bodyweight, kg) × 1 (day). The minimal solubility was mainly extracted from the range of experimental water solubility in the EPA CompTox Chemical Dashboard. Symbol † means that minimal solubility was from median of experimental water solubility, if there was no range of experimental measurement. Symbol * means that minimal solubility was extracted from range of predicted water solubility since there were no experimental measurements.

[b] Extracted from https://comptox.epa.gov/dashboard/.

[c] Upper 95%-tile of exposure for ochratoxin A was extracted from the upper bound value of exposure estimate under 95th percentile dietary exposure in the adult age group = 12.65 ng/kg BW/day.

[d] The BDDCS is used to classify the drugs based on solubility (dose number) and extent of metabolism (Tab. 1). The breakpoint of dose number is 1.0 (mg mL^{-1}). If the dose number is ≤1.0, the chemical is considered to possess high solubility, and if the dose number is >1.0, the drug is considered to possess low solubility (Benet et al. 2011; Hosey et al., 2016). The extent of metabolism has a positive relationship with LogP. When LogP is greater than 2, there is a high probability that the chemical has a high extent of metabolism; When LogP is less than 0, there is a high probability that the chemical has a low extent of metabolism. However, if LogP is between 0 and 2, it is hard to predict the extent of metabolism; thus, the classification was assigned in two classes based on solubility. Label # means that we changed classes based on reported information (ATSDR, 2020; Abraham et al., 2010, listed in order).

Tab. S4: Raw data of human fraction absorption (%) and *in vitro* apparent permeability (×10^{-6} cm/s) for drugs presented in Figure S9

Chemical	*In vitro* P_{app}	Fa	BDDCS[a]	pH value	Inhibitor	Reference
Acebutalol	4.80	40	N.C.	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	0.79	46		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Acetaminophen	19.90	95	I	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	36.31	100		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
	9.22	80		AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Acetylsalicilic acid	3.38	84	I	AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Acyclovir	0.38	19	IV	pH 7.4	w/o	Matsson et al., 2005
	0.85	32		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Alfentanil	270.00	100	I	pH 7.4	w/o	Matsson et al., 2005
Alprenolol	240.00	96	I	pH 7.4	w/o	Matsson et al., 2005
Amoxicillin	0.49	51	III	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Antipyrine	28.80	100	I	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	215.00	97		pH 7.4	w/o	Matsson et al., 2005
	33.88	100		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Atenolol	2.50	50	III	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	1.00	54		pH 7.4	w/o	Matsson et al., 2005
	0.46	58		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
	0.21	50		AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Atropine sulphate	8.27	98	III	AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Betaxolol	12.30	100	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
BMS-180291	19.50	100	N.C.	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
BMS-189664	2.00	10	N.C.	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
Bosentan	0.65	56	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Bromocriptine	1.23	7	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
BvAraU	4.10	82	N.C.	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
Caffeine	33.10	100	I	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	33.11	100		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
	21.08	100		AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Carbamazepine	42.66	73	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
	17.01	84		AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Cephalexin	47.11	98	III	pH 7.4	w/o	Miret et al., 2004
	0.38	92		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Chloramphenicol	47.38	90	I	pH 7.4	w/o	Miret et al., 2004
Chlorothiazide	4.95	13	IV	pH 7.4	w/o	Miret et al., 2004
Chlorpromazine	19.95	88	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Cimetidine	4.90	95	III	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	0.67	80		pH 7.4	w/o	Matsson et al., 2005
	1.26	72		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
	0.52	64		AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Ciprofloxacin	1.26	73	IV	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Clodronic acid	0.06	3	III	pH 7.4	w/o	Matsson et al., 2005
Clonidine	26.30	79	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Clozapine	30.90	75	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Colchicine	2.08	44	III	AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Creatinine	1.20	70	N.C.	pH 7.4	w/o	Matsson et al., 2005
Desipramine	21.50	95	I	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	10.72	78		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Dexamethasone	12.00	100	I	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
Diazepam	35.48	100	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
	16.98	100		AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Diclofenac	17.78	100	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Didanosine	0.25	42	III	pH 7.4	w/o	Matsson et al., 2005

Chemical	*In vitro* P_{app}	Fa	BDDCS[a]	pH value	Inhibitor	Reference
Digoxin	1.30	81	III	pH 7.4	w/o	Matsson et al., 2005
	1.28	81		AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Diltiazem	29.51	88	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Doxycycline	11.22	94	III	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Etoposide	1.55	54	IV	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Famotidine	0.69	51	III	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Fluconazole	15.14	90	III	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Foscarnet	0.04	17	III	pH 7.4	w/o	Matsson et al., 2005
	0.03	9		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Furosemide	13.59	61	IV	pH 7.4	w/o	Miret et al., 2004
	0.24	46		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Gabapentin	0.01	62	III	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Ganciclovir	0.23	5	III	pH 7.4	w/o	Matsson et al., 2005
	0.43	9		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Glycylsarcosine	0.50	100	N.C.	pH 7.4	w/o	Matsson et al., 2005
Guanabenz	11.10	79	I	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
Hydralazine	14.10	90	I	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
Hydrochlorothiazide	0.87	72	III	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Hydrocortisone	15.14	100	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Ibuprofen	39.50	100	II	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	26.30	85		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Imipramine	6.76	100	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
	3.18	100		AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Inulin	1.00	5	N.C.	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
Ketoconazole	9.50	76	II	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
Ketoprofen	33.11	100	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Lactulose	0.27	1	I	pH 7.4	w/o	Matsson et al., 2005
l-DOPA	0.89	100	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Varma et al., 2012
Lobucavir	0.88	50	N.C.	pH 7.4	w/o	Matsson et al., 2005
Losartan	0.89	100	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Lucifer yellow	0.10	0	N.C.	pH 7.4	w/o	Miret et al., 2004
Mannitol	3.20	15	III	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	0.19	26		pH 7.4	w/o	Matsson et al., 2005
	0.28	16		AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Meloxicam	19.50	98	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Metformin	0.66	55	III	pH 7.4	w/o	Matsson et al., 2005
	0.63	52		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Methotrexate	0.03	59	III	pH 7.4	w/o	Matsson et al., 2005
	0.79	72		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Methylprednisolone	11.75	100	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Metolazone	4.30	64	IV	pH 7.4	w/o	Matsson et al., 2005
Metoprolol	13.70	95	I	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	91.00	100		pH 7.4	w/o	Matsson et al., 2005
	25.12	100		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Morphine	3.55	100	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Nadalol	1.70	35	III	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	0.28	30		pH 7.4	w/o	Matsson et al., 2005
	0.72	35		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Naloxone	21.38	20	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Naproxen	78.24	99	II	pH 7.4	w/o	Miret et al., 2004 (pH7.4)
	21.88	100		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
	42.40	100		AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
Naproxen sodium	40.10	100	II	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005

Chemical	*In vitro* P_{app}	Fa	BDDCS[a]	pH value	Inhibitor	Reference
Nicotine	6.55	100	I	AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Nitrendipine	11.75	100	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Norfloxacin	1.44	71	IV	pH 7.4	w/o	Miret et al., 2004
Olsalazine	0.05	3	I	pH 7.4	w/o	Matsson et al., 2005
Ondansetron	45.71	94	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Orphenadrine	5.80	95	I	AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Oxacillin	13.66	33	III	pH 7.4	w/o	Miret et al., 2004
Oxazepam	60.26	100	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Phenobarbital	23.58	90	I	AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Phenytoin	32.36	100	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Pindolol	55.00	92	I	pH 7.4	w/o	Matsson et al., 2005
	19.50	93		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Pirenzepine	0.44	34	III	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Pravastatin	3.30	34	III	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	1.45	51		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Prazosin	5.50	86	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Propofol	16.98	100	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Propranolol	11.10	90	I	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	204.00	100		pH 7.4	w/o	Matsson et al., 2005
	71.17	92		pH 7.4	w/o	Miret et al., 2004
	23.44	100		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
	17.02	99		AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Quinidine	11.48	96	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Raffinose	0.05	0	N.C.	pH 7.4	w/o	Matsson et al., 2005
Ranitidine	2.40	50	III	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	0.49	62		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Salicylic acid	44.00	100	I	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
Scopolamine	11.75	100	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Sildenafil	30.90	57	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Sodium valproate	31.44	100	N.C.	AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Sulfamethoxazole	26.30	100	II	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	13.18	100		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Sulfasalazine	2.20	13	II	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	0.16	12		pH 7.4	w/o	Matsson et al., 2005
Sulfisoxazole	24.50	100	IV	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
Sulpiride	0.21	30	III	pH 7.4	w/o	Matsson et al., 2005
	0.22	29		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Sumatriptan	1.58	84	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Terbutaline	2.90	73	III	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	0.23	73		pH 7.4	w/o	Matsson et al., 2005
	0.69	28		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Tetracycline	20.76	78	III	pH 7.4	w/o	Miret et al., 2004
	2.00	79		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Theophylline	65.93	99	I	pH 7.4	w/o	Miret et al., 2004
	24.55	98		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Timolol	4.70	72	I	AP: pH 6.5 / BL: pH 7.4	w/o	Marino et al., 2005
	12.02	100	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Tolbutamide	52.48	87	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Trimethoprim	31.62	65	III	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Valaciclovir	2.30	36	N.C.	pH 7.4	w/o	Matsson et al., 2005
Verapamil	15.49	100	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
	2.98	100		AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Warfarin	34.71	99	II	pH 7.4	w/o	Miret et al., 2004

Chemical	*In vitro* P_{app}	Fa	BDDCS[a]	pH value	Inhibitor	Reference
	23.44	93		Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
	23.75	98		AP: pH 6.5 / BL: pH 7.4	w/o	Turco et al., 2011
Zidovudine	8.71	100	I	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012
Ziprasidone	5.89	100	II	Ranging from 6.8 to 7.4	w/o	Paixão et al., 2010, Paixão et al., 2012

[a] The Biopharmaceutics Drug Disposition Classification System (BDDCS) is referred to in Benet et al. (2011), Bocci et al. (2022), and Hosey et al. (2016) for drug classification. N.C., not classified.

Tab. S5: Summary of the physiologically specific parameters

Parameter	Description	Point value	Reference
BDM	Body weight, kg	70	–
Blood flow-related parameters			
sc_F_total	Total cardiac output scaling coefficient, L/hr/kg	15	Perdaems et al., 2010
f_Flow_stom	Fraction of cardiac output flow into stomach, -	0.024	Perdaems et al., 2010
f_Flow_dudo	Fraction of cardiac output flow into duodenum, -	0.016	Perdaems et al., 2010
f_Flow_jeju	Fraction of cardiac output flow into jejunum, -	0.056	Perdaems et al., 2010
f_Flow_ileum	Fraction of cardiac output flow into ileum, -	0.033	Perdaems et al., 2010
f_Flow_cecum	Fraction of cardiac output flow into cecum, -	0.006	Perdaems et al., 2010
f_Flow_colon	Fraction of cardiac output flow into colon, -	0.038	Perdaems et al., 2010
f_Flow_liver	Fraction of cardiac output flow into liver, -	0.250	Perdaems et al., 2010
f_Flow_kidney	Fraction of cardiac output flow into kidney, -	0.210	Perdaems et al., 2010
f_Flow_body	Fraction of cardiac output flow into other part of body, -	0.540	Perdaems et al., 2010
Tissue & lumen scaling parameters to body weight			
f_BDM_stom	Body weight fraction of stomach, -	0.0021	Perdaems et al., 2010
f_BDM_dudo	Body weight fraction of duodenum, -	0.0003	Perdaems et al., 2010
f_BDM_jeju	Body weight fraction of jejunum, -	0.0009	Perdaems et al., 2010
f_BDM_ileum	Body weight fraction of ileum, -	0.0006	Perdaems et al., 2010
f_BDM_cecum	Body weight fraction of cecum, -	0.0005	Perdaems et al., 2010
f_BDM_colon	Body weight fraction of colon, -	0.0048	Perdaems et al., 2010
f_BDM_liver	Body weight fraction of liver, -	0.0243	Perdaems et al., 2010
f_BDM_kidney	Body weight fraction of kidney, -	0.0096	Perdaems et al., 2010
f_BDM_body	Body weight fraction of other part of body, -	0.8730	Perdaems et al., 2010
f_BDM_blood	Body weight fraction of blood, -	0.0650	Perdaems et al., 2010
G.I. tract-related parameters			
H_ep	Thickness of G.I. tract epithelium, dm	0.0003	Ando et al., 2015
Length_stom	Length of stomach, dm	2.83	Perdaems et al., 2010
Length_dudo	Length of duodenum, dm	1.41	Perdaems et al., 2010
Length_jeju	Length of jejunum, dm	11.68	Perdaems et al., 2010
Length_ileum	Length of ileum, dm	17.52	Perdaems et al., 2010
Length_cecum	Length of cecum, dm	1.70	Perdaems et al., 2010
Length_colon	Length of colon, dm	11.00	Perdaems et al., 2010
Radius_stom	Radius of stomach, dm	0.967	Perdaems et al., 2010
Radius_dudo	Radius of duodenum, dm	0.153	Perdaems et al., 2010
Radius_jeju	Radius of jejunum, dm	0.137	Perdaems et al., 2010
Radius_ileum	Radius of ileum, dm	0.098	Perdaems et al., 2010
Radius_cecum	Radius of cecum, dm	0.35	Perdaems et al., 2010
Radius_colon	Radius of colon, dm	0.25	Perdaems et al., 2010
T12_stom_lu	Transit half-lives in stomach lumina, hr	0.25	Perdaems et al., 2010
T12_dudo_lu	Transit half-lives in duodenum lumina, hr	0.25	Perdaems et al., 2010
T12_jeju_lu	Transit half-lives in jejunum lumina, hr	1.02	Perdaems et al., 2010
T12_ileum_lu	Transit half-lives in ileum lumina, hr	2.04	Perdaems et al., 2010
T12_cecum_lu	Transit half-lives in cecum lumina, hr	4.55	Perdaems et al., 2010
T12_colon_lu	Transit half-lives in colon lumina, hr	13.50	Perdaems et al., 2010
Microsomal proteins amount			
MicroProt_stom	Microsomal proteins of stomach, mg/g of tissue	0	–
MicroProt_dudo	Microsomal proteins of duodenum, mg/g of tissue	18	Paine et al., 1997
MicroProt_jeju	Microsomal proteins of jejunum, mg/g of tissue	25	Paine et al., 1997
MicroProt_ileum	Microsomal proteins of ileum, mg/g of tissue	24	Paine et al., 1997
MicroProt_cecum	Microsomal proteins of cecum, mg/g of tissue	0	–
MicroProt_colon	Microsomal proteins of colon, mg/g of tissue	0	–
MicroProt_liver	Microsomal proteins of liver, mg/g of tissue	45	Houston et al., 2012
MicroProt_kidney	Microsomal proteins of kidney, mg/g of tissue	13.6	Scotcher et al., 2017
Other physiological parameter			
GFR	Glomerular filtration rate, L/hr/1.73 m^2	7.2	[2]

[2] National Kidney Foundation. (2017). Retrieved May 11, 2022, from https://www.kidney.org/kidneydisease/siemens_hcp_gfr

Tab. S6: Summary of chemical-related parameters

Parameter	Description	Point value	Reference
Passive absorption related parameters			
f_Abs_stom	Absorption switches of stomach, –	0	–
f_Abs_duod	Absorption switches of duodenum, –	1	–
f_Abs_jeju	Absorption switches of jejunum, –	1	–
f_Abs_ileum	Absorption switches of ileum, –	1	–
f_Abs_cecum	Absorption switches of cecum, –	1	–
f_Abs_colon	Absorption switches of colon, –	1	–
Peff	Effective permeability of gut epithelium, dm/h	Changed	–
s_jeju_ratio	Switches of using jejunum permeability ratio	Changed	–
Peff_ratio_duod_jeju	Ratio of duodenum to jejunum permeability	Distribution	Table 1
Peff_ratio_ileum_jeju	Ratio of ileum to jejunum permeability	Distribution	Table 1
Peff_ratio_colon_jeju	Ratio of colon to jejunum permeability	Distribution	Table 1
Peff_ratio_duod_colon	Ratio of duodenum to colon permeability	Distribution	Table 1
Peff_ratio_jeju_ colon	Ratio of jejunum to colon permeability	Distribution	Table 1
Peff_ratio_ileum_colon	Ratio of ileum to colon permeability	Distribution	Table 1
Peff_ratio_ivive	*In vitro* to *in vivo* scaling factor	Distribution	Table 2
Ke_over_a_epit	Excretion over absorption rate constant ratios between lumen and epithelium, –	10^{-9}	Assumed
Ke_over_a_tiss	Excretion over absorption rate constant ratios between epithelium and tissue, –	10^{-9}	Assumed
Active transport related parameters			
Vmax_eff_stom	Maximum rate of efflux from stomach, micromole/h	10^{-9}	Assumed
Vmax_eff_duod	Maximum rate of efflux from duodenum, micromole/h	10^{-9}	Assumed
Vmax_eff_jeju	Maximum rate of efflux from jejunum, micromole/h	10^{-9}	Assumed
Vmax_eff_ileum	Maximum rate of efflux from ileum, micromole/h	10^{-9}	Assumed
Vmax_eff_cecum	Maximum rate of efflux from cecum, micromole/h	10^{-9}	Assumed
Vmax_eff_colon	Maximum rate of efflux from colon, micromole/h	10^{-9}	Assumed
Vmax_eff_liver	Maximum rate of efflux from liver, micromole/h	10^{-9}	Assumed
Vmax_inf_stom	Maximum rate of active influx to stomach, micromole/h	10^{-9}	Assumed
Vmax_inf_duod	Maximum rate of active influx to duodenum, micromole/h	10^{-9}	Assumed
Vmax_inf_jeju	Maximum rate of active influx to jejunum, micromole/h	10^{-9}	Assumed
Vmax_inf_ileum	Maximum rate of active influx to ileum, micromole/h	10^{-9}	Assumed
Vmax_inf_cecum	Maximum rate of active influx to cecum, micromole/h	10^{-9}	Assumed
Vmax_inf_colon	Maximum rate of active influx to colon, micromole/h	10^{-9}	Assumed
Vmax_inf_liver	Maximum rate of active influx to liver, micromole/h	10^{-9}	Assumed
Km_eff	Active efflux Km, microM	1	Assumed
Km_inf	Active influx Km, microM	1	Assumed
Distribution related parameters			
Ratio_BP	Blood over plasma concentration ratio, –	0.82	Xue et al., 2017
Fu_plasma	Fraction unbound in plasma, –	0.20	Hsieh et al., 2021
Fu_stom	Fraction unbound in stomach, –	0.16 [a]	Xue et al., 2017
Fu_duod	Fraction unbound in duodenum, –	0.16 [a]	Xue et al., 2017
Fu_jeju	Fraction unbound in jejunum, –	0.16 [a]	Xue et al., 2017
Fu_ileum	Fraction unbound in ileum, –	0.16 [a]	Xue et al., 2017
Fu_cecum	Fraction unbound in cecum, –	0.16 [a]	Xue et al., 2017
Fu_colon	Fraction unbound in colon, –	0.16 [a]	Xue et al., 2017
Fu_liver	Fraction unbound in liver, –	0.16 [a]	Xue et al., 2017
Fu_kidney	Fraction unbound in kidney, –	0.16 [a]	Xue et al., 2017
Fu_body	Fraction unbound in the rest of body, –	0.16 [a]	Xue et al., 2017
Fu_vitro_plasma	Fraction unbound in in-vitro metabolic assay in stomach, –	0.16 [a]	Xue et al., 2017
Fu_vitro_stom	Fraction unbound in in-vitro metabolic assay in stomach, –	0.16 [a]	Xue et al., 2017
Fu_vitro_duod	Fraction unbound in in-vitro metabolic assay in duodenum, –	0.16 [a]	Xue et al., 2017
Fu_vitro_jeju	Fraction unbound in in-vitro metabolic assay in jejunum, –	0.16 [a]	Xue et al., 2017
Fu_vitro_ileum	Fraction unbound in in-vitro metabolic assay in ileum, –	0.16 [a]	Xue et al., 2017
Fu_vitro_cecum	Fraction unbound in in-vitro metabolic assay in cecum, –	0.16 [a]	Xue et al., 2017
Fu_vitro_colon	Fraction unbound in in-vitro metabolic assay in colon, –	0.16 [a]	Xue et al., 2017
Fu_vitro_liver	Fraction unbound in in-vitro metabolic assay in liver, –	0.07	Hsieh et al., 2021
Fu_vitro_kidney	Fraction unbound in in-vitro metabolic assay in kidney, –	0.16 [a]	Xue et al., 2017
Kpuu_stom	Partition coefficient of stomach, –	1	Assumed
Kpuu_duod	Partition coefficient of duodenum, –	1	Assumed
Kpuu_jeju	Partition coefficient of jejunum, –	1	Assumed
Kpuu_ileum	Partition coefficient of ileum, –	1	Assumed
Kpuu_cecum	Partition coefficient of cecum, –	1	Assumed
Kpuu_colon	Partition coefficient of colon, –	1	Assumed
Kpuu_liver	Partition coefficient of liver, –	4.54	Hsieh et al., 2021
Kpuu_kidney	Partition coefficient of kidney, –	1	Assumed
Kpuu_body	Partition coefficient of the rest of body, –	1	Assumed
Metabolism related parameters			
Vmax_met_vitro_intestine	Maximum metabolism rate in intestine, micromole/min/mg microsomal proteins	2.6×10^{-5}	Connarn et al., 2015
Vmax_met_vitro_liver	Maximum metabolism rate in liver, micromole/min/mg microsomal proteins	9×10^{-4}	Hsieh et al., 2021

Vmax_met_vitro_kidney	Maximum metabolism rate in liver, micromole/min/mg microsomal proteins	0	Assumed
Km_met_vitro_intestine	Metabolism K_m in intestine, micromole/min/mg microsomal proteins	573.4	Connarn et al., 2015
Km_met_vitro_liver	Metabolism K_m in liver, micromole/min/mg microsomal proteins	265.7	Connarn et al., 2015
Km_met_vitro_kidney	Metabolism K_m in liver, micromole/min/mg microsomal proteins	10^{-9}	Assumed
Other parameters			
ETS	Extraction ratio for tubular secretion	0	Assumed
f_reabs	Fraction of reabsorption in kidney	0	Assumed

[a] Assumed as same as Fu_plasma in Xue et al. (2018).

5 Supplementary Figures

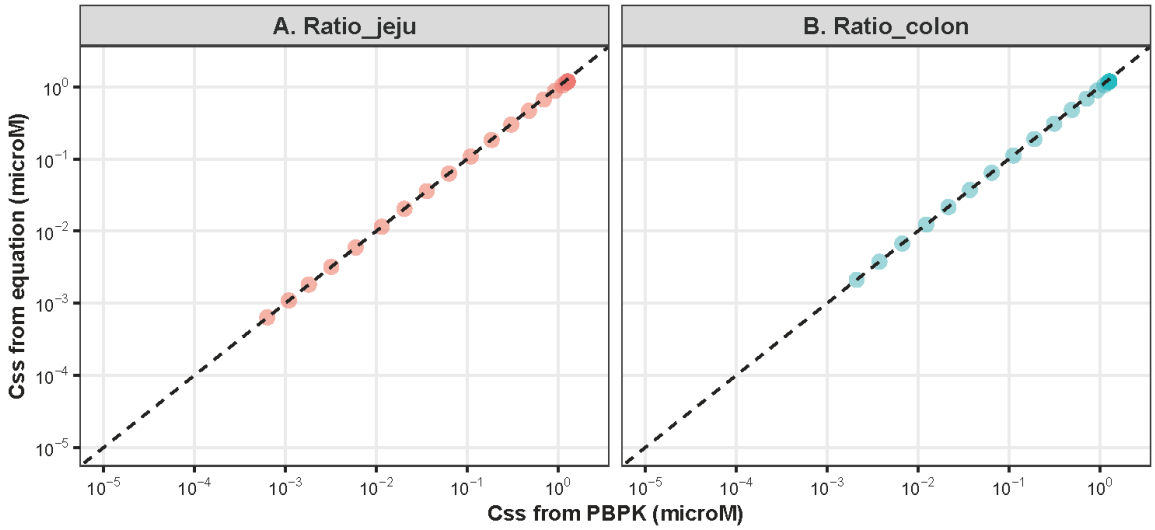


Fig. S7: Comparison of C_{SS} estimated using the updated steady-state equation and using the PECAT model with segment-specific absorption scale ratios: (A) P_i:$P_{jejunum}$ and (B) P_i:P_{colon}

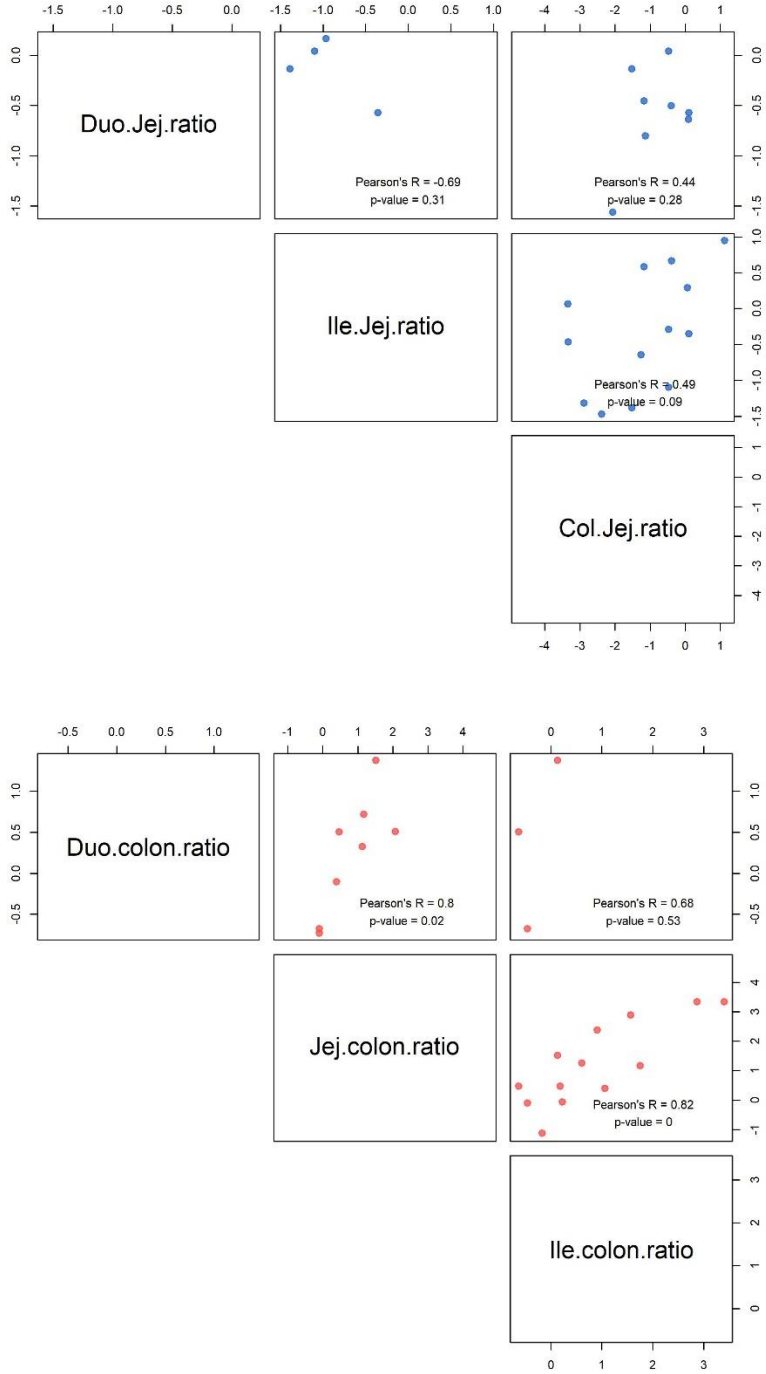
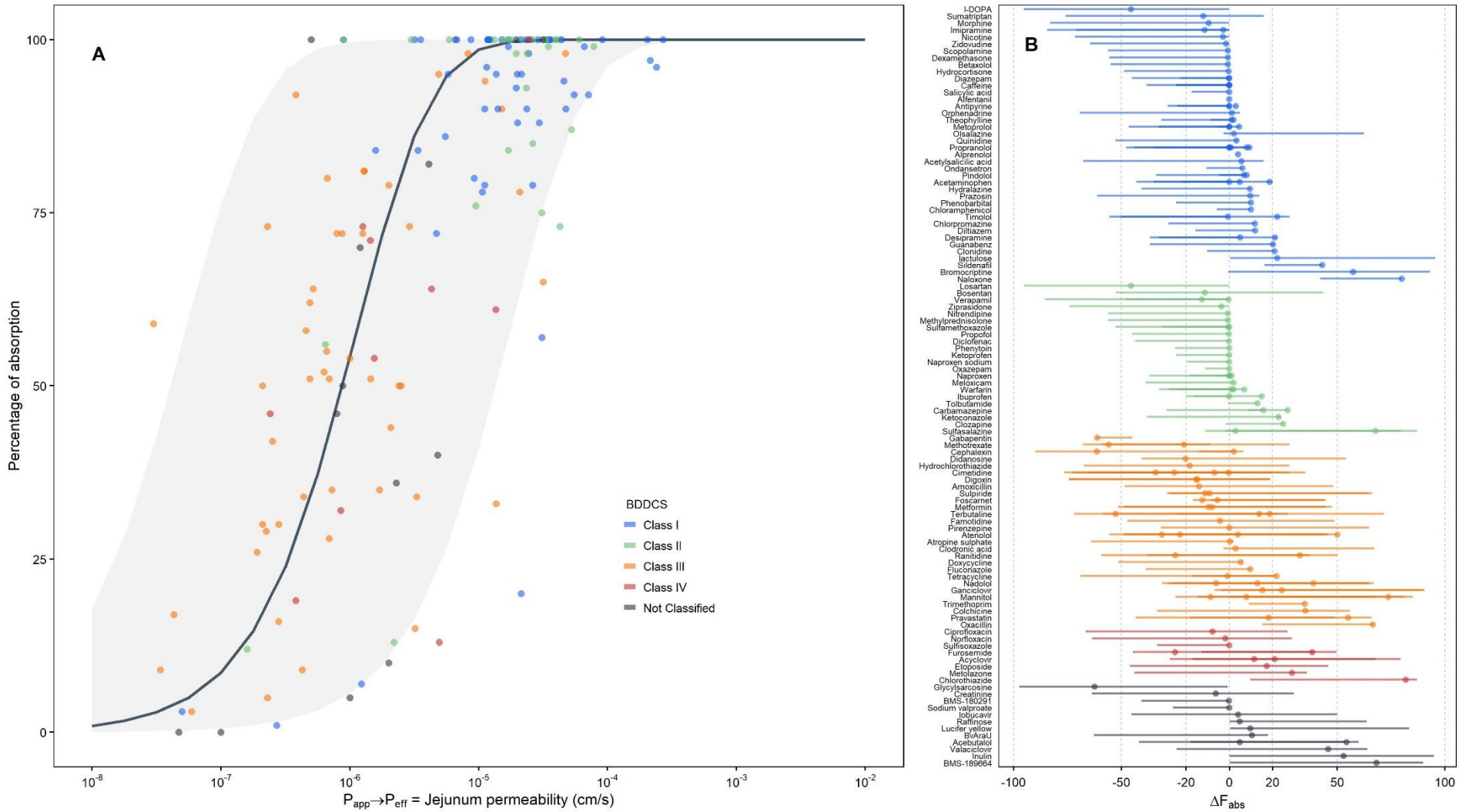


Fig. S8: Correlation matrixes of log-transformed regional intestinal permeability ratios based on permeability of (A) jejunum and (B) colon as denominator



Error			BDDCS			Overall
	Class I	Class II	Class III	Class IV	Not classified	
Mean absolute error	9.19	8.97	22.05	23.40	24.92	15.26
Mean error	6.07	4.03	–0.29	16.39	14.28	5.02

Fig. S9: (A) Comparison of observed and predicted F_{abs} related to permeability (cm/s) in Table S4 under the scenario that P_{eff} was converted from P_{app} using the IVIVC ratio and assumed to be equal to jejunum permeability. (B) Median differences between the observed and predicted percentage of absorption (ΔF_{abs}) with 95% CI. The table demonstrates the mean absolute errors and mean errors based on BDDCS classes.

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