Physiologically-based pharmacokinetic tissue compartment model selection in drug development and risk assessment

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Supporting Information

Table 1S Drug names and values for log*P(o:w)*, fu_p, and fu_t in rat

#	Drug Name	log*P(o:w)*[q]	fu_p[r]	fu_t[s]
1	5-ethyl-5-methyl-barbiturate	0.02[a]	1[a]	1.000
2	5-ethyl-5-n-heptyl-barbiturate	3.64[a]	0.07[a]	0.131
3	5-ethyl-5-n-hexyl-barbiturate	3.08[a]	0.18[a]	0.305
4	5-ethyl-5-n-octyl-barbiturate	3.85[a]	0.03[a]	0.058
5	5-ethyl-5-n-pentyl-barbiturate	2.23[a]	0.486[a]	0.654
6	5-ethyl-5-n-propyl-barbiturate	0.87[a]	0.86[a]	0.925
7	5-Fluorouracil	-0.89	0.642[g]	0.782
8	6-Mercaptopurine	0.6[c]	0.847[g]	0.917
9	Acebutolol-R	1.71	0.79[l]	0.883
10	Acebutolol-S	1.71	0.73[l]	0.844
11	Acetaminophen	0.46	0.88	0.936
12	Acitretin	6.4	0.01	0.020
13	Alfentanil	2.16	0.158	0.273
14	Amiodarone	7.57	0.05	0.095
15	Amlodipine	3	0.06	0.113
16	Barbital	0.65	0.964	0.982
17	Biperiden	4.25	0.135	0.238
18	Bisoprolol	1.87	0.85[l]	0.919
19	Butobarbital	1.7[a]	0.6[a]	0.750
20	Chlorpromazine	5.41	0.106	0.192
21	Cocaine	2.3	0.63	0.773
22	Cyclophosphamide	0.63	0.65[g]	0.788
23	Cyclosporin	2.92[b]	0.06	0.114
24	Diazepam	2.82	0.137	0.241
25	Dideoxyinosine	-1.24[b]	0.965	0.982
26	Digoxin	1.26[b]	0.613	0.760
27	Diltiazem	2.7	0.25	0.400
28	Disopyramide	2.58	0.235	0.381
29	Enprofylline	0.33	0.226	0.369
30	Epiroprim	2.89	0.097	0.177

31	Ethanol	-0.31	1	1.000
32	Ethoxybenzamide	0.77[b]	0.5	0.667
33	Etomidate	3.05	0.191	0.321
34	Exaprolol	3.68[b]	0.54	0.701
35	Fentanyl	4.05	0.15[l]	0.261
36	Imipramine	4.8	0.24	0.387
37	Ketoprofen	3.12	0.029	0.056
38	Lidocaine	2.44	0.38	0.551
39	Mefloquine	4.49[b]	0.024	0.047
40	Mephenytoin	1.69	0.63	0.773
41	Methadone	3.93	0.254	0.405
42	Methotrexate	-1.85	0.373[g]	0.543
43	Methylphenidate	0.2[b]	0.77	0.870
44	Metoprolol-R	1.88	0.8l	0.889
45	Metoprolol-S	1.88	0.81[l]	0.895
46	Midazolam	2.95[b]	0.027	0.053
47	Morphine	0.89	0.7[l]	0.824
48	Nicotine	1.17	0.84	0.913
49	Nortriptyline	4.51	0.1[g]	0.182
50	Oxazepam	2.24	0.15	0.261
51	Oxprenolol-R	2.1	0.24[l]	0.387
52	Oxprenolol-S	2.1	0.36[l]	0.529
53	para-Phenylbenzoic acid	3.75	0.028[i]	0.054
54	Pefloxacin	0.27	0.797[k]	0.887
55	Pentazocine	4.64	0.54	0.701
56	Pentobarbital	2.1	0.574	0.729
57	Phencyclidine	4.69	0.47	0.639
58	Phenytoin	2.47	0.09[h]	0.164
59	Pindolol-R	1.75	0.51[l]	0.675
60	Pindolol-S	1.75	0.76[l]	0.864
61	Prednisolone	1.62	0.6	0.750
62	Procainamide	0.88	0.92	0.958
63	Propafenone	3.37[c]	0.125[f]	0.222
64	Propranolol	3.48	0.078[e]	0.145
65	Protriptyline	4.89[c]	0.18[g]	0.305
66	Quinidine	3.44	0.3	0.462
67	Remoxipride	2.1	0.74	0.851
68	Salicylic acid	2.26	0.4	0.571
69	Sildenafil	2.75[b]	0.05	0.095
70	Tamsulosin	2.47[c]	0.21[j]	0.347

71	Theophylline	-0.02	0.4	0.571
72	Thiopental	2.85	0.131	0.232
73	Timolol-S	1.83	0.63[l]	0.773
74	Valproic acid	2.75	0.366[d]	0.536
75	Verapamil	3.79	0.05	0.095

[q]Log*P(o:w)* data - from a-Blakey[13], et al., b-Poulin, et al., 2002[11], c-estimated value from EPI Suite[12]; all other values without superscripts are from the EPI suite experimental database

[r]fu_p data - from a-Blakey, et al.[13], d-Dickinson, et al.[18], e- Evans, et al.[17], f-Higuchi, et al.[16], g-Jusko, et al.[21], h-Kato, et al.[14], i-Kawahara, et al.[20], j-Matsushima, et al.[22], k-Montay, et al.[19], l-Poulin, et al. 2009[23], m-Singh, et al.[15]; all other values are from Poulin, et al. 2002[11]

[s]fu_t was computed from fu_p making the assumptions of Poulin, et al. 2002[11], where fu_t is computed as described by Eq.(16)

Table 2S Organ and tissue composition for the rat[a]

Tissue	Fractional Water	Fractional Neutral Lipid	Fractional Phospholipid
Bone	0.35	0.0222	0.0005
Brain	0.75	0.0393	0.0532
Heart	0.77	0.0117	0.0141
Intestine	0.70	0.032	0.015
Lung	0.78	0.0199	0.017
Muscle	0.74	0.009	0.01
Plasma	0.96	0.00147	0.00083
Skin	0.70	0.0205	0.0155
Spleen	0.77	0.0077	0.0136

[a]Data from Poulin, et al. 2000[9]

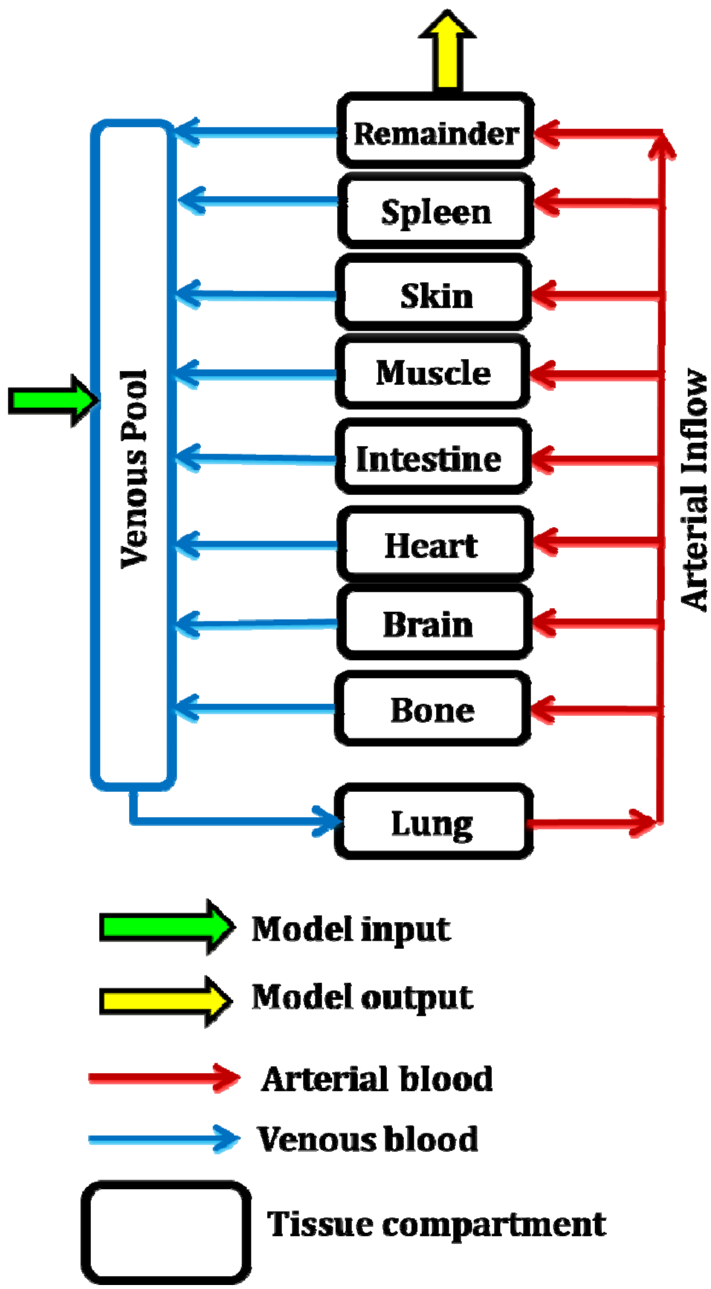
Table 3S *A priori* predicted tissue:plasma partition coefficients for 75 drugs in the rat[a]

Drug #	$P_{t:p}$							
	Bone	Brain	Heart	Intestine	Lung	Muscle	Skin	Spleen
1	0.39	0.88	0.83	0.78	0.85	0.79	0.77	0.82
2	6.19	15.30	4.44	10.12	6.95	3.36	6.98	3.30
3	5.31	13.10	3.88	8.69	6.01	2.96	6.03	2.91
4	6.22	15.38	4.45	10.16	6.97	3.36	7.01	3.30
5	2.46	6.03	2.07	4.10	2.99	1.65	2.96	1.65
6	0.49	1.14	0.86	0.94	0.93	0.80	0.86	0.83
7	0.30	0.68	0.67	0.61	0.68	0.64	0.61	0.67
8	0.42	0.96	0.81	0.82	0.85	0.76	0.77	0.79
9	1.28	3.09	1.36	2.20	1.77	1.16	1.71	1.18
10	1.23	2.99	1.32	2.13	1.71	1.12	1.65	1.14
11	0.40	0.92	0.80	0.79	0.84	0.76	0.76	0.79
12	6.56	16.23	4.68	10.72	7.34	3.52	7.39	3.46
13	1.71	4.20	1.48	2.87	2.11	1.19	2.08	1.19
14	6.83	16.88	4.87	11.15	7.64	3.66	7.68	3.60
15	4.49	11.09	3.31	7.36	5.10	2.52	5.12	2.48
16	0.46	1.05	0.86	0.89	0.92	0.81	0.83	0.84
17	7.16	17.70	5.11	11.70	8.02	3.85	8.06	3.78
18	1.71	4.15	1.67	2.90	2.25	1.39	2.19	1.41
19	1.12	2.72	1.21	1.94	1.56	1.03	1.51	1.05
20	7.17	17.74	5.11	11.72	8.03	3.85	8.07	3.78
21	3.01	7.39	2.47	5.00	3.61	1.96	3.58	1.96
22	0.38	0.87	0.72	0.74	0.77	0.68	0.70	0.71
23	4.20	10.37	3.11	6.89	4.79	2.38	4.80	2.35
24	4.10	10.11	3.07	6.73	4.69	2.35	4.70	2.32
25	0.36	0.81	0.80	0.73	0.81	0.76	0.73	0.80
26	0.62	1.46	0.87	1.12	1.01	0.78	0.95	0.81
27	3.96	9.77	3.01	6.52	4.57	2.32	4.57	2.29
28	3.38	8.34	2.62	5.58	3.94	2.03	3.93	2.01
29	0.25	0.58	0.52	0.50	0.54	0.49	0.49	0.51
30	4.23	10.44	3.14	6.94	4.83	2.40	4.84	2.37
31	0.38	0.85	0.82	0.76	0.84	0.78	0.75	0.82
32	0.37	0.86	0.68	0.72	0.73	0.63	0.66	0.66
33	5.24	12.94	3.84	8.59	5.94	2.93	5.96	2.88
34	8.99	22.23	6.45	14.70	10.09	4.88	10.15	4.79
35	7.13	17.63	5.10	11.65	7.99	3.84	8.03	3.78
36	7.99	19.76	5.70	13.05	8.94	4.29	9.00	4.22

37	4.75	11.74	3.47	7.79	5.38	2.64	5.40	2.60
38	3.13	7.70	2.49	5.18	3.69	1.95	3.67	1.94
39	6.54	16.17	4.67	10.69	7.32	3.52	7.36	3.45
40	1.13	2.73	1.22	1.95	1.57	1.04	1.52	1.06
41	7.66	18.95	5.48	12.52	8.59	4.14	8.64	4.06
42	0.25	0.56	0.56	0.51	0.57	0.53	0.51	0.56
43	0.35	0.80	0.74	0.71	0.76	0.70	0.69	0.73
44	1.69	4.11	1.64	2.87	2.22	1.37	2.16	1.38
45	1.70	4.13	1.65	2.89	2.23	1.37	2.17	1.39
46	4.18	10.31	3.09	6.85	4.75	2.36	4.76	2.32
47	0.46	1.06	0.79	0.87	0.86	0.73	0.79	0.76
48	0.64	1.50	0.95	1.17	1.08	0.86	1.01	0.89
49	7.03	17.39	5.02	11.49	7.87	3.78	7.92	3.71
50	1.93	4.74	1.62	3.22	2.35	1.29	2.32	1.29
51	1.67	4.08	1.47	2.79	2.08	1.19	2.04	1.19
52	1.83	4.47	1.61	3.07	2.28	1.30	2.24	1.31
53	6.10	15.07	4.37	9.96	6.84	3.30	6.87	3.24
54	0.37	0.83	0.75	0.73	0.78	0.72	0.71	0.75
55	9.89	24.45	7.05	16.15	11.06	5.31	11.13	5.22
56	2.12	5.18	1.86	3.55	2.63	1.51	2.59	1.51
57	9.45	23.37	6.74	15.44	10.58	5.08	10.64	4.99
58	2.58	6.34	2.03	4.26	3.03	1.59	3.02	1.58
59	1.15	2.78	1.20	1.97	1.57	1.02	1.52	1.03
60	1.34	3.24	1.39	2.30	1.83	1.18	1.77	1.20
61	0.99	2.40	1.12	1.73	1.42	0.97	1.36	0.98
62	0.51	1.19	0.89	0.97	0.97	0.83	0.89	0.86
63	5.95	14.69	4.30	9.72	6.70	3.26	6.73	3.20
64	5.94	14.69	4.28	9.72	6.68	3.24	6.72	3.19
65	7.62	18.83	5.43	12.44	8.52	4.09	8.57	4.02
66	7.07	17.46	5.10	11.55	7.95	3.86	7.99	3.79
67	2.34	5.72	2.06	3.92	2.91	1.67	2.87	1.67
68	2.43	5.96	2.02	4.04	2.94	1.61	2.91	1.61
69	3.52	8.68	2.65	5.78	4.05	2.04	4.05	2.02
70	2.86	7.05	2.26	4.73	3.37	1.77	3.35	1.75
71	0.27	0.61	0.58	0.54	0.59	0.55	0.53	0.58
72	4.20	10.36	3.13	6.90	4.80	2.40	4.81	2.37
73	1.41	3.42	1.41	2.41	1.88	1.18	1.82	1.19
74	4.58	11.29	3.45	7.53	5.26	2.66	5.26	2.62
75	6.27	15.51	4.50	10.25	7.04	3.39	7.08	3.33

[a]$P_{t:p}$ was computed using tissue composition data, logP, fu_p and fu_t, as given by Eq.(17)

Whole-body Model Structure



Whole-body Model Equations

Bone, Brain, Heart, Intestine, Muscle, Skin, Spleen (the i^{th} partition coefficient, the j^{th} tissue):

PLT

$$\left.\begin{aligned}\frac{dc_{1,j}}{dt} &= \frac{F_j}{V_{1,j}}\left(c_{in,arterial} - c_{1,j}\right) - \frac{PS_j}{V_{1,j}}\left(c_{1,j} - \frac{c_{2,j}}{P_{t:p,i}}\right)\\ \frac{dc_{2,j}}{dt} &= +\frac{PS_j}{V_{2,j}}\left(c_{1,j} - \frac{c_{2,j}}{P_{t:p,i}}\right)\end{aligned}\right., \; c_{out,j} = c_{1,j}$$

WST

$$\frac{dc_j}{dt} = \frac{F_j}{V_j}\left(c_{in,arterial} - \frac{c_j}{P_{t:p,i}}\right), \; c_{out,j} = \frac{c_j}{P_{t:p,i}}$$

F-TAR

$$\frac{dc_{2,j}}{dt} = \frac{F_j}{V_{2,j}}\left(c_{in,arterial} - \frac{c_{2,j}}{P_{t:p,i}}\right), \; c_{1,j} = \frac{c_{2,j}}{P_{t:p,i}}$$

$$c_{out,j} = \left(1 + \frac{V_{1,j}}{P_{t:p,i}V_{2,j}}\right)\frac{c_{2,j}}{P_{t:p,i}} - c_{in,arterial}\frac{V_{1,j}}{P_{t:p,i}V_{2,j}}$$

Lung (the i^{th} partition coefficient):

PLT

$$\left.\begin{aligned}\frac{dc_{1,lung}}{dt} &= \frac{F_{lung}}{V_{1,lung}}\left(c_{in,vp} - c_{1,lung}\right) - \frac{PS_{lung}}{V_{1,lung}}\left(c_{1,lung} - \frac{c_{2,lung}}{P_{t:p,i}}\right)\\ \frac{dc_{2,lung}}{dt} &= +\frac{PS_{lung}}{V_{2,lung}}\left(c_{1,lung} - \frac{c_{2,lung}}{P_{t:p,i}}\right)\end{aligned}\right., \; c_{out,lung} = c_{1,lung} = c_{in,arterial}$$

WST

$$\frac{dc_{lung}}{dt} = \frac{F_{lung}}{V_{lung}}\left(c_{in,vp} - \frac{c_{lung}}{P_{t:p,i}}\right), \; c_{out,lung} = \frac{c_{lung}}{P_{t:p,i}} = c_{in,arterial}$$

F-TAR

$$\frac{dc_{2,lung}}{dt} = \frac{F_{lung}}{V_{2,lung}}\left(c_{in,vp} - \frac{c_{2,lung}}{P_{t:p,i}}\right),\ c_{1,lung} = \frac{c_{2,lung}}{P_{t:p,i}},$$

$$c_{out,lung} = \left(1 + \frac{V_{1,lung}}{P_{t:p,i}V_{2,lung}}\right)\frac{c_{2,lung}}{P_{t:p,i}} - c_{in,vp}\frac{V_{1,lung}}{P_{t:p,i}V_{2,lung}} = c_{in,arterial}$$

Remainder (the i^{th} partition coefficient):

PLT

$$\frac{dc_{1,remainder}}{dt} = \frac{F_{remainder}}{V_{1,remainder}}\left(c_{in,arterial} - c_{1,remainder}\right) - \frac{PS_{remainder}}{V_{1,remainder}}\left(c_{1,remainder} - \frac{c_{2,remainder}}{P_{t:p,i}}\right),$$

$$\frac{dc_{2,remainder}}{dt} = +\frac{PS_{remainder}}{V_{2,remainder}}\left(c_{1,remainder} - \frac{c_{2,remainder}}{P_{t:p,i}}\right) - \frac{CL_{remainder}}{V_{2,remainder}}c_{2,remainder}$$

$$c_{out,remainder} = c_{1,remainder}$$

WST

$$\frac{dc_{remainder}}{dt} = \frac{F_{remainder}}{V_{remainder}}\left(c_{in,arterial} - \frac{c_{remainder}}{P_{t:p,i}}\right) - \frac{CL_{remainder}}{V_{remainder}}c_{remainder}$$

$$c_{out,remainder} = \frac{c_{remainder}}{P_{t:p,i}}$$

F-TAR

$$\frac{dc_{2,remainder}}{dt} = \frac{F_{remainder}}{V_{2,remainder}}\left(c_{in,arterial} - \frac{c_{2,remainder}}{P_{t:p,i}}\right) - \frac{CL_{remainder}}{V_{2,remainder}}c_{remainder},\ c_{1,remainder} = \frac{c_{2,remainder}}{P_{t:p,i}},$$

$$c_{out,remainder} = \left(1 + \frac{V_{1,remainder}}{P_{t:p,i}V_{2,remainder}}\right)\frac{c_{2,remainder}}{P_{t:p,i}} - \left(\frac{V_{1,remainder}}{P_{t:p,i}V_{2,remainder}}\right)\left[c_{in,arterial} - \frac{CL_{remainder}}{F_{remainder}}c_{2,remainder}\right]$$

where clearance in the remainder compartment is CL = 0.05 ml sec^{-1}

Venous Pool:

WST, F-TAR

$$c_{in,vinflow} = \frac{\left(\sum_j c_{out,j}F_j\right)}{F_{CO}}$$

$$\frac{dc_{vp}}{dt} = \frac{F_{CO}}{V_{vp}}\left(c_{in,vinflow} - c_{vp}\right) + \frac{\text{Input}_{iv}}{V_{vp}}$$

where CO is cardiac output, the venous pool volume is set to 1 ml, and the input dose is given by Eq. (23).

Conditional statements for F-TAR code:

Step	F-TAR (Non-eliminating tissues)
1	$c_{out}^{*} = \left(1 + \frac{V_1}{P_{t:p}V_2}\right)\frac{c_2}{P_{t:p}} - c_{in}\frac{V_1}{P_{t:p}V_2}$
2	$c_{out} = \begin{cases} 0 & , \quad c_{out}^{*} \le 0 \\ c_{out}^{*} & , \quad c_{out}^{*} > 0 \end{cases}$
3	$\frac{dc_2}{dt} = \begin{cases} \frac{Fc_{in}}{V_2 + V_1 / P_{t:p}} & , \quad c_{out}^{*} \le 0 \\ \frac{F}{V_2}\left(c_{in} - \frac{c_2}{P_{t:p}}\right) & , \quad c_{out}^{*} > 0 \end{cases}$
4	Solve for c_2 and compute $c_1 = \frac{c_2}{P_{t:p}}$
Step	**F-TAR (Remainder)**
1	$c_{out}^{*} = \left(1 + \frac{V_1}{P_{t:p}V_2}\right)\frac{c_2}{P_{t:p}} - \left(\frac{V_1}{P_{t:p}V_2}\right)\left[c_{in} - \frac{CL}{F}c_2\right]$
2	$c_{out} = \begin{cases} 0 & , \quad c_{out}^{*} \le 0 \\ c_{out}^{*} & , \quad c_{out}^{*} > 0 \end{cases}$
3	$\frac{dc_2}{dt} = \begin{cases} \frac{Fc_{in} - CLc_2}{V_2 + V_1 / P_{t:p}} & , \quad c_{out}^{*} \le 0 \\ \frac{F}{V_2}\left(c_{in} - \frac{c_2}{P_{t:p}}\right) - \frac{CL}{V_2}c_2 & , \quad c_{out}^{*} > 0 \end{cases}$
4	Solve for c_2 and compute $c_1 = \frac{c_2}{P_{t:p}}$