

SUPPLEMENTAL INFORMATION

Does Addition of Protein to Hepatocyte or Microsomal In Vitro Incubations Provide A Useful Improvement in In Vitro-In Vivo Extrapolation (IVIVE)

Predictability?

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Table S-1 Pharmacokinetic parameters of drugs from human hepatocytes and in vivo measures

Drug	BDDCS	Charge	$f_{u,b}^a$	$f_{u,p}^a$	$f_{u,hep}$	Observed		Predicted						Reference	
						$CL_{H,b}^a$ ml/min/kg	$CL_{H,p}^b$ ml/min/kg	$CL_{int,in vivo,unbound}^d$ (mL/min/kg)		$CL_{H,b}$ (mL/min/kg)		$CL_{H,p}$ (mL/min/kg)			
								Without Serum	With Serum	Without Serum	With Serum	Without Serum	With Serum		
Carbamazepine	2	neutral	0.31	0.26	0.84 ^a	-	1.6	-	2.46 ^c	5.77	0.734	1.65	0.605	1.32	
Phenytoin	2	Acid	0.11	0.11	0.84 ^a	-	5.3	0.37	9.00 ^c	1.28	0.945	0.14	0.911	0.139	
Procainamide	3	Base	0.84 ^e	0.84	0.92 ^f	-	10 ^e	10	3.93 ^c	0.477	2.85	0.393	2.56	0.387	(1)
Quinidine	1	Base	0.21	0.2	0.64 ^a	-	4.1	4	22.1 ^c	1.85	3.79	0.38	3.18	0.357	
Theophylline	1	neutral	0.45	0.59	0.96 ^a	-	0.47	0.86	1.28 ^c	0.191	0.559	0.0854	0.707	0.111	
Antipyrine	1	neutral	0.99	0.99	1 ^c	1	0.55	0.64	1.38 ^c	0.595	1.28	0.573	1.22	0.56	(2)

Bosentan	2	Acid	0.064	0.035	1 ^c	0.026	3.5	2.1	4.51 ^c	93.1	0.285	4.63	0.156	2.53	
Mibepradil	2	Acid	0.012 ^c	0.012 ^c	1 ^c	0.012	4 ^e	4	32.7 ^c	377	0.385	3.71	0.379	3.24	
Midazolam	1	Base	0.043	0.025	0.817 ^c	0.021	9.2	5.3	61.5 ^c	252	0.317	2.17	0.348	2.19	
Naloxone	1	neutral	0.51	0.62	1 ^c	0.596	18	23	69.5 ^c	38.1	2.35	7.12	1.36	4.06	
Oxazepam	2	neutral	0.043	0.048	0.8 ^c	0.05	1.2	1.1	7.49 ^c	56.5	13.1	10	9.01	7.69	
Alprazolam	1	Base	0.31	0.29	0.843 ^c	0.581	0.78	0.74	1.22 ^c	3.09	0.371	0.917	0.343	0.832	
Antipyrine	1	neutral	0.99	0.99	0.907 ^c	0.655	0.55	0.64	0.283 ^c	0.784	0.277	0.748	0.274	0.727	
Caffeine	1	neutral	0.65	0.68	1 ^c	0.834	1.2	1.4	0.514 ^c	0.308	0.329	0.198	0.339	0.206	
Carbamazepine	2	neutral	0.31	0.26	0.84 ^c	0.411	1.6	-	6.1 ^c	1.25	1.73	0.38	1.39	0.316	
Chlorpromazine	1	Base	0.043	0.037	0.395 ^c	0.082	11	16	278 ^c	573	7.58	11.3	5.41	7.41	
Clozapine	2	Base	0.054	0.053	0.481 ^c	0.1	4.1	2.5	61.9 ^c	51.4	2.88	2.45	2.55	2.2	
Desipramine	1	Base	0.21	0.18	0.819 ^c	0.357	11	11	178 ^c	203	13.3	13.9	8.41	8.69	
Diazepam	1	neutral	0.036	0.022	0.643 ^c	0.33	0.57	0.38	4.79 ^c	0.778	0.171	0.028	0.104	0.0171	
Diclofenac	2	Acid	0.0091	0.005	0.05 ^c	0.011	7.7	3.5	688 ^c	887	4.81	5.81	2.64	3.19	
Diltiazem	1	Base	0.22	0.22	0.894 ^c	0.684	12	13	8.9 ^c	21.8	1.79	3.89	1.67	3.37	(3)
Imipramine	1	Base	0.13	0.13	0.821 ^c	0.32	13	13	96 ^c	217	7.79	11.9	5.96	8.12	
Indomethacin	2	Acid	0.019	0.01	0.307 ^c	0.015	2.1	1.3	9.2 ^c	291	0.173	4.36	0.0913	2.32	
Labetalol	1	Base	0.38	0.5	0.928 ^c	0.463	14	23	28.5 ^c	33.8	7.11	7.93	6.33	6.81	
Lorazepam	1	neutral	0.08	0.082	0.474 ^c	0.246	1.1	1	2.17 ^c	2.09	0.172	0.166	0.175	0.169	
Naloxone	1	neutral	0.51	0.62	0.834 ^c	0.852	18	23	82.2 ^c	44	13.9	10.8	9.32	8.04	
Naproxen	2	Acid	0.001	0.001	0.028 ^c	0.631	0.12	0.07	9.17 ^c	1.22	0.00917	0.00122	0.00916	0.00122	
Nitrendipine	2	zwitterion	0.029	0.02	0.347 ^c	0.055	20	25	141 ^c	121	3.41	3.01	2.26	2	
Pindolol	1	Base	0.56	0.56	1 ^c	0.992	3.7	7.7	4.88 ^c	3.88	2.41	1.97	2.2	1.83	

Sildenafil	1	Base	0.04	0.04	0.681 ^c	0.139	7.6	9	23.4 ^c	97.9	0.895	3.29	0.864	2.92		
Timolol	1	Base	0.59	0.9	1 ^c	0.858	9.7	8.5	5.65 ^c	5.99	2.87	3.02	3.52	3.66		
Verapamil	1	Base	0.096	0.081	0.838 ^c	0.442	16	18	76.9 ^c	104	5.44	6.74	4.03	4.84		
Bufuralol	1	Base	0.19 ^e	0.19	0.66 ^f	-	8.9 ^e	8.9	18.8 ^c	11.8	3.04	2.03	2.72	1.88		
Diclofenac	2	Acid	0.0091	0.005	0.94 ^a	-	7.7	3.5	32.4 ^c	179	0.291	1.51	0.16	0.829	(4)	
Midazolam	1	Base	0.043	0.025	0.92 ^a	-	9.2	5.3	7.23 ^c	80.7	0.306	2.97	0.178	1.71		
Alprenolol	1	Base	0.27	0.22	0.85 ^a	-	14	15	59 ^a	58.4	9	8.95	6.07	6.04		
Carbamazepine	2	neutral	0.31	0.26	0.84 ^a	-	1.6	-	6.1 ^a	2.17	1.73	0.652	1.39	0.538		
Clozapine	2	Base	0.054	0.053	0.7 ^a	-	4.1	2.5	22 ^a	38.8	1.12	1.9	1.06	1.74		
Desipramine	1	Base	0.21	0.18	0.16 ^a	-	11	11	77 ^a	41.4	9.08	6.12	6.26	4.5		
Diclofenac	2	Acid	0.0091	0.005	0.94 ^a	-	7.7	3.5	168 ^a	128	1.42	1.11	0.782	0.608		
Flumazenil	1	neutral	0.6	0.58	0.94 ^a	-	15	16	16 ^a	7.53	6.56	3.71	5.12	3.16		
Gemfibrozil	2	Acid	0.026	0.014	0.93 ^a	-	3.1	-	134 ^a	116	2.98	2.62	1.61	1.42		
Haloperidol	2	Base	0.1	0.08	0.56 ^a	-	9.6	7.8	13 ^a	61	1.22	4.71	0.953	3.42	(5)	
Imipramine	1	Base	0.13	0.13	0.18 ^a	-	13	13	90 ^a	217	7.48	11.9	5.77	8.12		
Ketanserin	2	Base	0.097	0.068	0.87 ^a	-	9.7	6.7	136 ^a	52.9	8.06	4.11	5.11	2.73		
Midazolam	1	Base	0.043	0.025	0.92 ^a	-	9.2	5.3	42 ^a	154	1.66	5.02	0.961	2.88		
Nifedipine	2	zwitterion	0.03	0.041	0.79 ^a	-	5.4	7.3	60 ^a	169	1.66	4.07	2.02	4.31		
Omeprazole	1	neutral	0.067	0.04	0.87 ^a	-	11	8.4	8.4 ^a	18	0.548	1.14	0.326	0.676		
Ranitidine	3	Base	0.8	0.84	0.95 ^a	-	2.7	9.6	3.4 ^a	4.89	2.4	3.29	2.28	3.02		
Zaleplon	2	neutral	0.4	0.4	0.92 ^a	-	16	16	7.3 ^a	8.99	2.56	3.06	2.32	2.73		
Antipyrine	1	neutral	0.99	0.99	0.95 ^a	-	0.55	0.64	1.3 ^a	0.0778	1.21	0.0768	1.16	0.0765		
Caffeine	1	neutral	0.65	0.68	0.96 ^a	-	1.2	1.4	5.3 ^a	0.491	2.95	0.314	2.74	0.324	(6)	

Diazepam	1	neutral	0.036	0.022	0.54 ^a	-	0.57	0.38	5.6 ^a	5.84	0.2	0.208	0.122	0.127	
Diclofenac	2	Acid	0.0091	0.005	0.94 ^a	-	7.7	3.5	168 ^a	395	1.42	3.07	0.782	1.69	
Imipramine	1	Base	0.13	0.13	0.18 ^a	-	13	13	90 ^a	35.2	7.48	3.74	5.77	3.26	
Lidocaine	1	Base	0.34	0.29	0.9 ^a	-	14	16	13 ^a	21.5	3.64	5.41	2.83	4.03	
Metoprolol	1	Base	0.83	0.89	0.9 ^a	-	12	13	16 ^a	4.24	8.09	3.01	6.33	2.84	
Naloxone	1	neutral	0.51	0.62	0.93 ^a	-	18	23	167 ^a	75.8	16.7	13.5	10.3	9.18	
Phenacetin	2	neutral	0.57	0.57	0.91 ^a	-	20	21	24 ^a	66.3	8.24	13.4	6.22	8.76	
Propranolol	1	Base	0.15	0.13	0.63 ^a	-	15	12	50 ^a	45	5.51	5.09	4.14	3.87	
Quinidine	1	Base	0.21	0.2	0.64 ^a	-	4.1	4	17 ^a	7.83	3.04	1.52	2.62	1.38	
Timolol	1	Base	0.59	0.9	0.9 ^a	-	9.7	8.5	9.8 ^a	1.97	4.52	1.1	4.97	1.53	
Verapamil	1	Base	0.096	0.081	0.52 ^a	-	16	18	106 ^a	147	6.82	8.41	4.9	5.83	
Atorvastatin	2	Acid	0.0467 ^c	0.0308 ^c	0.93 ^f	-	13.5 ^c	8.91 ^c	66.8 ^c	197	2.71	6.38	1.74	3.97	
Bosentan	2	Acid	0.00981 ^c	0.0081 ^c	0.81 ^a	-	2.85 ^c	2.37 ^c	73.6 ^c	289	0.697	2.5	0.569	1.95	
Cerivastatin	1	Acid	0.0127 ^c	0.0073 ^c	0.90 ^f	-	5 ^c	2.9 ^c	221 ^c	617	2.47	5.69	1.42	3.24	
Fluvastatin	1	Acid	0.0069 ^c	0.0043 ^c	0.94 ^f	-	14 ^c	8.68 ^c	170 ^c	1090	1.11	5.52	0.683	3.31	
Glibenclamide	2	Acid	0.00171 ^c	0.0008 ^c	0.87 ^f	-	2.3 ^c	1.06 ^c	95.0 ^c	444	0.161	0.732	0.0743	0.339	(7)
Nateglinide	2	Acid	0.00994 ^c	0.005 ^c	0.93 ^f	-	3.05 ^c	1.53 ^c	34.5 ^c	113	0.337	1.07	0.169	0.535	
Pitavastatin	4	Acid	0.00932 ^c	0.0054 ^c	0.93 ^f	-	9.64 ^c	5.59 ^c	100 ^c	227	0.891	1.92	0.516	1.11	
Repaglinide	2	Acid	0.0109 ^c	0.0068 ^c	0.86 ^f	-	11.6 ^c	7.19 ^c	117 ^c	531	1.2	4.52	0.74	2.73	
Rosuvastatin	3	Acid	0.195 ^c	0.134 ^c	0.96 ^f	-	12.1 ^c	8.35 ^c	10.7 ^c	25.6	1.9	4.02	1.28	2.63	
Valsartan	4	Acid	0.00301 ^c	0.0017 ^c	0.95 ^f	-	0.678 ^c	0.373 ^c	5.05 ^c	306	0.0152	0.883	0.00833	0.484	

^aWood et al., 2017; ^bLombardo et al., 2018; ^cThe values were cited from the studies in the reference column;

^dValues were calculated using consistent scaling factors. The physiological scaling factor utilized for hepatocellularity was 120×10^6 hepatocytes/g liver and the liver weight was 21.4 g/kg body weight;

^eValues were derived from the quotient of $f_{u,p}$ or $CL_{H,p}$ and blood-to-plasma partitioning ratio (R_{BP}). For the drugs that did not have reported R_{BP} values, it was assumed to be equal to 1 for a basic or neutral compound and 0.55 (1-hematocrit) for an acidic compound;

^fValues were calculated using Eq. S1.

$$f_{u,hep} = \frac{1}{1 + 125 \cdot V_R \cdot 10^{0.072 \cdot \log P/D^2 + 0.067 \cdot \log P/D - 1.126}} \quad (S1)$$

Log P/D is either the log P value for basic and neutral drugs or the log D value for acidic drug; and V_R is the volume ratio of hepatocytes to medium (0.005 for 1 \times 10⁶ cells/ml).

Table S-2 Pharmacokinetic parameters of drugs from human microsomes and in vivo measures

Drug	BDDCS	Charge	$f_{u,b}$	$f_{u,p}$	$f_{u,inc}^d$	Observed		Predicted						Reference	
						$CL_{H,b}$	$CL_{H,p}^b$	$CL_{int,in vivo,unbound}^d$	$CL_{H,b}$	$CL_{H,p}$	$(mL/min/kg)$	$(mL/min/kg)$	$(mL/min/kg)$	$(mL/min/kg)$	
						Without	With	$(ml/min/kg)$	$(ml/min/kg)$	Without	With	Without	With	Without	With

				Albumin	Albumin			Albumin							
Diclofenac	2	Acid	0.0091 ^a	0.005 ^a	0.84-0.90	0.002-0.029	7.7 ^a	3.5	268	300	0.377	0.941	0.206	0.515	(10)
Tolbutamide	2	Acid	0.076 ^a	0.05 ^a	0.93-0.99	0.011-0.095	0.35 ^a	0.21	1.31	0.519	1.21	0.178	1.16	0.177	
Phenytoin	2	Acid	0.11 ^a	0.11 ^a	0.36	0.25	5.3 ^a	0.37	0.428	3.94	2.95	0.278	2.74	0.288	(11)
Diclofenac	2	Acid	0.0091 ^a	0.005 ^a	0.98	0.02	7.7 ^a	3.5	651	1020	9.08	6.12	6.26	4.5	
Gemfibrozil	2	Acid	0.026 ^a	0.014 ^a	0.90	0.01	3.1 ^a	1.7	222	1580	7.48	11.9	5.77	8.12	
Mycophenolic acid	2	Acid	0.0333 ^c	0.02 ^b	0.83	0.18	3.88 ^c	2.33	66.9	199	1.73	0.652	1.39	0.538	(12)
Naloxone	1	neutral	0.51 ^a	0.62 ^a	1.00	0.96	18 ^a	23	8.56	47.6	1.66	5.02	0.961	2.88	
Propofol	2	neutral	0.0182 ^c	0.016 ^b	0.69	0.25	40.9 ^c	36	58	172	1.66	4.07	2.02	4.31	
Telmisartan	2	Acid	0.00323 ^c	0.004 ^b	0.65	0.07	6.77 ^c	8.4	65.8	338	1.42	1.11	0.782	0.608	
Phenytoin	2	Acid	0.11 ^a	0.11 ^a	1	0.126	5.3 ^a	0.37	0.809	18	0.355	0.818	0.389	0.877	(13)
Coumarin	1	neutral	0.17 ^c	0.17 ^c	0.92	0.89	23.6 ^c	23.6	1210	1250	0.151	0.702	0.154	0.699	
Diclofenac	2	Acid	0.0091 ^a	0.005 ^a	0.93	0.026	7.7 ^a	3.5	89	439	1.66	10.1	0.961	5.74	(14)
Midazolam	1	Base	0.043 ^a	0.025 ^a	1	0.025	9.2 ^a	5.3	342	553	16.7	13	10.3	8.99	
Phenacetin	2	neutral	0.57 ^a	0.57 ^a	1	0.97	20 ^a	21	5.73	44.4	5.61	3.71	4.6	3.24	
Zidovudine	1	zwitterion	0.82 ^a	0.8 ^a	1	1	19 ^a	25	0.565	8.53	1.12	1.9	1.06	1.74	(15)

Phenytoin	2	Acid	0.11 ^a	0.11 ^a	1	0.51	5.3 ^a	0.37	0.736	0.565	0.0688	0.445	0.0389	0.251	(16)
Propofol	2	neutral	0.016 ^c	0.016 ^b	0.7	0.2	36 ^c	36	6.85	58.2	2.98	2.62	1.61	1.42	(17)
Phenytoin	2	acid	0.11 ^a	0.11 ^a	1	0.2	5.3 ^a	0.37	0.496	2.78	0.548	1.14	0.326	0.676	(18)
Tolbutamide	2	Acid	0.076 ^a	0.05 ^a	1	0.012-0.098	0.35 ^a	0.21	2.05	9.33	9	8.95	6.07	6.04	
Estradiol	1	neutral	0.016 ^c	0.016 ^b	0.14	0.039	30 ^c	30	248	94.2	2.4	3.29	2.28	3.02	
Propofol	2	neutral	0.016 ^c	0.016 ^b	1	0.17	36 ^c	36	12	85.6	6.56	3.71	5.12	3.16	(19)
Zidovudine	1	zwitterion	0.82 ^a	0.8 ^a	0.69	0.69	19 ^a	25	4.37	40.2	1.22	4.71	0.953	3.42	
Paclitaxel	2	neutral	0.12 ^c	0.12 ^b	0.66	0.44	6.4 ^c	6.4	16.6	57.2	0.863	0.204	1.07	0.263	(20)
Omeprazole	1	neutral	0.067 ^a	0.04 ^a	1	0.26	11 ^a	8.4	11.8	23.1	5.51	7.8	4.14	5.56	(21)

^aWood et al., 2017; ^bLombardo et al., 2018;

^cValues were derived from the quotient of $f_{u,p}$ or $CL_{H,p}$ and blood-to-plasma partitioning ratio (R_{BP}). For the drugs that did not have reported R_{BP} values, it was assumed to be equal to 1 for a basic or neutral compound and 0.55 (1-hematocrit) for an acidic compound; ^dValues were cited from the studies in the reference column.

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