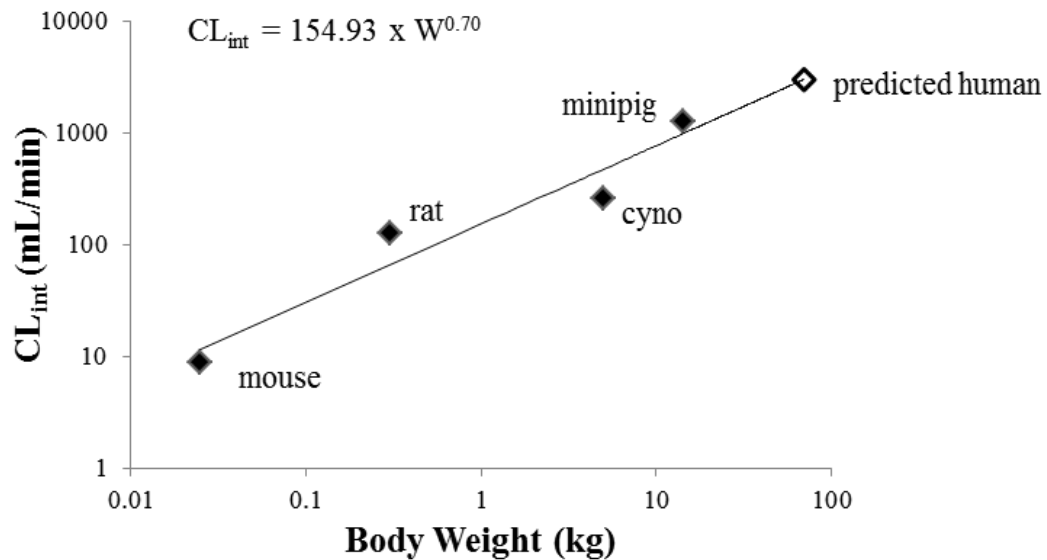


A novel in vitro allometric scaling methodology for aldehyde oxidase substrates to enable selection of appropriate species for traditional allometry

Supplemental Information.

Supplemental Figure 1.

Representative plot of S9 CL_{int} vs Body Weight to obtain the allometric coefficients a and b, used to calculate a predicted human S9 CL_{int} (eq. 6). Solid shapes represent experimental data obtained from incubations with S9 of the indicated species in the presence of NADPH. The open symbol represents the predicted human S9 CL_{int} value, calculated from the simple allometric equation.



Supplemental Table 1.

Species-specific hepatic scaling factors, hepatic blood flows, and body weights obtained from the literature for human and nonclinical species used in the estimation of hepatic intrinsic clearance (CL_{int} , eq. 1) and hepatic clearance (CL_{HEP} , eq. 2) obtained from incubations of substrate in hepatic S9 fractions.

Species	Scaling Factor (g liver/kg body weight)	Hepatic Blood Flow (mL/min/kg)	Body Weight (kg)
Mouse	87.5 ^a	90 ^a	0.02 ^a
Rat	45 ^d	70 ^c	0.25 ^{a,c}
Guinea pig	45 ^c	61 ^c	0.344 ^c
Cynomolgus	30 ^a	44 ^a	4
Rhesus	30 ^a	44 ^a	8
Minipig	17 ^b	28 ^b	14.2 ^b
Human	20 ^d	21 ^a	70 ^a

^a Davies B and Morris T. (1993). Physiological parameters in laboratory animals and humans. *Pharm Res* 10(7):1093-95.

^b Suenderhauf C and Parrott N. (2013). A physiologically based pharmacokinetic model of minipig: data compilation and model implementation. *Pharm Res* 30(1):1-15.

^c Boxenbaum H. (1980). Interspecies variation in liver weight, hepatic blood flow, and antipyrine intrinsic clearance: extrapolation of data to benzodiazepines and phenytoin. *J Pharmicokinet Biopharm* 8(2):165-76.

^d Lin JH, Chiba M, Balani SK, et al. (1996). Species differences in the pharmacokinetics and metabolism of indinavir, a potent human immunodeficiency virus protease inhibitor. *Drug Metab Dispos* 24(10):1111-20.

Supplemental Table 2. Average absolute fold-error (AAFE), average fold-error (AFE), and percentage of compounds predicted within 2 or 3 fold-error of observed CL_{int} measured in human S9, as predicted by multispecies allometry.

Multispecies simple allometry	AAFE	AFE	% within 2 fold	% within 3 fold
Minipig/Rhesus/Rat/Mouse	1.9	1.2	40%	80%
Minipig/Cyno/Rat/Mouse	2.0	1.5	40%	60%
Minipig/Rhesus/Gpig/Mouse	1.9	1.2	40%	80%
Minipig/Cyno/Gpig/Mouse	2.0	1.5	60%	60%
Rhesus/Rat/Mouse	1.7	1.7	80%	80%
Cyno/Rat/Mouse	3.3	3.3	20%	60%
Rhesus/Gpig/Mouse	2.2	1.9	60%	80%
Cyno/Gpig/Mouse	3.5	3.5	20%	40%
Minipig/Rhesus/Rat	2.3	1.2	40%	60%
Minipig/Cyno/Rat	2.4	1.4	40%	60%
Minipig/Rhesus/Gpig	2.2	1.0	40%	80%
Minipig/Cyno/Gpig	2.3	1.1	40%	60%
Minipig/Gpig/Mouse	2.4	1.0	40%	60%
Minipig/Rat/Mouse	2.3	0.92	40%	60%

Cyno = cynomolgus monkey; Gpig = guinea pig

Supplemental Figure 2. Plots of observed human S9 CL_{int} vs that predicted from multi-species allometry. Inner dotted line represents unity, solid line represents 2-fold-error, and outer dashed line represents 3-fold-error. Zaleplon (\bullet), O^6 -benzylguanine (\blacksquare), zonisipride (\circ), BIBX1382 (\square), and SGX523 (\ast). Cyno, cynomolgus monkey; Gpig, guinea pig; Mpig, minipig

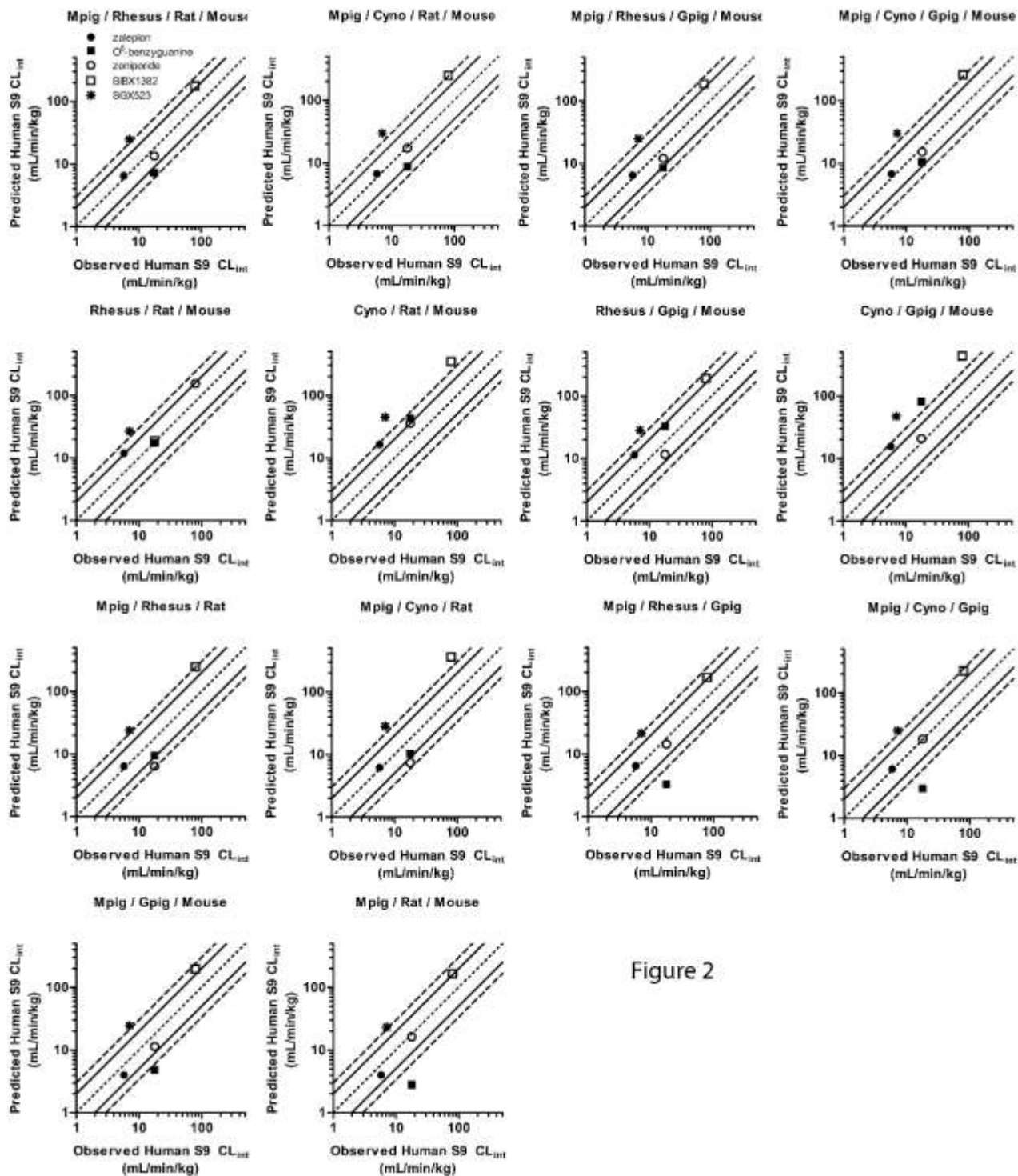


Figure 2

Supplemental Table 3.

Human predicted CL_{int}, fold-error of prediction, and allometric exponent obtained from multispecies simple allometry. Cyno, cynomolgus monkey; Gpig, guinea pig

CL _{int} (mL/min/kg)															
	Zaleplon			O ⁶ -Benzylguanine			Zoniporide			BIBX1382			SGX523		
Human Observed CL _{int}	5.8			17.8			17.9			80.2			7.1		
	Predicted CL _{int}	Fold Error	Exponent (b)	Predicted CL _{int}	Fold Error	Exponent (b)	Predicted CL _{int}	Fold Error	Exponent (b)	Predicted CL _{int}	Fold Error	Exponent (b)	Predicted CL _{int}	Fold Error	Exponent (b)
Minipig/Rhesus/Rat/Mouse	6.52	1.1	0.837	7.31	0.41	0.897	13.5	0.75	0.539	177	2.2	1.24	24.6	3.5	0.940
Minipig/Cyno/Rat/Mouse	6.82	1.2	0.837	8.82	0.49	0.908	17.3	0.97	0.571	248	3.1	1.28	29.8	4.2	0.962
Minipig/Rhesus/Gpig/Mouse	6.48	1.1	0.838	8.64	0.48	0.819	12.1	0.68	0.608	187	2.3	1.20	25.0	3.5	0.933
Minipig/Cyno/Gpig/Mouse	6.75	1.2	0.837	10.5	0.59	0.834	15.4	0.86	0.636	260	3.2	1.24	30.3	4.3	0.955
Rhesus/Rat/Mouse	11.9	2.0	0.924	18.9	1.1	1.03	17.6	1.0	0.577	155	1.9	1.22	26.8	3.8	0.952
Cyno/Rat/Mouse	16.5	2.8	0.968	43.0	2.4	1.14	35.9	2.0	0.679	348	4.3	1.33	45.0	6.4	1.02
Rhesus/Gpig/Mouse	11.5	2.0	0.921	32.5	1.8	1.01	11.6	0.65	0.602	190	2.4	1.21	28.4	4.0	0.951
Cyno/Gpig/Mouse	15.5	2.7	0.962	81.5	4.6	1.14	20.8	1.2	0.681	432	5.4	1.32	47.4	6.7	1.02
Minipig/Rhesus/Rat	6.42	1.1	0.831	9.48	0.53	1.00	6.42	0.36	0.242	247	3.1	1.37	23.9	3.4	0.929
Minipig/Cyno/Rat	6.20	1.1	0.802	10.3	0.58	0.965	7.36	0.41	0.262	359	4.5	1.41	28.4	4.0	0.945
Minipig/Rhesus/Gpig	6.50	1.1	0.839	3.27	0.18	0.431	14.4	0.81	0.677	167	2.1	1.16	21.5	3.0	0.871
Minipig/Cyno/Gpig	6.13	1.1	0.802	3.00	0.17	0.374	18.5	1.0	0.701	226	2.8	1.19	24.9	3.5	0.884
Minipig/Gpig/Mouse	3.98	0.68	0.773	4.83	0.27	0.742	11.4	0.64	0.600	197	2.5	1.21	24.5	3.5	0.930
Minipig/Rat/Mouse	3.98	0.68	0.772	2.85	0.16	0.773	16.4	0.92	0.565	165	2.1	1.23	23.2	3.3	0.932

Supplemental Table 4.Human predicted CL_{int} and fold-error of prediction obtained from single-species scaling.

CL_{int} (mL/min/kg)										
	Zaleplon		O⁶-Benzylguanine		Zoniporide		BIBX1382		SGX523	
Human Observed CL_{int}	5.8		17.8		17.9		80.2		7.1	
	Predicted CL_{int}	Fold Error	Predicted CL_{int}	Fold Error	Predicted CL_{int}	Fold Error	Predicted CL_{int}	Fold Error	Predicted CL_{int}	Fold Error
Cynomolgus monkey	9.94	1.7	20.8	1.2	30.7	1.7	88.7	1.1	21.7	3.1
Rhesus monkey	8.74	1.5	13.3	0.75	17.6	1.0	66.4	0.83	17.2	2.4
Rat	3.81	0.65	2.04	0.11	114	6.4	7.52	0.09	8.64	1.2
Mouse	3.17	0.54	2.69	0.15	43.1	2.4	4.32	0.05	5.13	0.72
Minipig	3.73	0.64	2.97	0.17	15.7	0.88	89.8	1.1	17.1	2.4
Guinea Pig	3.76	0.64	16.0	0.90	21.2	1.2	19.2	0.24	11.2	1.6