

Table A.3. Average-fold error (AFE) of human CL prediction using liver blood flow method

| Drugs | Mouse | | Rat | | Dog | | Monkey | |
|------------|-------|-------|-------|-------|-------|-------|--------|-------|
| | Small | Macro | Small | Macro | Small | Macro | Small | Macro |
| # of drugs | 36 | 25 | 78 | 40 | 78 | 19 | 63 | 43 |
| AFE | 4.04 | 2.38 | 3.47 | 1.98 | 2.83 | 2.06 | 2.02 | 1.63 |

Small, small-molecule drugs; Macro, macro-molecule drugs

Table A.4. Average-fold error (AFE) of human CL predictions using multiple species scaling: comparison of small- versus macro- molecule drugs

| | | SA | ROE | MA | SA+MA |
|----------------|----------------|------|------|------|-------|
| Small-molecule | Hepatic (n=50) | 3.14 | 2.18 | 2.37 | 2.16 |
| | Renal (n=19) | 1.84 | 1.95 | 1.73 | 1.66 |
| | Mixed (n=12) | 2.25 | 1.99 | 2.09 | 1.97 |
| | All (n=81) | 2.64 | 2.10 | 2.16 | 2.00 |
| Macro-molecule | (n=36) | 1.67 | 2.06 | 1.87 | 1.95 |

SA, simple allometry; ROE, exponent rule-corrected SA (exponent \geq 1, corrected by BRW; $0.71 \leq$ exponent $<$ 1, corrected by MLP; exponent $<$ 0.71, SA); MA, multiexponential allometry; SA+MA, exponent rule-corrected MA (exponent \geq 0.71, MA; exponent $<$ 0.71, SA).
Hepatic: drug molecules are mainly eliminated hepatically; Renal: drug molecules are mainly eliminated renally; Mixed: drug molecules are eliminated by both hepatic and renal routes.

Table A.5. Average-fold error (AFE) of human clearance predictions using multiple species scaling for small-molecule drugs mainly hepatically eliminated with low (< 0.3), medium (0.3 – 0.7), and high (> 0.7) extraction ratio

| | | SA | ROE | MA | SA+MA |
|----------------|---------------|------|------|------|-------|
| Small-molecule | Low (n=27) | 4.51 | 2.81 | 3.31 | 2.79 |
| | Medium (n=16) | 2.46 | 1.59 | 1.47 | 1.55 |
| | High (n=7) | 1.35 | 1.71 | 1.99 | 1.74 |
| | All (n=50) | 3.14 | 2.18 | 2.37 | 2.16 |

SA, simple allometry; ROE, exponent rule-corrected SA (exponent \geq 1, corrected by BRW; $0.71\leq$ exponent $<$ 1, corrected by MLP; exponent $<$ 0.71, SA); MA, multiexponential allometry; SA+MA, exponent rule-corrected MA (exponent \geq 0.71, MA; exponent $<$ 0.71, SA)

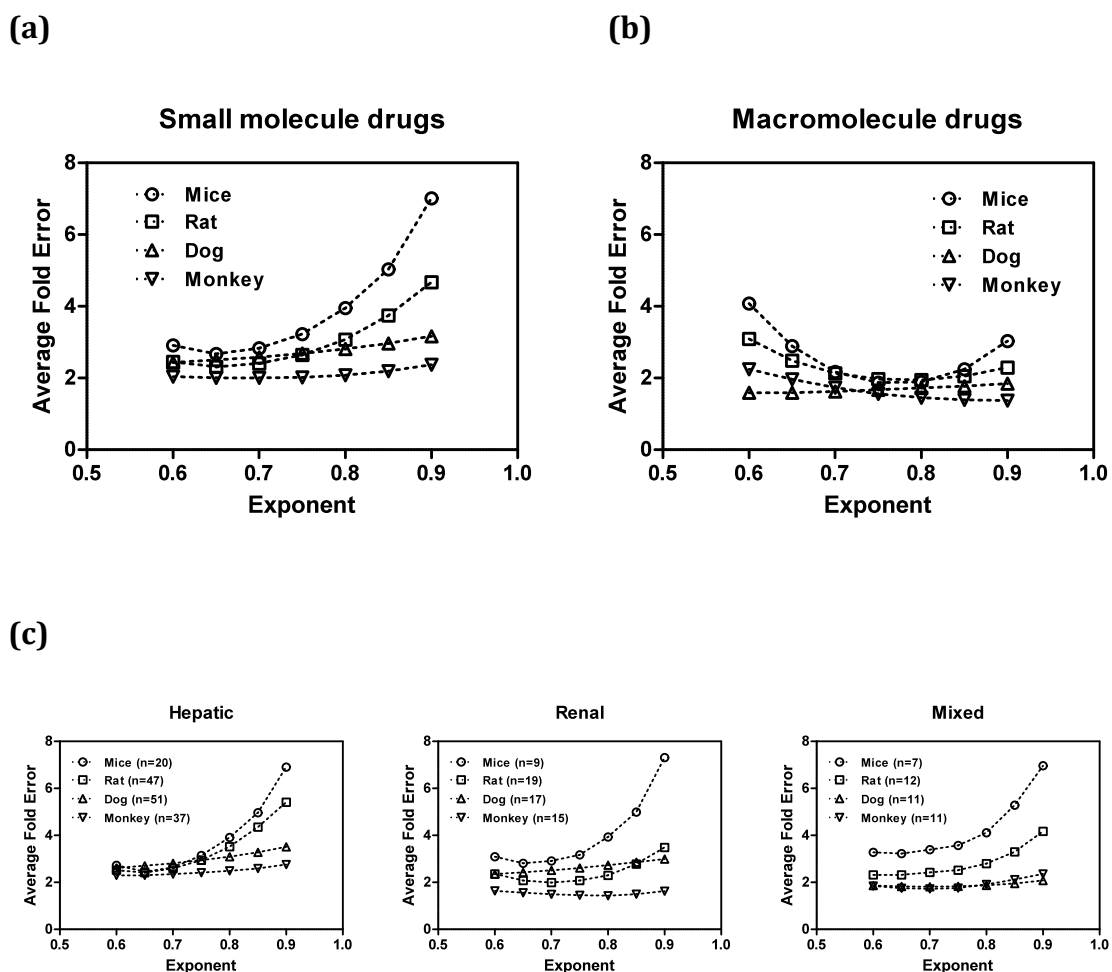


Figure A.1. Average fold-error (AFE) for human clearance predictions using single animal species with allometry exponent fixed in the range of 0.6 – 0.9.

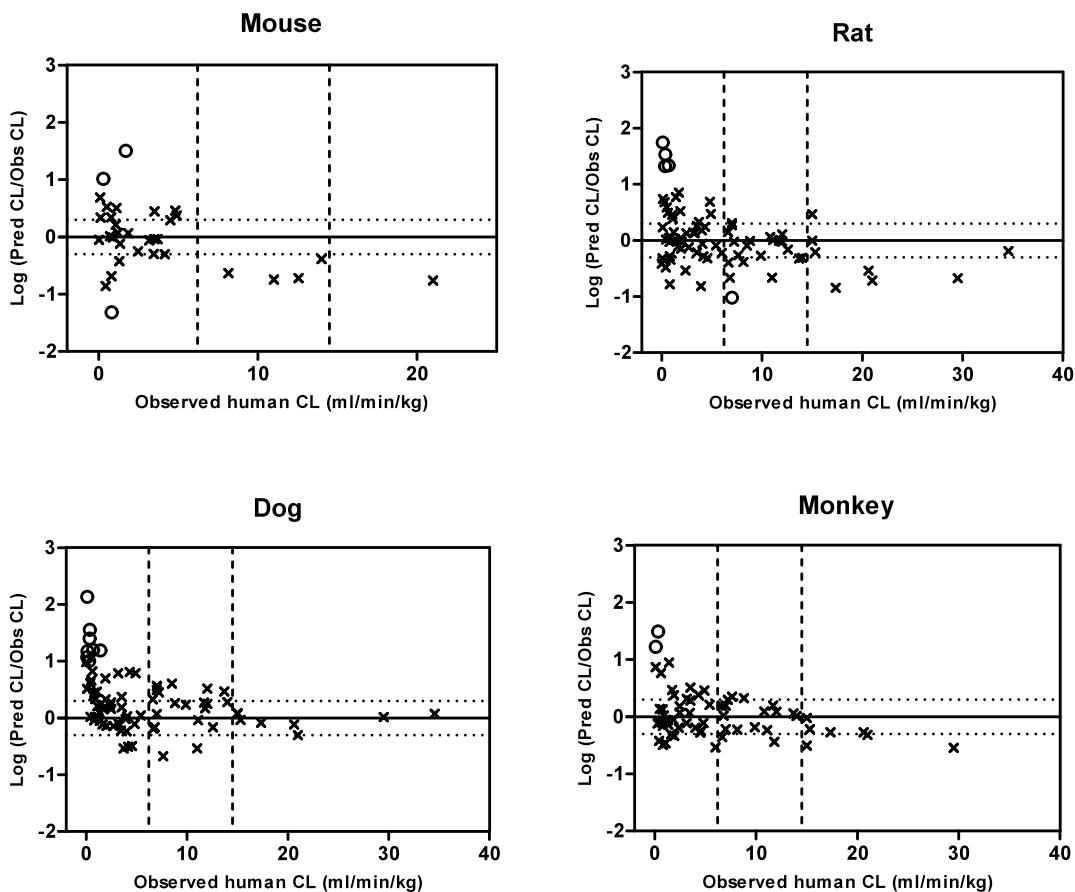


Figure A.2. Correlation between the prediction accuracy [ratio of predicted / observed (Pred/Obs)] and the observed value of human clearance (CL) for small-molecule drugs using single species allometric scaling with fixed exponent of 0.65 (the average optimal value from Figure A.1). The solid horizontal line represents the identity with Pred/Obs ratio = 1 and the upper and lower dotted horizontal lines represent 2-fold above and 2-fold below the identity, respectively. Several outliers with prediction error of greater than 10 were denoted as open circles. The two dotted vertical lines represent the criteria dividing small-molecules with low (hepatic extraction ratio < 0.3), intermediate, and high (hepatic extraction ratio > 0.7) clearance drugs.

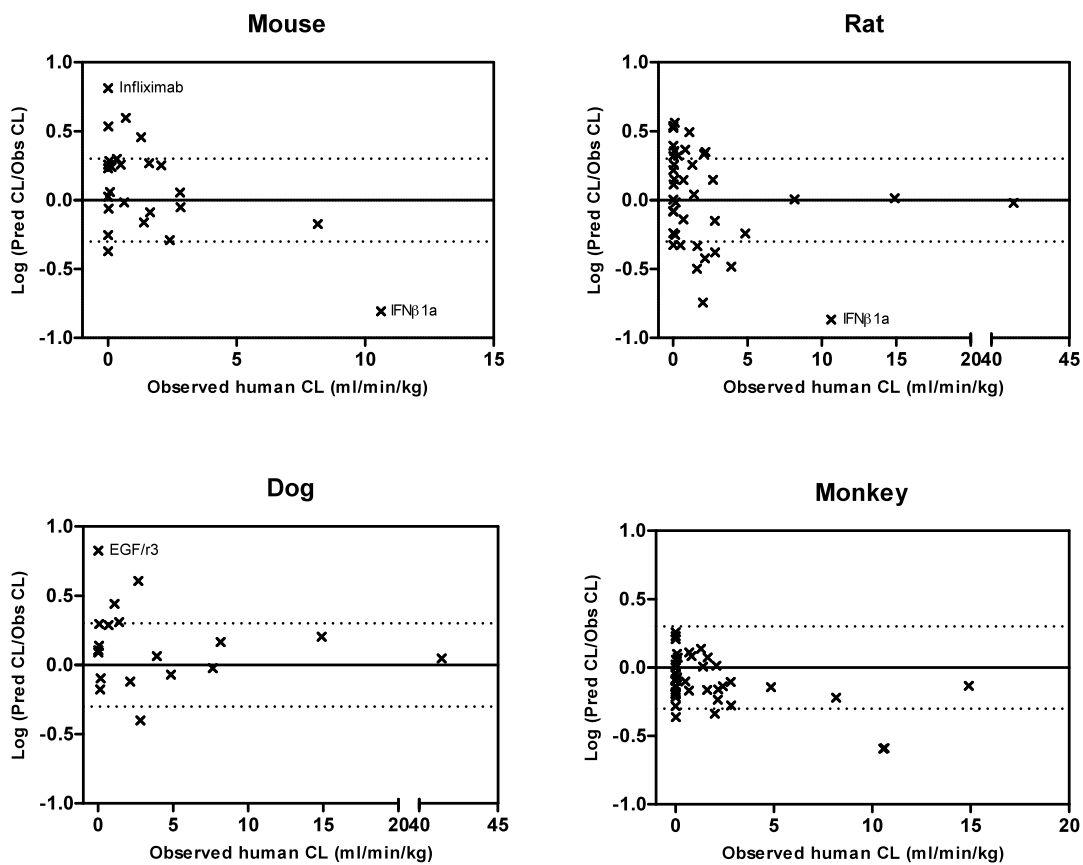


Figure A.3. Correlation between the prediction accuracy [ratio of predicted / observed (Pred/Obs)] and the observed value of human clearance (CL) for macro-molecule drugs using single species allometric scaling with fixed exponent of 0.80 (the average optimal value from Figure A.1). The solid horizontal line represents the identity with Pred/Obs ratio = 1 and the upper and lower dotted horizontal lines represent 2-fold above and 2-fold below the identity, respectively.

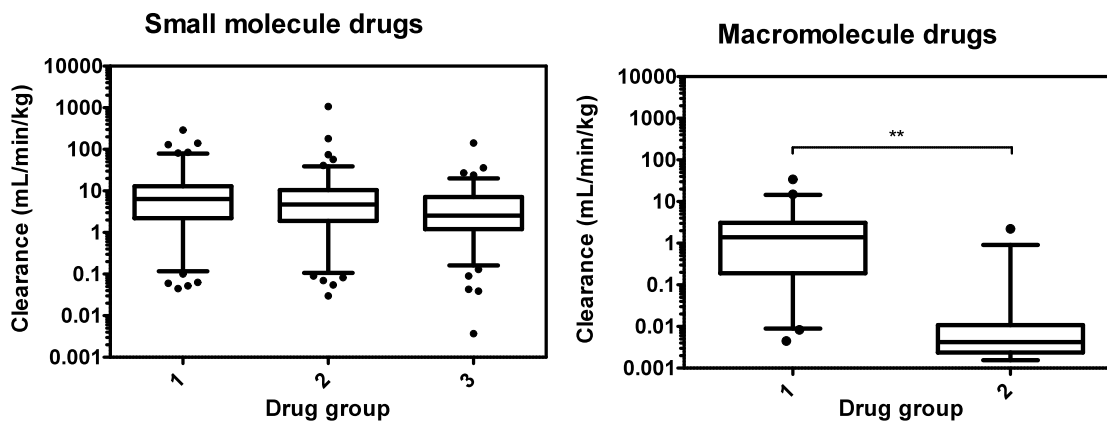


Figure A.4. Relationship between human clearance and molecular weight for small- and macro-molecule drugs. Whiskers of box and whiskers plots represent the 5 - 95th percentile of data. For small-molecules: group 1, MW < 300Da (n=233); group 2, 300 ≤ MW < 400Da (n=221); group 3, 400 ≤ MW (n=221). For macro-molecules: group 1, MW < 69kDa (n=47) and group 2 (n=30), MW ≥ 69kDa (** p < 0.01 as determined by t-test).

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