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Allometric Scaling of Xenobiotic Clearance: Uncertainty versus Universality

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ABSTRACT Statistical analysis and Monte Carlo simulation were used to characterize uncertainty in the allometric exponent (**b**) of xenobiotic clearance (CL). CL values for 115 xenobiotics were from published studies in which at least 3 species were used for the purpose of interspecies comparison of pharmacokinetics. The **b** value for each xenobiotic was calculated along with its confidence interval (CI). For 24 xenobiotics (21%), there was no correlation between log CL and log body weight. For the other 91 cases, the mean ± standard deviation of the **b** values was 0.74 ± 0.16; range: 0.29 to 1.2. Most (81%) of these individual **b** values did not differ from either 0.67 or 0.75 at $P = 0.05$. When CL values for the subset of 91 substances were normalized to a common body weight coefficient (**a**), the **b** value for the 460 adjusted CL values was 0.74; the 99% CI was 0.71 to 0.76, which excluded 0.67. Monte Carlo simulation indicated that the wide range of observed **b** values could have resulted from random variability in CL values determined in a limited number of species, even though the underlying **b** value was 0.75. From the normalized CL values, 4 xenobiotic subgroups were examined: those that were (i) protein, and those that were (ii) eliminated mainly by renal excretion, (iii) by metabolism, or (iv) by renal excretion and metabolism combined. All subgroups except (ii) showed a **b** value not different from 0.75. The **b** value for the renal excretion subgroup (21 xenobiotics, 105 CL values) was 0.65, which differed from 0.75 but not from 0.67.

KEYWORDS: allometric scaling, body-weight exponent, clearance, metabolism, metabolic rate, pharmacokinetics, Monte Carlo simulation, power law

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INTRODUCTION

Biological structures and processes ranging from cellular metabolism to population dynamics are affected by the size of the organism[1,2] . Although the sizes of mammalian species span 7 orders of magnitude, interspecies similarities in structural, physiological, and biochemical attributes result in an empirical power law (the allometric equation) that characterizes the dependency of biological variables on body mass:

$$Y = a\,BW^{b}$$

where Y is the dependent biological variable of interest, **a** is a normalization constant known as the allometric coefficient, BW is the body weight, and **b** is the allometric exponent. The exponential form can be transformed into a linear function:

$$\text{Log } Y = \text{Log } \mathbf{a} + \mathbf{b}\,(\text{Log BW}),$$

and **a** and **b** can be estimated from the intercept and slope of a linear regression analysis. The magnitude of **b** characterizes the rate of change of a biological variable subjected to a change of body mass and reflects the geometric and dynamic constraints of the body[3,4] .

Although allometric scaling of physiological parameters has been a century-long endeavor, no consensus has been reached as to whether a universal scaling exponent exists. In particular, discussion has centered on whether the basal metabolic rate scales as the 2/3 or 3/4 power of the body mass[1,2,3-9] .

Allometric scaling has been applied in pharmacokinetics for approximately 2 decades. The major interest has been prediction of pharmacokinetic parameters in man from parameter values determined in animals[10-15] . Clearance has been the most studied parameter, as it determines the drug-dosing rate. In most cases, the pharmacokinetics of a new drug was studied in several animal species, and the allometric relationship between pharmacokinetic parameters

and body weight was determined using linear regression of the log-transformed data. One or more of the following observations apply to most such studies: (i) Little attention was given to uncertainty in the **a** and **b** values; although the correlation coefficient was frequently reported, the confidence intervals of the **a** and **b** values were infrequently addressed. (ii) The **a** and **b** values were used for interspecies extrapolation of pharmacokinetics without analysis of the uncertainty in the predicted parameter values. (iii) The **b** value of clearance was compared with either the value 2/3 from "surface law" or 3/4 from "Kleiber's law" and the allometric scaling of basal metabolic rate.

This paper addresses the possible impact of the uncertainty in allometric scaling parameters on predicted pharmacokinetic parameter values. We combined a statistical analysis of the allometric exponent of clearance from 115 xenobiotics and a Monte Carlo simulation to characterize the uncertainty in the allometric exponent for clearance and to investigate whether a universal exponent may exist for the scaling of xenobiotic clearance.

MATERIALS AND METHODS

Data collection and statistical analysis

Clearance (CL) and BW data for 115 substances were collected from published studies in which at least 3 animal species were used for the purpose of interspecies comparison of pharmacokinetics[16-90]. A total of 18 species (16 mammals, 2 birds) with body weights spanning 10^4 were involved (**Table 1**). Previously published studies generally did not control or standardize across species the (i) dosage, (ii) numbers of individuals studied per species, (iii) principal investigator, (iv) blood sampling regime, or (v) gender.

Table 1. Allometric Scaling Parameters Obtained from Linear Regressions of the Log-Log-Transformed CL versus BW Data of 115 Xenobiotics (a: allometric coefficient; b: allometric exponent) (Table located at the end of article).

Linear regression was performed on the log-transformed data according to the equation, Log CL = log **a** + **b** * log BW. Values for **a** and **b** were obtained from the intercept and the slope of the regression, along with the coefficient of determination (r^2). Statistical inferences about **b** were performed in the following form:

$H_0 : \mathbf{b} = ß_i$

$H_1 : \mathbf{b} \neq ß_i$, i = 0, 1, 2

Where $ß = 0$, $ß_1 = 2/3$, and $ß_2 = 3/4$, respectively. The 95% and 99% confidence intervals (CI) were also calculated for each b value. In addition, the CL values for each individual xenobiotic were normalized so that all compounds had the same a value. Linear regression analysis was applied to the pooled, normalized CL versus BW data for the 91 xenobiotics that showed statistically significant correlation between log CL and log BW in Table 1 .

Monte Carlo simulation

The power function CL = **a** BW **b** was used to generate a set of error-free CL versus BW data. The values for BW were 0.02, 0.25, 2.5, 5, 14, and 70 kg, which represented the body weights of mouse, rat, rabbit, monkey, dog, and human, respectively. The values of **a** and **b** used in the simulation were 100 and 0.75, respectively. Random error was added to the calculated CL values, assuming a normal distribution of error with either a 20% or a 30% coefficient of variation (CV), using the function RANDOM in Mathematica 4.0. (Wolfram Research, Champaign, IL) The **b** and *r* values were obtained by applying linear regression analyses on the log-log-transformed error-containing CL versus BW data using the Mathematica function REGRESS. Ten scenarios with a variety of sampling regimens that covered different numbers of animal species (3-6) with various body weight ranges (varying 5.6- to 3500-fold) were simulated (n = 100 per scenario). The simulations mimicked the sampling patterns commonly adopted in the published interspecies pharmacokinetics studies.

RESULTS

The allometric scaling parameters and their statistics are listed in **Table 1** . Of 115 compounds, 24 (21%) showed no correlation between clearance and body weight; in other words, there was a lack of statistical significance for the regression ($P > 0.05$). This generally occurred when only 3 species were used. Among the remaining 91 cases, the mean ± standard deviation of the **b** values was 0.74 ± 0.16 with a wide range from 0.29 to 1.2 (**Figure 1**). The frequency distribution of the **b** values appeared to be Gaussian. The mean significantly differed from 0.67 ($P < 0.001$) but not from 0.75. When the **b** value of each substance was tested

statistically against both 0.67 and 0.75, the majority of the cases (81% and 98% at the level of significance equal to 0.05 and 0.01, respectively) failed to reject the null hypotheses raised against both values (**Table 1**); in other words, individual **b** values did not differ from 0.67 and 0.75. The wide range for **b** of 95% and 99% CI highlighted the uncertainty associated with the determination of **b** values in most studies.

The 10 animal groups studied by Monte Carlo simulation had mean **b** values (n = 100 per simulation) close to the assigned true value, 0.75 (**Table 2**). However, the 95% CI in the majority of the scenarios failed to distinguish the expected value 0.75 from 0.67. Only Scenario 3 at the level of 20% CV excluded the possibility that **b** was 0.67 with 95% confidence. When the experimental error was set at 30% CV, none of the simulations distinguished between **b** values of 0.67 and 0.75 with 95% confidence. The mean r values ranged from 0.925 to 0.996, suggesting that the simulated experiments with a 20% and a 30% CV in experimental bias were not particularly noisy. The frequency distributions of **b** values are shown in **Figure 2** .

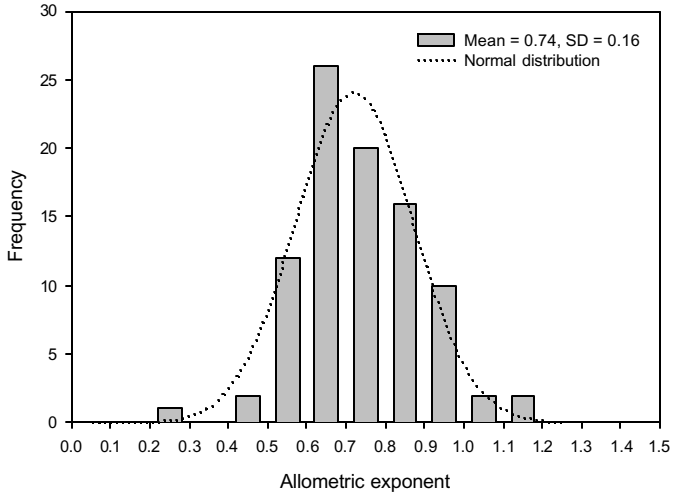

Figure 1.The frequency distribution of the b values for the 91 xenobiotics that showed statistically significant correlation between log clearance (CL) and log body weight (BW) in Table 1 . The frequency of the b values from 0.2 to 1.2, at an interval of 0.1, was plotted against the midpoint of each interval of b values. The dotted line represents a fitted Gaussian distribution curve. SD = standard deviation.

Table 2. Simulated b Values in Different Scenarios with Varied Body Weight Ranges

								$b^{\dagger}$		$r^{\dagger\dagger}$	
Scenarios*	***ms***	***rt***	***rb***	***mk***	***dg***	***hm***	***Range*****	**20% CV**	**30% CV**	**20% CV**	**30% CV**
1	·	·	·				**125**	**0.75** (0.63–0.87)	**0.74** (0.53–0.95)	**0.996**	**0.986**
2	·	·	·	·			**250**	**0.74** (0.64–0.84)	**0.74** (0.58–0.91)	**0.994**	**0.988**
3	·	·	·	·	·		**700**	**0.75** (0.67–0.83)	**0.75** (0.62–0.88)	**0.996**	**0.990**
4	·	·	·	·	·	·	**3500**	**0.75** (0.69–0.81)	**0.75** (0.62–0.88)	0.996	**0.989**
5		·	·	·			**20**	**0.76** (0.57–0.94)	**0.72** (0.29–1.2)	**0.992**	**0.954**
6		·	·	·	·		**56**	**0.75** (0.60–0.88)	**0.73** (0.50–0.95)	**0.990**	**0.968**
7		·	·	·	·	·	**280**	**0.75** (0.65–0.85)	**0.76** (0.58–0.93)	**0.992**	**0.980**
8			·	·	·		**5.6**	**0.80** (0.50–1.1)	**0.74** (0.23–1.3)	**0.974**	**0.925**
9			·	·	·	·	**28**	**0.74** (0.58–0.90)	**0.75** (0.47–1.0)	**0.987**	**0.971**
10				·	·	·	**14**	**0.74** (0.50–0.98)	**0.73** (0.44–1.0)	**0.988**	**0.969**

*** ms: mouse, 0.02 kg; rt: rat, 0.25 kg; rb: rabbit, 2.5 kg; mk: monkey, 5 kg; dg: dog, 14 kg; hm: human, 70 kg. ; ** Range = maximum body weight/minimum body weight in each scenario; † The mean b value with 95% confidence interval (boldface in parentheses) was obtained from 100 simulations where linear regression analyses were applied to the log-log-transformed CL versus BW data with either a 20% or a 30% coefficient of variation (CV) in clearance; †† The mean correlation coefficient (r) of linear regression from 100 simulated experiments per scenario.**

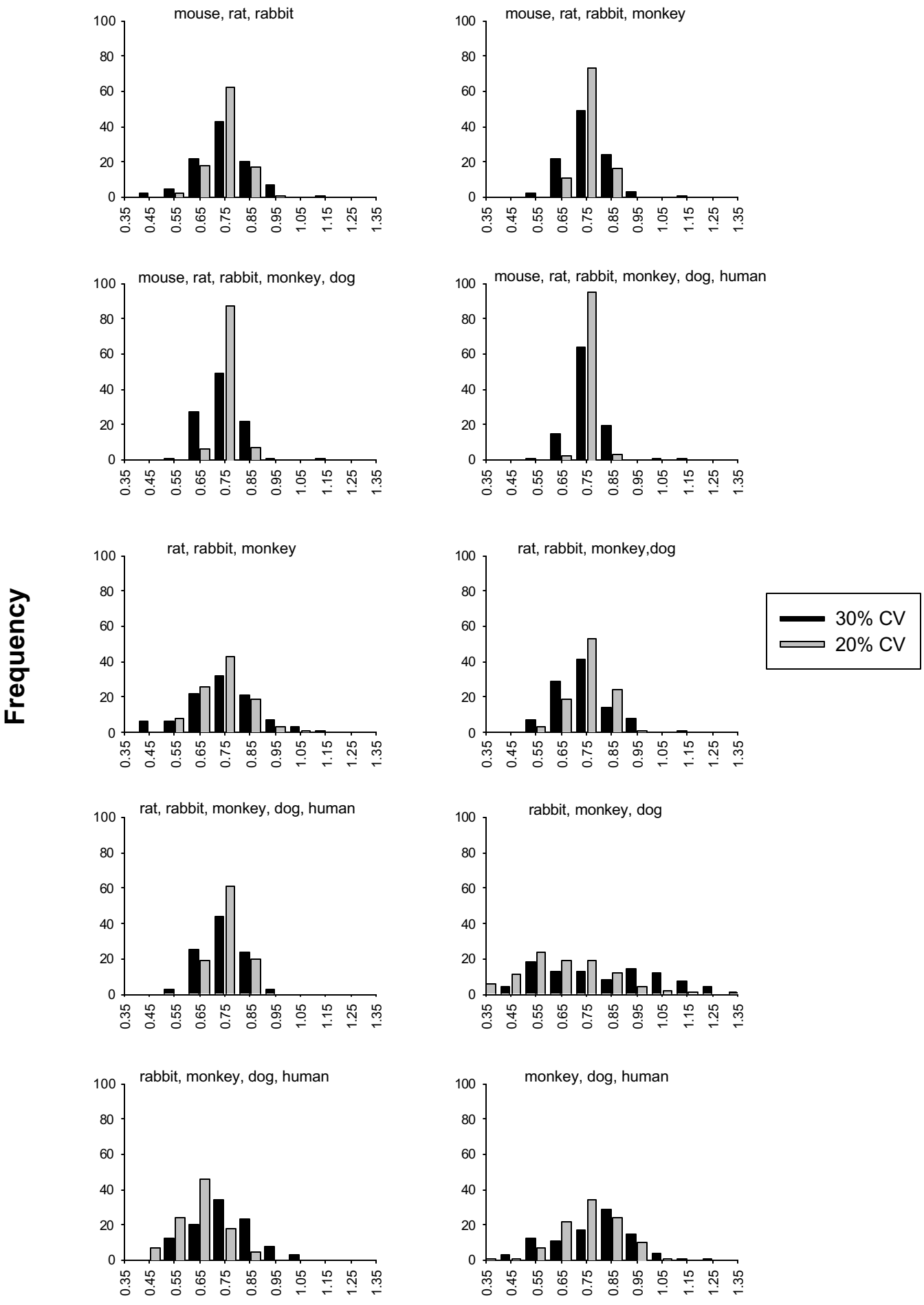
mouse, rat, rabbit
mouse, rat, rabbit, monkey
mouse, rat, rabbit, monkey, dog
mouse, rat, rabbit, monkey, dog, human
rat, rabbit, monkey
rat, rabbit, monkey,dog
rat, rabbit, monkey, dog, human
rabbit, monkey, dog
rabbit, monkey, dog, human
monkey, dog, human
Frequency
30% CV
20% CV

Figure 2 (previous page). The frequency distribution of the simulated b values in the 10 scenarios where the number of animal species and the range of body weight were varied. The b values were obtained by applying linear regression analyses on the log-log-transformed, error-containing clearance (CL) versus body weight (BW) data with either a 20% (gray) or a 30% (black) coefficient of variation (CV) in CL.

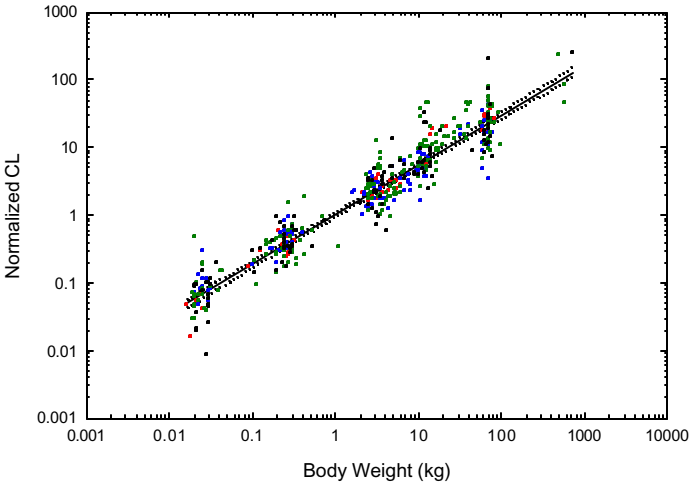

Figure 3. The relationship between normalized clearances ($CL_{normalized}$) and body weights (BW) for the 91 xenobiotics (n = 460) that showed statistically significant correlation between log CL and log BW in Table 1 . The relationship follows the equation: log $CL_{normalized}$ = 0.74 log BW + 0.015, r^2 = 0.917. The 99% confidence interval of the regression slope was 0.71 to 0.76. The different colors represent different subgroups of xenobiotics: red, protein; blue, xenobiotics that were eliminated mainly (< 70%) by renal excretion; green, xenobiotics that were eliminated mainly (< 70%) by metabolism; black, xenobiotics that were eliminated by both renal excretion and metabolism. The result of each subgroup can be viewed in the Web version by moving the cursor to each symbol legend.

Table 3. Summary of the Statistical Results in Figure 3.

Group*	No. of Xenobiotics	No. of Data Points	Slope, b	(95% CI)	(99% CI)
1	9	41	0.78	0.73–0.83	0.72–0.84
2	21	105	0.65	0.62–0.69	0.61–0.70
3	39	203	0.75	0.72–0.78	0.70–0.79
4	22	111	0.76	0.71–0.81	0.70–0.82
Overall	91	460	0.74	0.72–0.76	0.71–0.76

Note: CI = confidence interval

* Group 1 = protein; group 2 = xenobiotics that were eliminated mainly by renal excretion; group 3 = xenobiotics that were eliminated mainly by extensive metabolism; group 4 = xenobiotics that were eliminated by both renal excretion and nonrenal metabolism

Figure 3 shows the relationship between normalized clearances and body weights (n = 460) for the 91 xenobiotics that showed a statistically significant correlation in **Table 1** . The regression slope was 0.74, and the 99% CI was 0.71 to 0.76. The normalized clearances were divided into four groups: 9 proteins (Group 1, n = 41), 21 compounds eliminated mainly via renal excretion (Group 2, n = 105), 39 compounds eliminated mainly via extensive metabolism (Group 3, n = 203), and 22 compounds eliminated by both renal excretion and metabolism (Group 4, n = 111) (**Figure 3**). The summary of the regression results appears in **Table 3** . While Groups 1, 3, and 4 had **b** values close to 0.75 and significantly different from 0.67 ($P < 0.001$), Group 2 had a **b** value close to 0.67 and significantly different from 0.75 ($P < 0.001$).

DISCUSSION

Successful prediction of human clearance values using allometric scaling and clearance values measured in animals depends heavily on the accuracy of the **b** value. Retrospective analysis of published results for 115 substances indicated that the commonly used experimental designs result in considerable uncertainty for this parameter (**Table 1**).

CL values for 24 of the substances listed in **Table 1** failed to follow the allometric equation at the 95% confidence level. The failures appeared to result from the following factors: (i) Only 3 species were studied in 16 cases, which severely limited the robustness of the statistics. In the remaining 8 failed cases, 1 or more of the following occurred: (ii) The species were studied in different labs in 3 cases, (iii) small (n = 2) or unequal (n = 2-10) numbers of animals per species were studied in 4 cases, (iv) different dosages among species were used in 2 cases, and (v) high interspecies variability in UDP-glucuronosyltransferase activity was proposed in 1 case[75] . The failure of these 24 cases to follow the allometric equation appeared for the most part, therefore, to result from deficiencies in experimental design-in other words, failure of detection rather than failure of the particular substance's CL to follow the allometric relationship.

How well did allometry applied to animal CL values predict the human CL value? One indication is how close the human CL value fell to the fitted line. Of the 91 substances that followed the allometric equation, 68 included human as 1 of the species. In 41 cases, the human CL value fell below the line, and in 27 cases it fell above (**Figure 4**). The mean deviation was only 0.62%, and the majority of deviations were less than 50%. It therefore appeared that for most of the 68 substances studied with human as one of the species, the human CL value did not deviate systematically or extraordinarily from the fitted allometric equation. The tendency, noted by others[10,12] , of the CL value for human to be lower than that predicted from animal CL values was therefore not apparent in this large data set.

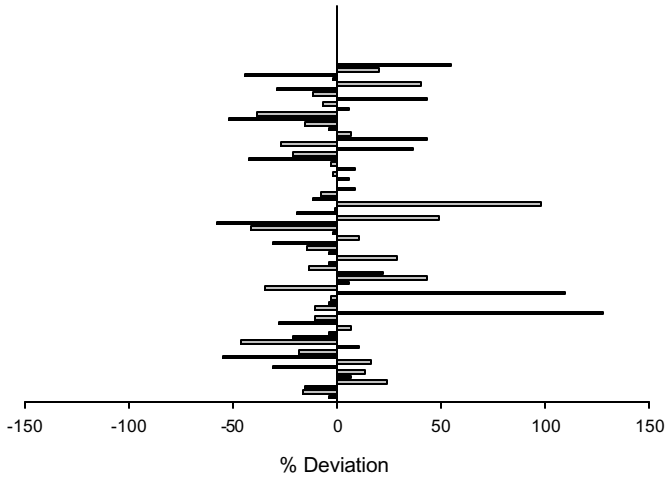

Figure 4.The deviation between the fitted and the observed human clearance (CL) for 68 xenobiotics. The fitted human CL of each xenobiotic was obtained by applying linear regression on the log-log-transformed CL versus BW data from different animal species including human. The deviation was calculated as 100*($CL_{observed}$ - CL_{fitted})/CL_{fitted} . The mean deviation was 0.62%.

The **b** values for the 91 substances that followed the allometric equation appeared to be normally distributed around a mean value of 0.74, but the range of values was quite broad (**Figure 1**). Although impossible to answer definitively with these data, the question of whether there is a "universal" **b** value is of interest. Does the distribution shown in **Figure 1** reflect a universal value with deviation from the mean due to measurement errors, or are there different **b** values for the various mechanisms involved in clearance? The Monte Carlo simulations indicated that introduction of modest amounts of random error in CL determinations (**Figure 2**) resulted in a distribution of **b** values not unlike that shown in **Figure 1** . This result supported the possibility that a universal **b** value operates and that the range of values seen in **Table 1** resulted from random error in CL determination coupled with the uncertainty that accrued from use of a limited number of species. However, examination of subsets of the 91 substances segregated by elimination pathway showed a **b** value around 0.75, except for substances cleared primarily by the kidneys; the **b** value for this subgroup was 0.65 (see below), and the CI excluded a value larger than 0.70.

The central tendency of the **b** values is of interest, particularly given the recent interest in the question of whether basal metabolic rate scales with a **b** value of 0.67 or 0.75[3,4,8,9] . When examined individually, the 95% CI of the **b** values for most of the 91 substances included both values, although the mean for all the **b** values tended toward 0.75. So that all CL values could be viewed together, a normalization process was used that assumed a common a value for all 91 substances, and CL values were adjusted accordingly (**Figure 3**). Fit of the allometric equation to this data set gave a **b** value of 0.74, and its CI included 0.75 and excluded 0.67. Normalized CL values were randomly scattered about the line, with one exception: In the body weight range 20 to 50 kg (dog, minipig, sheep, and goat), the normalized CL values generally fell above the line.

The 91 substances were segregated by molecular size (protein) and by major elimination pathway (renal excretion, metabolism, combination of both) (**Figure 3**). With the exception of the renal excretion subgroup, the normalized CL values for the subgroups showed **b** values similar to the combined group and their CIs included 0.75 and excluded 0.67 (**Table 3**). The renal excretion subgroup (21 substances and 105 CL values), however, showed a **b** value of 0.65 with a CI that excluded 0.75. This result was surprising as it appeared to contradict **b** values of 0.77 reported for

both mammalian glomerular filtration rate and effective renal plasma flow[91-93] , although it was consistent with a **b** value of 0.66 reported for intraspecies scaling of inulin-based glomerular filtration rate in humans[94] and with a **b** value of 0.69 for scaling creatinine clearance[95] .

Whether the metabolic rate scales to the 2/3 or the 3/4 power of body weight has been the subject of debate for many years. No consensus has been reached. The surface law that suggested a proportional relationship between the metabolic rate and the body surface area was first conceptualized in the 19th century. It has gained support from empirical data[6, 96] as well as statistical[6,9] and theoretical[6, 97] results. In 1932, Kleiber's empirical analysis led to the 3/4-power law, which has recently been generalized as the quarter-power law by West et al.[3,4] . Different theoretical analyses based on nutrient-supply networks[3,8] and 4-dimensional biology[4] all suggested that the quarter-power law is the universal scaling law in biology[98] . However, the claim of universality was challenged by Dodds et al.[9] , whose statistical and theoretical reanalyses cannot exclude 0.67 as the scaling exponent of the basal metabolic rate.

The logic behind the pursuit of a universal law for the scaling of energy metabolism across animal species is mainly based on the assumption that an optimal design of structure and function operates across animal species[3,4,8, 99-101] . Given the fact that all mammals use the same energy source (oxygen) and energy transport systems (cardiovascular, pulmonary) and given the possibility that evolutionary force may result in a design principle that optimizes energy metabolism systems across species, the existence of such a law might be possible. However, available data and analyses have not led to a conclusion.

A large body of literature data has indicated that the allometric scaling relationship applies to the clearance of a variety of xenobiotics. It has been speculated that xenobiotic clearance is related to metabolic rate, and clearance **b** values have frequently been compared with either 0.67 or 0.75. The **b** values obtained from the scaling of clearance for a variety of xenobiotics tended to be scattered. Our analysis indicated that the **b** value generally fell within a broad range between 0 and 1 or even higher. The scatter of **b** values may have resulted from the uncertainty that accrued from the regression analysis of a limited number of data points as discussed above. In addition, the scatter may have involved the variability in pharmacokinetic properties among different xenobiotics. This variability rendered the prediction of the **b** value extremely difficult. Moreover, the discussion of "universality" of the **b** value was less possible in this regard. From the pharmacokinetics point of view, lack of a unique **b** value for all drugs may be considered as a norm. In this regard, the uncertainty and variability became a universal phenomenon. To determine whether a unique **b** value exists for the scaling of CL, a more rigorous experimental design has to be included to control the uncertainty that may obscure the conclusion. Although a study that includes the CL data for a variety of drugs covering the animal species with a scope similar to that of its counterpart in scaling basal metabolic rate might be sufficient, it would also be extremely unrealistic. Therefore, from the perspective of pharmacokinetics where the drug is the center of discussion, it is almost impossible to address whether the **b** value of CL tended to be dominated by 1 or 2 values. However, from the perspective of physiology where the function of a body is of interest, systematic analysis of currently available data in interspecies scaling of CL may provide some insight into the interspecies scaling of energy metabolism. The rationale behind this line of reasoning was that the elimination of a xenobiotic from a body is a manifestation of physiological processes such as blood flow and oxygen consumption. Interestingly, the two competitive exponent values, but not others, in theorizing the scaling of energy metabolism reappeared in our analysis. The value 0.75 appeared to be the central tendency of the **b** values for the CL of most compounds, except for that of drugs whose elimination was mainly via kidney.

CONCLUSION

Whether allometric scaling could be used for the prediction of the first-time-in-man dose has been debated[102,103] . **Figure 4** shows that a reasonable error range can be achieved when human CL is predicted by the animal data for some drugs.

However, the success shown in the retrospective analysis does not necessarily warrant success in prospective applications. As indicated by our analyses on the uncertainty of **b** values and as illustrated in Bonate and Howard's commentary[102], caution is needed when allometric scaling is applied in a prospective manner. In addition, the use of a deterministic equation in predicting individual CL data may be questionable because the intersubject variability cannot be accounted for. Nevertheless, allometric scaling could be an alternative tool, if the mean CL for a population is to be estimated and if the uncertainty is adequately addressed. When the uncertainty in the determination of a **b** value is relatively large, a fixed-exponent approach might be feasible. In this regard, 0.75 might be used for substances that are eliminated mainly by metabolism or by metabolism and excretion combined, whereas 0.67 might apply for drugs that are eliminated mainly by renal excretion.

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REFERENCES

1. Schmidt-Nielsen K. Scaling: Why Is Animal Size So Important? Princeton, NJ: Cambridge University Press, 1983.

2. Calder WA III. Size, Function and Life History. Cambridge, MA: Harvard University Press, 1984.

3. West GB, Brown JH, Enquist BJ. A general model for the origin of allometric scaling laws in biology. Science. 1997;276:122-126.

4. West GB, Brown JH, Enquist BJ. The fourth dimension of life: Fractal geometry and allometric scaling of organisms. Science. 1999;284:1677-1679.

5. Kleiber M. Body size and metabolism. Hilgardia. 1932;6:315-353.

6. Heusner AA. Energy metabolism and body size. I. Is the 0.75 mass exponent of Kleiber's equation a statistical artifact? Respir Physiol. 1982;48:1-12.

7. Feldman HA, McMahon TA. The 3/4 mass exponent for energy metabolism is not a statistical artifact. Respir Physiol. 1983;52:149-163.

8. Banavar JR, Maritan A, Rinaldo A. Size and form in efficient transportation networks. Nature. 1999;399:130-132.

9. Dodds PS, Rothman DH, Weitz JS. Re-examination of the "3/4-law" of metabolism. J Theor Biol. 2001;209:9-27.

10.Boxenbaum H. Interspecies scaling, allometry, physiological time, and the ground plan of pharmacokinetics. J Pharmacokin Biopharm. 1982;10:201-227.

11.Sawada Y, Hanano M, Sugiyama Y, Iga T. Prediction of disposition of beta-lactam antibiotics in humans from pharmacokinetic parameters in animals. J Pharmacokin Biopharm. 1984;12:241-261.

12.Mordenti J. Man versus beast: Pharmacokinetic scaling in mammals. J Pharm Sci. 1986;75:1028-1040.

13.Mahmood I, Balian JD. Interspecies scaling: Prediction clearance of drugs in humans. Three different approaches. Xenobiotica. 1996;26:887-895.

14.Feng MR, Lou X, Brown RR, Hutchaleelaha A. Allometric pharmacokinetic scaling: Towards the prediction of human oral pharmacokinetics. Pharm Res. 2000;17:410-418.

15.Mahmood I. Interspecies scaling of renally secreted drugs. Life Sci. 1998;63:2365-2371.

16.McGovren SP, Williams MG, Stewart JC. Interspecies comparison of acivicin pharmacokinetics. Drug Metab Dispo. 1988;16:18-22.

17.Brazzell RK, Park YH, Wooldridge CB, et al. Interspecies comparison of the pharmacokinetics of aldose reductase inhibitors. Drug Metab Dispos. 1990;18:435-440.

18.Bjorkman S, Redke F. Clearance of fentanyl, alfentanil, methohexitone, thiopentone and ketamine in relation to estimated hepatic blood flow in several animal species: Application to prediction of clearance in man. J Pharm Pharmacol. 2000;52:1065-1074.

19.Cherkofsky SC. 1-Aminocyclopropanecarboxylic acid: Mouse to man interspecies pharmacokinetic comparisons and allometric relationships. J Pharm Sci. 1995;84:1231-1235.

20.Robbie G, Chiou WL. Elucidation of human amphotericin B pharmacokinetics: Identification of a new potential factor affecting interspecies pharmacokinetic scaling. Pharm Res. 1998;15:1630-1636.

21.Paxton JW, Kim SN, Whitfield LR. Pharmacokinetic and toxicity scaling of the antitumor agents amsacrine and CI-921, a new analogue, in mice, rats, rabbits, dogs, and humans. Cancer Res. 1990;50:2692-2697.

22.GreneLerouge NAM, Bazin-Redureau MI, Debray M, Schermann JM. Interspecies scaling of clearance and volume of distribution for digoxin-specific Fab. Toxicol Appl Pharmacol. 1996;138:84-89.

23.Lave T, Dupin S, Schmidt C, Chou RC, Jaeck D, Coassolo PH. Integration of in vitro data into allometric scaling to predict hepatic metabolic clearance in man: Application to 10 extensively metabolized drugs. J Pharm Sci. 1997;86:584-590.

24.Bazin-Redureau M, Pepin S, Hong G, Debray M, Scherrmann JM. Interspecies scaling of clearance and volume of distribution for horse antivenom $F(ab')_2$. Toxicol Appl Pharmacol. 1998;150:295-300.

25.Lashev LD, Pashov DA, Marinkov TN. Interspecies differences in the pharmacokinetics of kanamycin and apramycin. Vet Res Comm. 1992;16:293-300.

26.Patel BA, Boudinot FD, Schinazi RF, Gallo JM, Chu CK. Comparative pharmacokinetics and interspecies scaling of 3'-azido-3'-deoxy-thymidine (AZT) in several mammalian species. J Pharmacobio-Dyn. 1990;13:206-211.

27.Kurihara A, Naganuma H, Hisaoka M, Tokiwa H, Kawahara Y. Prediction of human pharmacokinetics of panipenem-betamipron, a new carbapenem, from animal data. Antimicrob Ag Chemother. 1992;36:1810-1816.

28.Mehta SC, Lu DR. Interspecies pharmacokinetic scaling of BSH in mice, rats, rabbits, and humans. Biopharm Drug Dispos. 1995;16:735-744.

29.Bonati M, Latini R, Tognoni G. Interspecies comparison of in vivo caffeine pharmacokinetics in man, monkey, rabbit, rat, and mouse. Drug Metab Rev. 1984-85;15:1355-1383.

30.Kaye B, Brearley CJ, Cussans NJ, Herron M, Humphrey MJ, Mollatt AR. Formation and pharmacokinetics of the active drug candoxatrilat in mouse, rat, rabbit, dog and man following

administration of the produg candoxatril. Xenobiotica. 1997;27:1091-1102.

31.Mordenti J, Chen SA, Moore JA, Ferraiolo BL, Green JD. Interspecies scaling of clearance and volume of distribution data for five therapeutic proteins. Pharm Res. 1991;8:1351-1359.

32.Sawada Y, Hanano M, Sugiyama Y, Iga T. Prediction of the disposition of β-lactam antibiotics in humans from pharmacokinetic parameters in animals. J Pharmacokinet Biopharm. 1984;12:241-261.

33.Matsushita H, Suzuki H, Sugiyama Y, et al. Prediction of the pharmacokinetics of cefodizime and cefotetan in humans from pharmacokinetic parameters in animals. J Pharmacobio-Dyn. 1990;13:602-611.

34.Mordenti J. Pharmacokinetic scale-up: Accurate prediction of human pharmacokinetic profiles from animal data. J Pharm Sci. 1985;74:1097-1099.

35.Feng MR, Loo J, Wright J. Disposition of the antipsychotic agent CI-1007 in rats, monkeys, dogs, and human cytochrome p450 2D6 extensive metabolizers: Species comparison and allometric scaling. Drug Metab Dispos. 1998;26:982-988.

36.Hildebrand M. Inter-species extrapolation of pharmacokinetic data of three prostacyclin-mimetics. Prostaglandins. 1994;48:297-312.

37.Ericsson H, Tholander B, Bjorkman JA, Nordlander M, Regardh CG. Pharmacokinetics of new calcium channel antagonist clevidipine in the rat, rabbit, and dog and pharmacokinetic/pharmacodynamic relationship in anesthetized dogs. Drug Metab Dispo. 1999;27:558-564.

38.Sangalli L, Bortolotti A, Jiritano L, Bonati M. Cyclosporine pharmacokinetics in rats and interspecies comparison in dogs, rabbits, rats, and humans. Drug Metab Dispo. 1998;16:749-753.

39.Kim SH, Kim WB, Lee MG. Interspecies pharmacokinetic scaling of a new carbapenem, DA-1131, in mice, rats, rabbits and dogs, and prediction of human pharmacokinetics. Biopharm Drug Dispos. 1998;19:231-235.

40.Klotz U, Antonin K-H, Bieck PR. Pharmacokinetics and plasma binding of diazepam in man, dog, rabbit, guinea pig and rat. J Pharmacol Exp Ther. 1976;199:67-73.

41.Kaul S, Daudekar KA, Schilling BE, Barbhaiya RH. Toxicokinetics of 2',3'-deoxythymidine, stavudine (D4T). Drug Metab Dispos. 1999;27:1-12.

42.Sanwald-Ducray P, Dow J. Prediction of the pharmacokinetic parameters of reduced-dolasetron in man using in vitro-in vivo and interspecies allometric scaling. Xenobiotica. 1997;27:189-201.

43.Kawakami J, Yamamoto K, Sawada Y, Iga T. Prediction of brain delivery of ofloxacin, a new quinolone, in the human from animal data. J Pharmacokinet Biopharm. 1994;22:207-227.

44.Tsunekawa Y, Hasegawa T, Nadai M, Takagi K, Nabeshima T. Interspecies differences and scaling for the pharmacokinetics of xanthine derivatives. J Pharm Pharmacol. 1992;44:594-599.

45.Bregante MA, Saez P, Aramayona JJ, et al. Comparative pharmacokinetics of enrofloxacin in mice, rats, rabbits, sheep, and cows. Am J Vet Res. 1999;60:1111-1116.

46.Duthu GS. Interspecies correlation of the pharmacokinetics of erythromycin, oleandomycin, and tylosin. J Pharm Sci. 1995;74:943-946.

47.Efthymiopoulos C, Battaglia R, Strolin Benedetti M. Animal pharmacokinetics and interspecies scaling of FCE 22101, a penem antibiotic. J Antimicrob Chemother. 1991;27:517-526.

48.Jezequel SG. Fluconazole: Interspecies scaling and allometric relationships of pharmacokinetic properties. J Pharm Pharmacol. 1994;46:196-199.

49.Segre G, Bianchi E, Zanolo G. Pharmacokinetics of flunoxaprofen in rats, dogs, and monkeys. J Pharm Sci. 1988;77:670-673.

50.Khor SP, Amyx H, Davis ST, Nelson D, Baccanari DP, Spector T. Dihydropyrimidine dehydrogenase inactivation and 5-fluorouracil pharmacokinetics: Allometric scaling of animal data, pharmacokinetics and toxicodynamics of 5-fluorouracil in humans. Cancer Chemother Pharmacol. 1997;39:233-238.

51.Clark B, Smith DA. Metabolism and excretion of a chromone carboxylic acid (FPL 52757) in various animal species. Xenobiotica. 1982;12:147-153.

52.Nakajima Y, Hattori K, Shinsei M, et al. Physiologically-based pharmacokinetic analysis of grepafloxacin. Biol Pharm Bull. 2000;23:1077-1083.

53.Baggot JD. Application of interspecies scaling to the bispyridinium oxime HI-6. Am J Vet Res. 1994;55:689-691.

54.Lave T, Levet-Trafit B, Schmitt-Hoffmann AH, et al. Interspecies scaling of interferon disposition and comparison of allometric scaling with concentration-time transformations. J Pharm Sci. 1995;84:1285-1290.

55.Sakai T, Hamada T, Awata N, Watanabe J. Pharmacokinetics of an antiallergic agent, 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)-1H-benzimidazole difumarate (KG-2413) after oral administration: Interspecies differences in rats, guinea pigs and dogs. J Pharmacobio-Dyn. 1989;12:530-536.

56.Lave T, Saner A, Coassolo P, Brandt R, Schmitt-Hoffman AH, Chou RC. Animal pharmacokinetics and interspecies scaling from animals to man of lamifiban, a new platelet aggregation inhibitor. J Pharm Pharmacol. 1996;48:573-577.

57.Richter WF, Gallati H, Schiller CD. Animal pharmacokinetics of the tumor necrosis factor receptor-immunoglobulin fusion protein lenercept and their extrapolation to humans. Drug Metab Dispos. 1999;27:21-25.

58.Lapka R, Rejholec V, Sechser T, Peterkova M, Smid M. Interspecies pharmacokinetic scaling of metazosin, a novel alpha-adrenergic antagonist. Biopharm Drug Dispo. 1989;10:581-589.

59.Ahr H-J, Boberg M, Brendel E, Krause HP, Steinke W. Pharmacokinetics of miglitol: Absorption, distribution, metabolism, and excretion following administration to rats, dogs, and man. Arzneim Forsch. 1997;47:734-745.

60.Siefert HM, Domdey-Bette A, Henninger K, Hucke F, Kohlsdorfer C, Stass HH. Pharmacokinetics of the 8-methoxyquinolone, moxifloxacin: A comparison in humans and other mammalian species. J Antimicrob Chemother. 1999;43 (Suppl. B):69-76.

61.Lave T, Portmann R, Schenker G, et al. Interspecies pharmacokinetic comparisons and allometric scaling of napsagatran, a low molecular weight thrombin inhibitor. J Pharm Pharmacol. 1999;51:85-91.

62.Higuchi S, Shiobara Y. Comparative pharmacokinetics of nicardipine hydrochloride, a new vasodilator, in various species. Xenobiotica. 1980;10:447-454.

63.Mitsuhashi Y, Sugiyama Y, Ozawa S, et al. Prediction of ACNU plasma concentration-time profiles in humans by animal scale-up. Cancer Chemother Pharmacol. 1990;27:20-26.

64.Yoshimura M, Kojima J, Ito T, Suzuki J. Pharmacokinetics of nipradilol (K-351), a new antihypertensive agent. I. Studies on interspecies variation in laboratory animals. J Pharmacobio-Dyn. 1985;8:738-750.

65.Gombar CT, Harrington GW, Pylypiw HM Jr, et al. Interspecies scaling of the pharmacokinetics of N-nitrosodimethylamine. Cancer Res. 1990;50:4366-4370.

66.Mukai H, Watanabe S, Tsuchida K, Morino A. Pharmacokinetics of NS-49, a phenethylamine class α_{1A}-adrenoceptor agonist, at therapeutic doses in several animal species and interspecies scaling of its pharmacokinetic parameters. Int J Pharm. 1999;186:215-222.

67.Owens SM, Hardwick WC, Blackall D. Phencyclidine pharmacokinetic scaling among species. J Pharmacol Exp Ther. 1987;242:96-101.

68.Ishigami M, Saburomaru K, Niino K, et al. Pharmacokinetics of procaterol in the rat, rabbit, and beagle dog. Arzneim Forsch. 1979;29:266-270.

69.Khor AP, McCarthy K, DuPont M, Murray K, Timony G. Pharmacokinetics, pharmacody namics, allometry, and dose selection of rPSGL-Ig for phase I trial. J Pharmacol Exp Ther. 2000;293:618-624.

70.Mordenti J, Osaka G, Garcia K, Thomsen K, Licko V, Meng G. Pharmacokinetics and interspecies scaling of recombinant human factor VIII. Toxicol Appl Pharmacol. 1996;136:75-78.

71.Coassolo P, Fischli W, Clozel J-P, Chou RC. Pharmacokinetics of remikiren, a potent orally active inhibitor of human renin, in rat, dog, and primates. Xenobiotica. 1996;26:333-345.

72.Widman M, Nilsson LB, Bryske B, Lundstrom J. Disposition of remoxipride in different species. Arzneim Forsch. 1993;43:287-297.

73.Lashev L, Pashov D, Kanelov I. Species specific pharmacokinetics of rolitetracycline. J Vet Med A. 1995;42:201-208.

74.Herault JP, Donat F, Barzu T, et al. Pharmacokinetic study of three synthetic AT-binding pentasaccharides in various animal species-extrapolation to humans. Blood Coagul Fibrinol. 1997;8:161-167.

75.Ward KW, Azzarano LM, Bondinell WE, et al. Preclinical pharmacokinetics and interspecies scaling of a novel vitronectin receptor antagonist. Drug Metab Dispos. 1999;27:1232-1241.

76.Lin C, Gupta S, Loebenberg D, Cayen MN. Pharmacokinetics of an everninomicin (SCH 27899) in mice, rats, rabbits, and cynomolgus monkeys following intravenous administration. Antimicrob Ag Chemother. 2000;44:916-919.

77.Chung M, Radwanski E, Loebenberg D, et al. Interspecies pharmacokinetic scaling of Sch 34343. J Antimicrob Chemother. 1985;15 (Suppl. C):227-233.

78.Hinderling PH, Dilea C, Koziol T, Millington G. Comparative kinetics of sematilide in four species. Drug Metab Dispo. 1993;21:662-669.

79.Walker DK, Ackland MJ, James GC, et al. Pharmacokinetics and metabolism of sildenafil in mouse, rat, rabbit, dog, and man. Xenobiotica. 1999;29:297-310.

80.Brocks DR, Freed MI, Martin DE, et al. Interspecies pharmacokinetics of a novel hematoregulatory peptide (SK&F 107647) in rats, dogs, and oncologic patients. Pharm Res. 1996;13:794-797.

81.Cosson VF, Fuseau E, Efthymiopoulos C, Bye A. Mixed effect modeling of sumatriptan pharmacokinetics during drug development. I: Interspecies allometric scaling. J Pharmacokin Biopharm. 1997;25:149-167.

82.Leusch A, Troger W, Greischel A, Roth W. Pharmacokinetics of the M1-agonist talsaclidine in mouse, rat, rabbit, and monkey, and extrapolation to man. Xenobiotica. 2000;30:797-813.

83.van Hoogdalem EJ, Soeishi Y, Matsushima H, Higuchi S. Disposition of the selective α_{1A}-adrenoceptor antagonist tamsulosin in humans: Comparison with data from interspecies scaling. J Pharm Sci. 1997;86:1156-1161.

84.Cruze CA, Kelm GR, Meredith MP. Interspecies scaling of tebufelone pharmacokinetic data and application to preclinical toxicology. Pharm Res. 1995;12:895-901.

85.Gaspari F, Bonati M. Interspecies metabolism and pharmacokinetic scaling of theophylline disposition. Drug Metab Rev. 1990;22:179-207.

86.Davi H, Tronquet C, Calx J, et al. Disposition of tiludronate (Skelid) in animals. Xenobiotica. 1999;29:1017-1031.

87.Pahlman I, Kankaanranta S, Palmer L. Pharmacokinetics of tolterodine, a muscarinic receptor antagonist, in mouse, rat and dog. Arzneim Forsch. 2001;51:134-144.

88.Tanaka E, Ishikawa A, Horie T. In vivo and in vitro trimethadione oxidation activity of the liver from various animal species including mouse, hamster, rat, rabbit, dog, monkey and human. Human Exp Toxicol. 1999;18:12-16.

89.Izumi T, Enomoto S, Hosiyama K, et al. Prediction of the human pharmacokinetics of troglitazone, a new and extensively metabolized antidiabetic agent, after oral administration, with an animal scale-up approach. J Pharmacol Exp Ther. 1996;277:1630-1641.

90.Grindel JM, O'Neil PG, Yorgey KA, et al. The metabolism of zomepirac sodium I. Disposition in laboratory animals and man. Drug Metab Dispo. 1980;8:343-348.

91.Singer MA, Morton AR. Mouse to elephant: Biological scaling and Kt/V. Am J Kidney Dis. 2000;35:306-309.

92.Singer MA. Of mice and men and elephants: Metabolic rate sets glomerular filtration rate. Am J Kidney Dis. 2001;37:164-178.

93.Edwards NA. Scaling of renal functions in mammals. Comp Biochem Physiol. 1975;52A:63-66.

94.Hayton WL. Maturation and growth of renal function: Dosing renally cleared drugs in children. AAPS PharmSci. 2000;2(1), article 3.

95.Adolph EF. Quantitative relations in the physiological constituents of mammals. Science. 1949;109:579-585.

96.Rubner M. Über den enifluss der körpergrösse auf stoff und kraftwechsel. Z Biol. 1883;19:535-562.

97.Heusner A. Energy metabolism and body size. II. Dimensional analysis and energetic non-similarity. Resp Physiol. 1982;48:13-25.

98.West GB. The origin of universal scaling laws in biology. Physica A. 1999;263:104-113.

99.Murray CD. The physiological principle of minimum work. I. The vascular system and the cost of blood volume. Proc Natl Acad Sci U S A. 1926;12:207-214.

100. Cohn DL. Optimal systems: I. The vascular system. Bull Math Biophys. 1954;16:59-74.

101. Cohn DL. Optimal systems: II. The vascular system. Bull Math Biophys. 1955;17:219-227.

102. Bonate PL, Howard D. Prospective allometic scaling: Does the emperor have clothes? J Clin Pharmacol. 2000;40:665-670.

103. Mahmood I. Critique of prospective allometric scaling: Does the emperor have clothes? J Clin Pharmacol. 2000;40:671-674.

Table 1. Allometric Scaling Parameters Obtained from Linear Regressions of the Log-Log-Transformed CL versus BW Data of 115 Xenobiotics (a: allometric coefficient; b: allometric exponent)

Compounds	a	b	r^2 [i]	P [ii]	95% CI of b	99% CI of b	Species [vii]	Ref
Acivin	3.9	0.57	0.976	***	**0.45 - 0.70** [iii]	0.37 - 0.78	ms, rt, mk, dg, hm	16
AL01567	0.41	0.93	0.834	*	0.17 - 1.7	n.d.	rt, mk, dg, cz, hm	17
AL01576	0.36	1.1	0.955	**	**0.75 - 1.4** [iv]	0.54 - 1.6	rt, mk, cz, hm	17
AL01750	0.39	0.98	0.829	*	0.16 - 1.8	n.d.	rt, dg, mk, cz	17
Alfentanil	47	0.75	0.975	***	0.59 - 0.92	0.48 - 1.0	rt, rb, dg, sh	18
1-Aminocyclopropanecarboxylate	2.6	0.72	0.902	*	0.28 - 1.2	n.d.	ms, rt, mk, hm	19
Amphotericin B	0.94	0.84	0.988	***	**0.77 - 0.91** [v]	**0.74 - 0.94** [iv]	ms, rt, rb, dg, hm	20
Amsacrine	38	0.46	0.906	*	0.19 - 0.73	n.d.	ms, rt, rb, dg, hm	21
Anti-digoxin Fab	1.0	0.67	0.992	0.06	n.d. [vi]	n.d.	ms, rt, rb	22
Antipyrine	6.9	0.57	0.716	0.15	n.d.	n.d.	rt, rb, dg, hm	23
Antivenom Fab2	0.033	0.53	0.990	0.06	n.d.	n.d.	ms, rt, rb	24
Apramycin	2.8	0.80	0.924	**	0.38 - 1.2	0.028 - 1.6	sh, rb, ck, pn	25
AZT	26	0.96	0.982	**	**0.72 - 1.2** [iv]	0.52 - 1.4	ms, rt, mk, dg, hm	26
Betamipron	16	0.69	0.975	***	0.53 - 0.84	0.43 - 0.94	ms, gp, rt, rb, mk, dg	27
Bosentan	25	0.56	0.663	*	0.006 - 1.1	n.d.	ms, mt, rt, rb, hm	23
BSH	2.1	0.68	0.945	*	0.028 - 0.18	n.d.	ms, rt, rb, hm	28
Caffeine	6.3	0.74	0.981	**	0.55 - 0.93	0.39 - 1.1	ms, rt, rb, mk, hm	29
Candoxatrilat	9.6	0.66	0.986	***	0.52 - 0.81	0.39 - 0.93	ms, rt, rb, dg, hm	30
CD4-IgG	0.10	0.74	0.959	*	0.27 - 1.2	n.d.	rt, rb, mk, hm	31
Cefazolin	4.5	0.68	0.975	***	0.52 - 0.83	0.43 - 0.93	ms, rt, rb, dg, mk, hm	32
Cefmetazole	12	0.59	0.917	**	0.35 - 0.84	0.18 - 1.0	ms, rt, rb, dg, mk, hm	32
Cefodizime	1.5	1.0	0.926	**	0.48 - 1.5	0.047 - 1.9	ms, rt, rb, dg, mk	33
Cefoperazone	6.7	0.57	0.823	*	0.20 - 0.94	n.d.	ms, rt, rb, dg, mk, hm	32
Cefotetan	6.3	0.53	0.849	**	0.22 - 0.84	0.016 - 1.0	ms, rt, rb, dg, mk, hm	32
Cefpiramide	4.1	0.40	0.589	0.07	n.d.	n.d.	ms, rt, rb, dg, mk, hm	32
Ceftizoxime	11	0.57	0.986	**	0.37 - 0.78	0.10 - 1.1	ms, rt, mk, dg	34
CI-1007	35	0.90	0.998	*	0.44 - 1.4	n.d.	rt, mk, dg	35
CI-921	15	0.51	0.830	*	0.085 - 0.93	n.d.	ms, rt, rb, dg, hm	21
Cicaprost	37	0.83	0.956	***	0.59 - 1.1	0.42 - 1.2	ms, rt, rb, mk, pg, hm	36
Clevidipine	288	0.84	0.985	0.07	n.d.	n.d.	rt, rb, dg	37

Table 1. (continued)

Compounds	**a**	**b**	r^2 [i]	***P*** [ii]	**95% CI of b**	**99% CI of b**	**Species** [vii]	**Ref.**
Cyclosporin	5.8	0.99	0.931	*	0.17 - 1.8	n.d.	rt, rb, dg, hm	38
DA-1131	11	0.81	0.995	***	**0.71 - 0.93** [iv]	0.61 - 1.0	ms, rt, rb, dg, hm	39
Diazepam	89	0.2	0.135	0.5	n.d.	n.d.	rt, gp, rb, dg, hm	40
Didanosine	33	0.76	0.971	**	0.52 - 1.0	0.32 - 1.2	ms, rt, mk, dg, hm	41
Dolasetron	74	0.73	0.950	*	0.22 - 1.2	n.d.	rt, mk, dg, hm	42
Enoxacin	36	0.43	0.874	*	**0.13 - 0.73** [iii]	n.d.	ms, rt, mk, dg, hm	43
Enprofylline	6.0	0.72	0.852	**	0.30 - 1.1	0.028 - 1.4	ms, rt, gp, rb, dg, hm	44
Enrofloxacin	23	0.77	0.972	**	0.53 - 1.0	0.33 - 1.2	ms, rt, rb, sh, cw	45
Eptaloprost	115	0.83	0.985	0.08	n.d.	n.d.	rt, mk, hm	36
Erythromycin	37	0.66	0.966	***	0.49 - 0.83	0.37 - 0.94	ms, rt, rb, dg, hm, cw	46
FCE22101	11	0.76	0.909	*	0.027 - 1.5	n.d.	rt, rb, mk, dg	47
Fentanyl	60	0.88	0.990	0.06	n.d.	n.d.	rt, dg, pg	18
Fluconazole	1.2	0.70	0.992	***	0.63 - 0.77	0.58 - 0.82	ms, rt, gp, rb, ct, dg, hm	48
Flunoxaprofen	0.98	1.0	0.925	0.2	n.d.	n.d.	rt, dg, mk	49
5-Fluorouracil	7.6	0.74	0.991	**	0.52 - 0.95	0.24 - 1.2	ms, rt, dg, hm	50
FPL-52757	0.91	0.62	0.973	**	0.43 - 0.81	0.28 - 0.97	rt, rb, mk, dg, hm	51
Grepafloxacin	15	0.64	0.886	0.06	n.d.	n.d.	rt, rb, mk, dg	52
HI-6	9.8	0.76	0.972	***	0.61 - 0.91	0.53 - 0.99	ms, rt, rb, mk, dg, sh, hm	53
Iloprost	48	0.85	0.970	***	0.64 - 1.1	0.51 - 1.2	ms, rt, rb, dg, pg, hm	36
Interferon α	3.7	0.71	0.980	**	0.52 - 0.90	0.36 - 1.1	ms, rt, rb, dg, mk	54
Kanamycin	2.9	0.81	0.970	***	0.61 - 1.0	0.48 - 1.1	sh, gt, rb, ck, pn	25
Ketamine	119	0.56	0.632	0.1	n.d.	n.d.	rt, rb, pg	18
KG-2413	610	1.1	0.741	0.3	n.d.	n.d.	rt, gp, dg	55
Lamifiban	6.1	0.88	0.887	0.2	n.d.	n.d.	rt, dg, mk	56
Lamivudine	15	0.75	0.991	**	0.53 - 0.97	0.24 - 1.3	rt, mk, dg, hm	41
Lenercept	0.0079	1.1	0.998	**	**0.90 - 1.2** [v]	**0.71 - 1.4** [iv]	rt, rb, mk, dg	57
Lomefloxacin	10	0.79	0.992	***	0.66 - 0.92	0.56 - 1.0	ms, rt, mk, dg, hm	46
Metazocin	11	0.29	0.973	*	0.15 - 0.44	n.d.	ms, rt, rb, hm	58
Methohexitone	73	0.86	0.997	*	0.26 - 1.5	n.d.	rt, rb, dg	18
Mibefradil	62	0.62	0.923	**	0.29 - 0.95	0.018 - 1.2	rt, mt, rb, dg, hm	23
Midazolam	67	0.68	0.850	*	0.15 - 1.2	n.d.	rt, rb, dg, pg, hm	23

Table 1. (continued)

Compounds	**a**	**b**	r^{2} *(i)*	*P (ii)*	**95% CI of b**	**99% CI of b**	**Species** *(vii)*	**Ref.**
Miglitol	7.4	0.64	0.998	*	0.31 - 0.97	n.d.	rt, dg, hm	59
Mofarotene	14	0.84	0.983	**	0.51 - 1.2	n.d.	ms, rt, dg, hm	23
Moxalactam	5.0	0.66	0.992	***	**0.58 - 0.74** *(iii)*	0.53 - 0.79	ms, rt, rb, dg, mk, hm	32
Moxifloxacin	20	0.56	0.949	***	**0.38 - 0.74** *(iii)*	0.26 - 0.86	ms, rt, mk, dg	60
Napsagatran	50	0.74	0.842	0.08	n.d.	n.d.	rt, rb, dg, mk	61
Nicardipine	69	0.55	0.962	***	**0.40 - 0.70** *(iii)*	0.30 - 0.80	rt, dg, mk, hm	62
Nimustine	42	0.83	0.968	**	0.55 - 1.1	0.32 - 1.3	ms, rt, rb, dg, hm	63
Nipradilol	59	0.66	0.796	*	0.047 - 1.3	n.d.	rt, rb, mk, dg	64
N-Nitrosodimethylamine	59	0.93	0.972	***	**0.75 - 1.1** *(iv)*	0.65 - 1.2	ms, hr, rt, rb, mk, dg, pg	65
Norfloxacin	81	0.77	0.893	*	0.28 - 1.3	n.d	ms, rt, mk, dg, hm	43
NS-49	14	0.64	0.994	0.05	n.d.	n.d.	rt, rb, dg	66
Ofloxacin	7.5	0.64	0.946	*	0.17 - 1.1	n.d.	rt, mk, dg, hm	43
Oleandomycin	30	0.69	0.996	**	0.55 - 0.83	0.36 - 1.0	ms, rt, dg, hm	46
Panipenem	12	0.61	0.977	***	**0.48 - 0.74** *(iii)*	0.39 - 0.82	ms, gp, rt, rb, mk, dg	27
Pefloxacin	13	0.57	0.910	*	0.24 - 0.90	n.d.	ms, rt, mk, dg, hm	43
Phencyclidine	52	0.64	0.891	**	0.33 - 0.95	0.12 - 1.1	ms, rt, pn, mk, dg, hm	67
Procaterol	29	0.80	0.992	0.06	n.d.	n.d.	rt, rb, dg	68
Propranolol	98	0.64	0.81	0.10	n.d.	n.d.	rt, rb, dg, hm	23
P-selectin glycoprotein ligand-1	0.0060	0.93	0.939	**	0.49 - 1.4	0.13 - 1.7	ms, rt, mk, pg	69
Recombinant CD4	3.4	0.65	0.995	**	0.50 - 0.79	0.31 - 0.98	rt, rb, mk, hm	31
Recombinant growth hormone	6.8	0.71	0.995	**	0.55 - 0.87	0.34 - 1.1	ms, rt, mk, hm	31
Recombinant human factor VIII	0.16	0.71	0.999	*	0.45 - 0.97	n.d.	ms, rt, hm	70
Relaxin	6.0	0.80	0.992	***	0.66 - 0.93	0.55 - 1.0	ms, rt, rb, mk, hm	31
Remikiren	50	0.67	0.898	*	0.26 - 1.1	n.d.	rt, dg, mt, mk,	71
Remoxipride	29	0.42	0.710	0.07	n.d.	n.d.	ms, rt, hs, dg, hm	72
Ro 24-6173	69	0.64	0.976	*	0.33 - 0.95	n.d.	rt, rb, dg, hm	23
Rolitetracycline	11	0.89	0.989	***	**0.72 - 1.1** *(iv)*	0.58 - 1.2	rb, pg, pn, ck	73
Sanorg 32701	0.35	0.87	0.979	0.09	n.d.	n.d.	rt, rb, bb	74
SB-265123	15	0.80	0.812	0.1	n.d.	n.d.	ms, rt, mk, dg	75
Sch 27899	0.78	0.62	0.966	*	0.27 - 0.98	n.d.	ms, rt, rb, mk	76
Sch 34343	13	0.77	0.924	***	0.51 - 1.0	0.37 - 1.2	ms, rt, mk, rb, dg, hm	77

Table 1. (continued)

Compounds	**a**	**b**	r^{2} [i]	***P*** [ii]	**95% CI of b**	**99% CI of b**	**Species** [vii]	**Ref.**
Sematilide	20	0.66	0.982	**	0.39 - 0.94	0.034 - 1.3	rt, rb, dg, hm	78
Sildenafil	28	0.66	0.999	***	**0.59 - 0.73** [iii]	0.51 - 0.81	ms, rt, dg, hm	79
SK&F107647	7.2	0.63	0.964	0.1	n.d.	n.d.	rt, dg, hm	80
SR 80027	0.10	0.53	0.990	0.06	n.d.	n.d.	rt, rb, bb	74
SR90107A	0.68	0.55	0.978	*	0.30 - 0.79	n.d.	rt, rb, bb, hm	74
Stavudine	19	0.84	0.993	***	**0.71 - 0.97** [iv]	0.60 - 1.1	ms, rt, mk, rb, hm	41
Sumatriptan	32	0.84	0.973	*	0.42 - 1.3	n.d.	rt, rb, dg, hm	81
Talsaclidine	37	0.63	0.971	*	0.30 - 0.97	n.d.	ms, rt, mk, hm	82
Tamsulosin	61	0.59	0.993	0.05	n.d.	n.d.	rt, rb, dg	83
Tebufelone	31	0.79	0.963	*	0.32 - 1.3	n.d.	rt, mk, dg, hm	84
Theophylline	1.9	0.81	0.950	***	0.64 - 0.98	0.57 - 1.1	rt, gp, rb, ct, pg, hs, hm	85
Thiopentone	3.5	1.0	0.874	**	0.57 - 1.4	0.32 - 1.7	rt, rb, dg, sh	18
Tiludronate	1.5	0.56	0.977	**	0.40 - 0.71	0.27 - 0.84	ms, rt, rb, dg, bb	86
Tissue-plasminogen activator	17	0.84	0.986	***	**0.72 - 0.95** [iv]	0.66 - 1.0	ms, hs, rt, rb, mk, dg, hm	23
Tolcapone	12	0.65	0.927	*	0.095 - 1.2	n.d.	rt, rb, dg, hm	27
Tolterodine	62	0.62	0.978	*	0.34 - 0.90	n.d.	ms, rt, dg, hm	87
Tosufloxacin	64	0.80	0.919	*	0.36 - 1.24	n.d.	ms, rt, mk, dg, hm	43
Trimethadione	4.1	0.70	0.942	***	0.50 - 0.90	0.39 - 1.0	ms, hs, rt, rb, dg, mk, hm	88
Troglitazone	12	0.81	0.988	**	0.54 - 1.1	0.19 - 1.4	ms, rt, mk, dg	89
Tylosin	54	0.69	0.993	0.053	n.d.	n.d.	rt, dg, cw	48
Zalcitabine	15	0.82	0.983	***	0.62 - 1.0	0.45 - 1.2	ms, rt, ct, mk, hm	41
Zidovudine	26	0.95	0.981	**	**0.71 - 1.2** [iv]	0.51 - 1.4	ms, rt, mk, dg, hm	41
Zomepirac	1.6	1.2	0.902	**	0.63 - 1.7	0.28 - 2.0	ms, rt, rb, hs, mk, hm	90

Note: CL = clearance, BW = body weight, CI = confidence interval.
[i] Coefficient of determination.
[ii] Statistical testing against **b** = 0: $P < 0.05$ (*); $P < 0.01$ (**); $P < 0.001$ (***).
[iii] Excluding **b** = 0.75.
[iv] Excluding **b** = 0.67.
[v] Excluding both **b** = 0.75 and **b** = 0.67.
[vi] n.d.: not determined because of a lack of correlation between CL and BW at the significance level = 0.05 (column 6) and = 0.01 (column 7).
[vii] rt, rat; rb, rabbit; bb, baboon; mk, monkey; dg, dog; hm, human; ms, mouse; cz, chimpanzee; sh, sheep; ck, chicken; pn, pigeon; gp, guinea pig; pg, pig; ct, cat; cw, cow; gt, goat; mt, marmoset; hs, hamster.