Size Matters: Allometry and dose extrapolation from animals to humans

Converting doses used in animal studies to human doses

The dose at which a chemical produces no health effects in animal studies is often used to guide safe dose levels for that chemical in humans when human data are insufficient for this purpose. Examples of where animal data are used for this is first in human dosing of drugs and human health risk assessment. Allometric dose scaling attempts to predict the dose at which effects observed in animals might be observed in humans. Its use assumes that the health effect measured in the animal is relevant to humans.

Allometric dose scaling is based on results of a few studies in a small group of chemicals showing that ***larger animals require smaller doses on a mg/kg body weight basis as compared to smaller animals for the same health effects. The principle behind allometric dose scaling is that doses scale between species better on the basis or body surface area (mg/m^2) or metabolic rate (mg/kcal) than they do on a body weight (mg/kg) basis. The math behind this allometric scaling is that the increases in surface area or metabolic rate gets smaller with increasing body weight.*** In this document, we shall explore the data supporting the use of allometric dose scaling as well as the math and biology behind this concept. We shall also explore the limitations of its use.

The Data Behind Allometric Dose Scaling

Freireich and coworkers[1] demonstrated the relationship between dose and body surface area in 1966. Freireich compared the toxicity of 18 anticancer drugs given to 5 species (dogs, monkeys, rats, mice, and hamsters) to the dose at which roughly the same toxicity was observed in humans. In rats and mice, the dose they looked at was the minimally lethal dose (LD_{10}). In monkeys, dogs, hamsters and humans it was the highest dose that produced no death (the maximally tolerated dose or MTD). They considered the LD_{10} and the MTD to be roughly equivalent thresholds for toxicity. They found that when animal doses were expressed in mg/m^2 body surface area, good predictions of human the MTDs were obtained from all animals. Since it is difficult to measure body surface area directly in animals or in man, one can guesstimate it based on the relationship between body surface area and body weight using Meeh's Equation:

Total Body Surface Area or TBSA (in cm^2)=(some constant called K) x Body weight $^{2/3}$ (in grams).

Now Let's Talk About Meeh…Meeh's Equation That Is

The relationship between body surface area and body weight is best shown in an example. Table 1 shows the body weight and surface area in rats of three different sizes.

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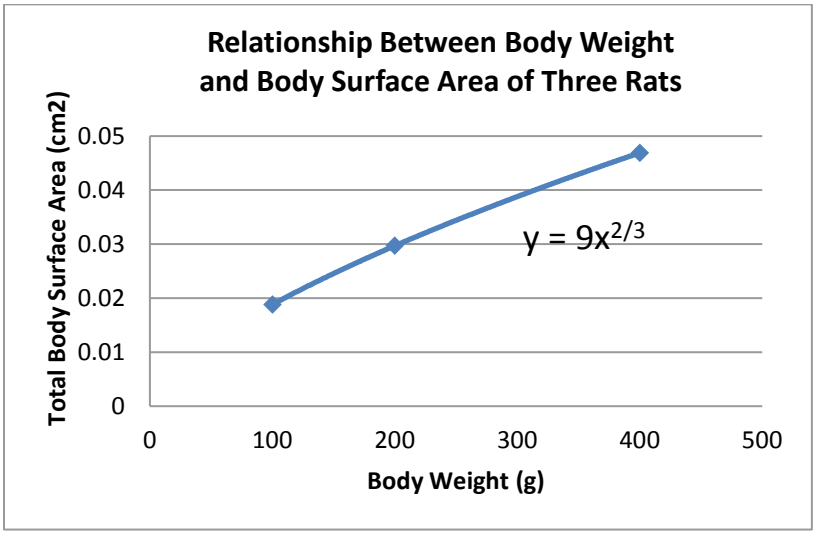
[1] Freireich, EJ, EA Gehan, DP Rall, LH Schmidt, and HE Skipper, 1966, Quantitative Comparison of Toxicity of Anticancer Agents in Mouse, Rat, Hamster, Dog, Monkey, and Man, Cancer Chemotherapy Reports, 50:219-244.

Table 1

	Small Rat	Medium Rat	Large Rat
Surface Area (SA)	188 cm^2	297 cm^2	469 cm^2
Mass	100 g	200 g	400 g
Surface Area: Mass Ratio (SA:M)	1.88	1.49	1.17

As the weight of the rat increases, so does the surface area, but the increase is not linear. When the body weight of the rat doubles the surface area doesn't double. ***Since mass increases more than surface area, the surface area to mass ratio decreases as the rat gets bigger***. If we plot the relationship between surface area and mass of these rats on a graph, it looks like this:

Figure 1



The equation of this line is $Y=9x^{2/3}$. This is a power function, which can be written more generally as

$$Y = KX^b$$

Where Y=Surface area of a rat (cm^2)

X=Mass of the rat (g)

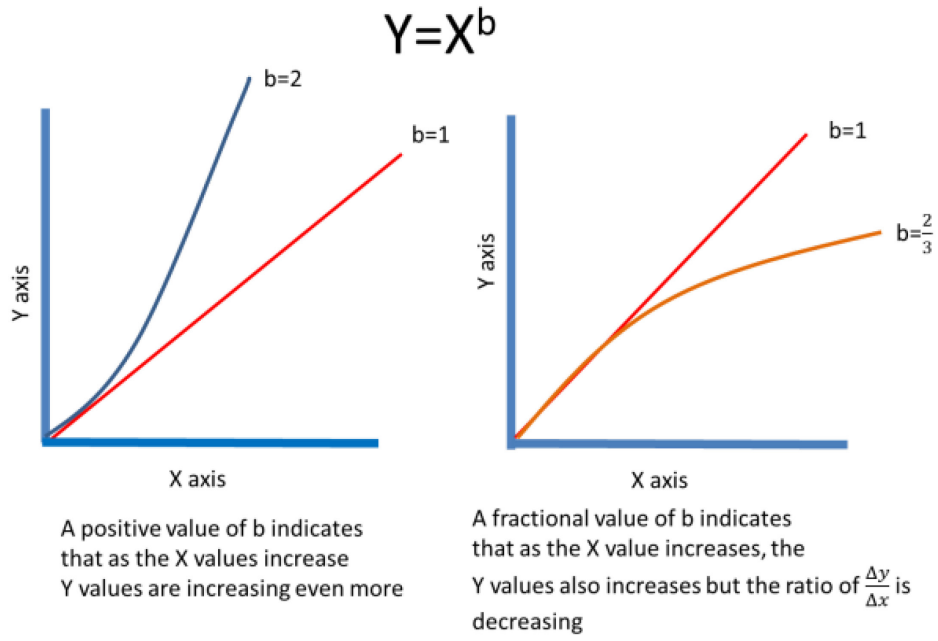
b=Exponential constant function which is $\frac{2}{3}$ or 0.67

K=Constant that converts the mass of any rat into total body surface area

Let's examine the functions of b and a in this equation.

The "b" quantifies how much the curve grows or decays as it moves along the x axis. To understand the function of b, let's set the value of b and K in $Y = KX^1$ to 1. That way, the equation becomes $= 1\ x\ X^1\ or\ Y = X^1$. If the value of b was equal to 1 in a power function, the relationship would be linear because it is consistent across all values of x and y. If surface area doubled when body weight doubled for the rats in Table 1, this would be a linear relationship. This is also called an **isometric** relationship. **Allometric** refers to relationships where b≠1, or where the relationship between x and y grows or shrinks as we move along the x axis. So, the relationship between body weight and total body surface is allometric because the relationship changes as as we move along the x-axis. If the value of b was >1, it would mean that the increase in surface area would be greater than the increase in body weight. This would happen if rats grew giant bat like wings as they increased in size. Clearly, this doesn't happen. In our case, the value of b is a positive fraction, a value of $\frac{2}{3}$. As we saw in Table 1, this means that as the mass increases, the surface area also increases, but that the increase in the surface area is smaller than the increase in mass. Figure 2 shows how changes in the value of b alter the shape of the curve.

Figure 2



The function of "K" in this equation

"K" is the proportionality constant. To understand the function of K, let's set the value of b in $Y = KX^1$ to 1. That way, the equation becomes $= KX$. Let's see what happens when we vary the value of K. When K=1, Y=X, so 100 g would equal 100 cm^2. If K=2, Y=2x, so 100 g would equal 200 cm^2. Regardless of the value of K in the equation, the relationship between X and Y always remains linear when b is set to 1. **So, K does not define the shape of the curve. What "K" does is convert the units of X into the proper units of Y, and moves the curve up or down**.

So, far we have been discussing only the relationship between body surface area and body weight for rats. In humans, the value of b is exactly the same as in the rat, but the value of K is higher. The same value of b means that in humans as in rats, the ratio of surface area to mass decreases with increasing body weight. In fact, you could plot species ranging in size from the tiniest shrew to the largest elephant on the same graph and the value of b remains $^{2/3}$ for the relationship between surface area and mass.

The values of K has been calculated based on actual measurements of surface area and mass in different animals[2]. K varies from species to species and even within a species. Generally speaking, the more spherically shaped the animal, the lower the value of K. This makes sense because spheres have the lowest surface area to volume ratio as compared to any geometric shape. If they measured the K value of Captain Underpants, he would probably have a low K value, while Gumby's would be higher.

Low K Value

High K Value

Since mice and rats have roughly similar builds, their K values are both 9. Hedgehogs with their round bodies and small limbs have a K value of about 7.5, while bats, with their large thin wings have a K value of over 50.

Hedgehogs have a low K value of 7.5

Bats have high a K value of over 50

Since humans and monkeys are flatter than rodents, their K values are higher, indicating a higher surface area for any given mass. Babies tend to be more spherical than adults, so their K values are also lower.

Can we Ignore the K Value?

Another common approach to scaling doses between species using body surface area normalization is to ignore the K values unique to each species and just use the relationship between the body weights to

[2] W. S. Spector (Ed.).Handbook of Biological Data, W. B. Saunders, Philadelphia, 1956, pp. 163–164, 339.

estimate dose in humans. This approach is simpler but less accurate. The effect of not including K values in the calculation will be greater for animals that vary more widely in K values. So, for all those researchers doing studies in hedgehogs and trying to extrapolate their results to bats are pretty much stuck with K factors if they want to do body weight scaling[3].

Back to Dose Scaling

These original data by Freirech were looked at again by another group much later (Travis and White, 1988). These investigators also added 13 more anticancer drugs to ones already looked at by Freirech. Travis and White found that for all of these anticancer drugs, human doses were better predicted when body weight was scaled to the power ¾ and not $\frac{2}{3}$. So, at least for these anticancer drugs, body weight ^{¾} seems to be a good way of predicting human doses. Dose scaling to body weight $^{3/4}$ is what the US EPA thinks risk assessors should use to scale from animal to human doses. It's also an approach sometimes used in veterinary medicine to scale drug doses between different species. Dose scaling to body weight ¾ yields higher human doses as compared to body weight $\frac{2}{3}$. Because of this, ***body weight to ¾ approach for human dose scaling is less conservative than the body weight*** $\frac{2}{3}$. This means that you'll get lower human equivalent doses if you use the body weight $\frac{2}{3}$ approach. This may be why the FDA uses the body weight $\frac{2}{3}$ approach for human dose scaling instead of body weight $^{3/4}$.

So, why does dose scale to Body Weight ¾ ? The answer lies in the observation that metabolic rate scales to Body Weight ¾ and we'll talk more about that next.

Metabolic Rate Scales to Body Weight 3/4

Metabolic rate is the rate at which the body breaks down fuels to keep cellular processes within the animal running. This relationship between body weight and metabolic rate was first described in by Max Kleiber in 1932 for a wide range of animals. Shown below is the original graph of body weight (measured in kg) plotted against heat production (measured in kcal). The term kcal is an abbreviation for kilocalorie which is unit of energy[4] that can be used to measure heat production but is also reflective of an animal's metabolic rate because heat is a byproduct of all metabolism. When the animal is neither getting bigger or losing weight (i.e. stable body weight), the metabolic rate is equal to the amount of energy the animal consumes from the diet (i.e.= kcal consumed).

On the graph, the dashed line marked "weight" would be the line if b=1 (i.e. metabolic rate increased linearly with increased body size). As shown in the graph, the metabolic rate increases at a slower rate as animals get bigger (just like with body surface area). The dashed line marked "surface" would be the line if b=$\frac{2}{3}$, if metabolic rate scaled according to the animal's surface area. The actual line is the red line,

[3] SafeDose would be happy to run the human equivalent dose calculator using Meeh's equation rather than with fixed species factors or equations based only on body weights. We just need the list of K values for all relevant species, and consider it done!

[4] A kcal is the amount of energy needed to increase the temperature of 1 kg of water by 1^{o}C

which describes the relationship as metabolic rate=body weight $\frac{3}{4}$, with the green dots being the observed values. So, the relationship between body weight and metabolic rate is a power function. If it is a power function, why then does the line not curve downwards as it moves along the x-axis? The reason is that when a power function is shown on a log-log plot such as this one, the power function becomes a straight line. One big advantage of a log-log plot is that you can show a much broader range of numbers on the graph, which is what you need when showing data from animals such as mice that weigh 0.20 kg all the way up to elephants that can weigh up to 6000 kg.

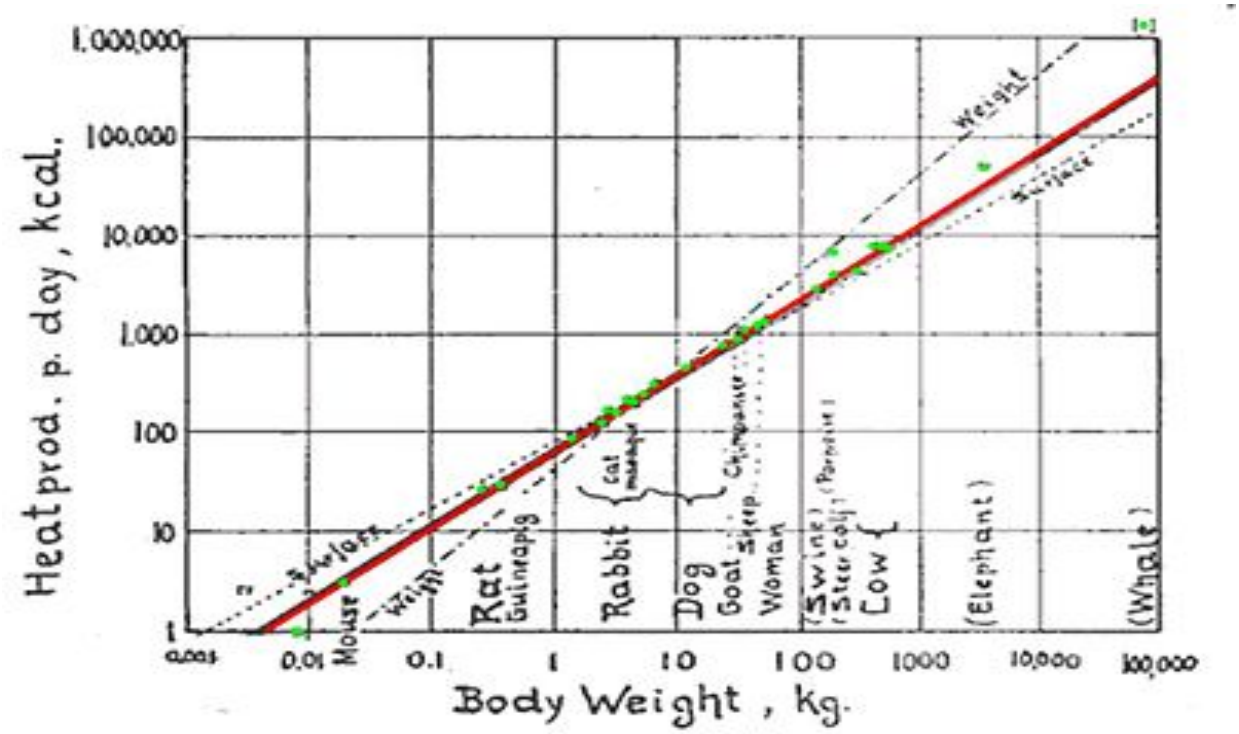


Fig. 1. Log. metabol. rate/log body weight

What does Metabolic Rate have to do with Body Surface Area?

Animals produce heat when fuels are metabolized to produce energy. This heat must be released to the environment in order for the body temperature to remain constant. This heat loss occurs over the surface of the animal's body. Smaller animals, having a larger surface area, release this heat quickly to the environment and cool down faster than large animals[5]. To compensate for higher heat loss across a larger surface area, smaller animals have higher metabolic rates so that they can generate more heat and keep their body temperatures constant. Higher metabolic rates also means that smaller animals have to eat more per unit mass to keep from starving and to stave off hypothermia. Many small endotherms have evolved to have rounder body shapes, so that they can reduce heat loss caused by their higher surface areas. Large animals like elephants have big ears and wrinkly skin which helps them cool off.

[5] This is true when environmental temperatures are below body temperatures

While body surface has a lot to do with metabolic rate, does it really explain everything? Maybe. Or Maybe Not. Body surface area scales with body weight to the power 2/3 while metabolic rate scales to body weight to the power ¾. This would seem to suggest that metabolic rate doesn't go down quite as much with increasing size as one might expect from the decrease in body surface area. One thing to remember is that these relationships are based on fitting the curves to the available data. Each of those curves has a confidence interval associated with it, or a range of values of b that could be correct. So, while the relationship is stated as "Body Surface Area scales to Body Weight $^{2/3}$" or "Metabolic Rate scales to Body Weight ^{¾}", it may be more accurate to state: "We are 95% sure that Metabolic Rate (or body surface area) scales to Body Weight with an exponent somewhere between X and Y", where X and Y define the high end and low end limits of the range. So, whether the values of b are really different for body surface area and metabolic rate isn't clear.

Dose Scaling: Metabolic Rate and Physiologic Time

So why would dose scale to metabolic rate? Large animals work at a slower metabolic pace than small animals. This means that their cells don't require the pace of nutrient and oxygen delivery that small animals require, so their systems have evolved physiologically to operate slower. Like metabolic rate, the speed of blood delivery to any organ is higher in smaller animals. Heart rate and breathing rate are also higher in small animals. For example, the heart rate of a shrew is about 1000 beats per minute, but that of an elephant is only 30 times in a minute. BUT, if you change the denominator from per minute to per lifetime, so that you're now comparing the number of beats or breathes that small mammals and large mammals takes over a lifetime, they're about the same. Why? Because bigger animals tend to live longer. It seems that both shrews and elephants are only good for about 800 million heart beats or 200 million breathes; Shrews just use up their allotted heart beats and breaths faster than elephants, with shews living about 2-3 years and elephants living 60 or more. So living fast really does mean you die young, allometrically speaking. Well, not quite…..technically, shrews don't die "young" when they live to the ripe old age of 2 or 3. They've completed all of the stages of their lives and are now just done. Weaning, puberty, adolescence, adulthood and senescence all took place but it just took the shrews less time to get through all that compared to an elephant. On the other hand, if an elephant had died at age 2 or 3, that really would be dying young. This gets us to the different ways of thinking about time. Time can be measured chronologically, which shrews, elephants and the rest of us experience at the same pace, with 1 second or 1 year being the same regardless of who we are, or it can be measured relative to specific events that happen within the system. This concept that time is relative is also called physiologic time. So, for a shrew or an elephant, one heart beat, one breath, the time it takes for a blood cell to go around the body or even an entire lifespan would be considered equal if measured in units of physiologic time, although vastly different in chronologic time. This concept of physiological time is taken into account when toxicologists say that a 1 year study in rodents is equivalent to about half a lifetime in humans. Chronologically, its only a year, but its half their lives, which has a dimension that is equivalent to about 35 years of ours, physiologically speaking anyway.

So, what does any of this have to do with dose scaling? Since organ blood flow and circulation time is greater in small animals, chemicals are expected to distribute to organs faster in small animals. This also

means that the chemicals would be expected to be delivered to the liver and kidneys faster, where they could be cleared away from the blood and removed from the body faster. Body size might also have an effect on how quickly tissues repair themselves after a chemical exposure. So, body size impacts a number of different elements that have an influence on the dose at which chemicals cause health effects.

Limitations of Allometric Scaling

So, how broadly can we use allometric dose scaling? The data supporting its use is pretty scant. We just don't know the boundaries of the sandbox. Can we use it for all chemicals? Drugs, Pesticides, Food Additives? Can we use it if the routes of exposure are different from oral? Does it apply to all health effects or only some of them? Does it work across all animal species? Does the relationship hold true for effects observed only after a short period of time or longer periods too? To define the sandbox boundaries, the equation developed based on one set of circumstances needs to be tested to see if holds up for another set of circumstances. That means a lot of research and compiling data on chemicals and scenarios where we have a pretty good idea of the doses at which effects occur in both humans and animals.

Let's Model It!

Another approach would be to abandon empirical approaches like allometric dose scaling in favour of more sophisticated approaches like PK-PD models. These take into consideration the differences in anatomical, physiological and biochemical traits between species. Models can also include known information on how doses for chemicals that are similar scale across species. The building of good models requires them to be fed with good data and have well thought out assumptions, since all models are subject to the Garbage In Garbage Out (GIGO) principle. One advantage of models is that they can get better and better over time, as they get refined based on new knowledge. Unfortunately, only a tiny fraction of chemicals that humans are exposed to have enough good quality data to build models that will yield accurate predictions of human doses, but this is changing. The building of large, public databases of PK-PD data collected from a range of species for different types of chemicals will help in achieving this goal.

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Definition. Hide under each occurrence of Metabolic Rate

Metabolic rate: Amount of energy an animal uses over a specific time. There are several ways of measuring metabolic rate. Common methods include measuring heat production or loss, the amount of oxygen consumed or carbon dioxide produced or the energy content of food consumed Metabolic rate can be measured in various units, such as calories, kilocalories, joules, oxygen consumed or carbon dioxide produced. All of these are expressed per unit time. Metabolic rate varies depending on activity level and other factors. As some of us are painfully aware, in order for body weight to stay constant, metabolic rate must equal the energy derived from the food. Basal metabolic rate is the rate at which the organism at rest in the calm and fasting state at a comfortable temperature expends energy.