Animal Scale-Up

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On the left is a drawing of a chemical plant. On the right of the page is a drawing of a biological plant. Both are sources of medications.

There are five simplified drawings on this page. In the center are test tubes in a test tube holder. Going clockwise at the right top of the page is a silhouette of a dog. Beneath the dog is an elephant. On the bottom left of the page is the silhouette of a couple holding hands. Above the couple is a cartoon drawing of a mouse.

The slide is meant to illustrate size differences between species that impact on dose selection.

This is a photograph of the torso of a woman wearing a lab apron holding one mouse and one rat in her hands.

This is a photograph of a woman looking down. It appears to be the top half of the photo mentioned on page 4.

This is a photograph of two elephants and a man holding the trunk of one of the elephants..

Graph showing diffusivity in water, $CM^2/S \times 10^5$ over molecular weight in urea, glycerol, Hexose, Sucrose, Raffinose and inulin.

The graph also illustrates capillary permeability, $CM/S \times 10^{4.}$

Capillary permeability and aqueous diffusivity of hydrophilic solutes versus molecular weight comparing a cat leg, human forearm, and a dog heart diffusivity.

Dedrick RL et al, ASAIO J 5:1-8, 1982

Allometric equation

$P = a(BW)^m$

Where P = physiological property or anatomic size
A = empirical coefficient
BW = body weight
m = allometric exponent

Allometric chart showing a plot of physiologic property over body weight for P approximately (BW) and P approximately (BW) 0.7

Graph showing heat production (kcal/day) over body weight (kg) for mouse, rat, guinea pig, cats, rabbits, macaque, goat, chimpanzee, sheep, steer, cow and elephant As the weight of the animals increases, so does their heat production (kcal/day).

McMahon T. Science 179:1201-1204, 1973

Graph showing peritoneal transfer, PA or clearance, mL/min over body weight, kg for Urea and Inulin. Urea's PA or clearance, mL/min is higher.

Dedrick RL et al, ASAIO J 5:1-8, 1982

Line chart showing plasma 5-FU [(ng/mL)/(mg/kg)] over time (hr) in dog, human, rat, and mouse

Dose-normalized plasma 5-FU concentrations in humans and animals lacking dihydropyrimidine dehydrogenase activity. The human data were obtained from a patient who was genetically deficient in DPD. The animals were treated with 776C85 to induce the DPD-deficient state

Khor SP et al. Cancer Chemother Pharmacol 39:233-238, 1997

Graph showing 5 Fluorouracil Concentration (ng/mL(mg/($kg^{.995}$)) over Apolysichrons (Time/$B^{0.26}$) in dog, human, rat and mouse compared with predicted.

Complex Dedrick plot of 5-FU in humans and different animal species with DPD deficiency. The human data were obtained from a patient who was genetically deficient in DPD. The animals were treated with 776C85 to induce the DPD-deficient state

Khor SP et al. Cancer Chemother Pharmacol 39:233-238, 1997

Compartmental model for Ara-C Pharmacokinetics

Dedrick RL et al, Biochem Pharmacol 21:1-16, 1972

Mass balance equation

$$V_K \frac{dC_K}{dt} = Q_K C_B - Q_K C_K - CL_K C_B - \left[\frac{V_{max,K} C_K}{[K_{m,K} + C_K]}\right]$$

Were V = compartment volume, ml
C – drug concentration, µg/ml
T = time, min
Q = blood flow rate, ml/min
V_{max} = maximum rate of metabolism, µg/min ml
K = Michaelis constant, µg/ml
CL = non-metabolic clearance, ml/min
and the subscripts K and B refer to kidney and arterial blood, respectively.

Graph showing plasma concentration (μg/ml) over time (minutes) for ARA – C alone and ARA – C + ARA – U (delayed ARA- C elimination).

Dedrick RL et al, Biochem Pharmacol 21:1-16, 1972

Renal Clearance showing Clearance, ml/min over body wt, kg.

Kidney clearance of Ara-C and Ara-U vs body weight for mice, monkeys, dogs and humans

Dedrick RL et al, Biochem Pharmacol 22:2405-2417, 1973

Graph showing in vivo intrinsic clearance, ml/min/SRW in rats over microsomal clearance, uL/min/mg

Houston JB, Biochem Pharmacol 47:1469-1479, 1994

In vivo intrinsic clearance, ml/min/SRW in rats over hepatocyte clearance, uL/min/10^6 cells

Houston JB, Biochem Pharmacol 47:1469-1479, 1994

Scatter chart showing Clint, in vivo (mL/min/g liver) in humans over Clint, in vitro (mL/min/g liver)

Ito et al, Ann Rev Pharmacol Toxicol 38:461-499, 1998

Scatter chart showing Midazolam clearance human/transplant. Chart shows observed Cl_T, 1/min over predicted Bl_H(1'OH), l/min

Data from Thummel et al, J PET 271:549-556, 1994.