Animal Scale-Up

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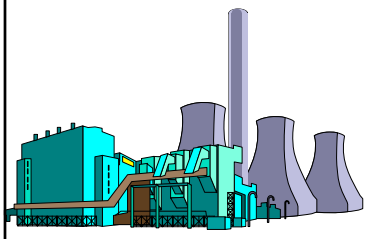
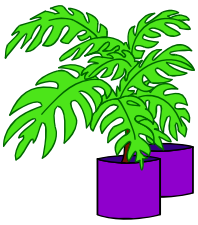
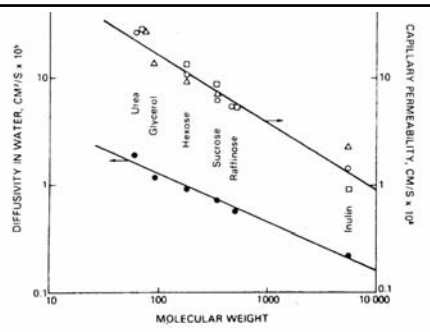


Chemical Plant



Biological Plant



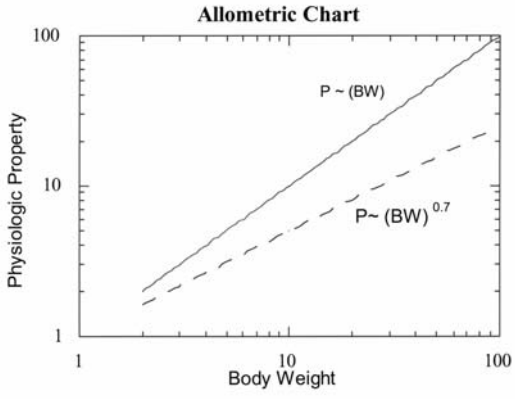
Capillary permeability and aqueous diffusivity of hydrophilic solutes versus molecular weight. Key: (○) *cat leg;* (□) *human forearm;* (△) *dog heart;* (●) *diffusivity*

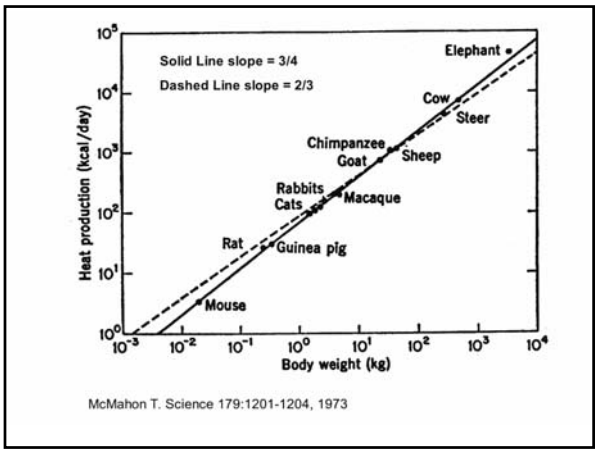
Dedrick RL et al, ASAIO J 5:1-8, 1982

ALLOMETRIC EQUATION

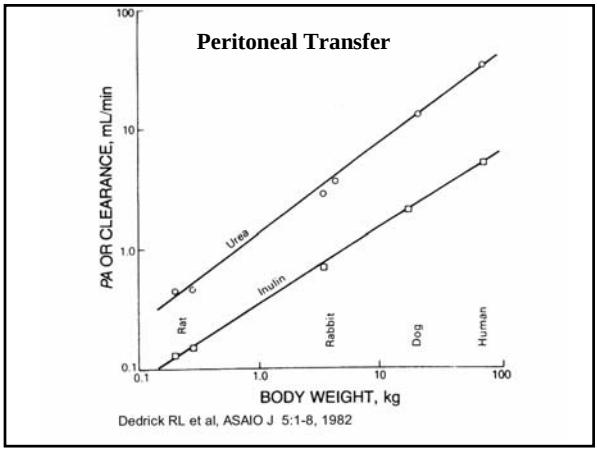
$$P = a(BW)^m$$

where P = physiological property or anatomic size
a = empirical coefficient
BW = body weight
m = allometric exponent

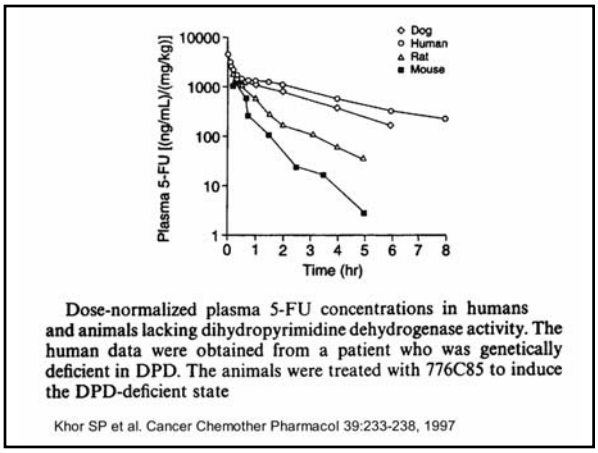




McMahon T. Science 179:1201-1204, 1973

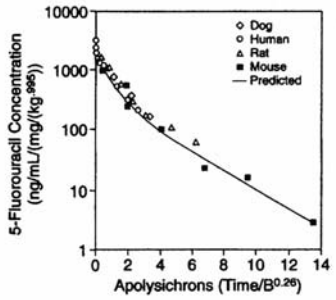


Dedrick RL et al, ASAIO J 5:1-8, 1982



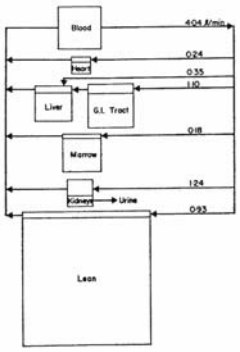
Dose-normalized plasma 5-FU concentrations in humans and animals lacking dihydropyrimidine dehydrogenase activity. The human data were obtained from a patient who was genetically deficient in DPD. The animals were treated with 776C85 to induce the DPD-deficient state

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



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 gentically 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



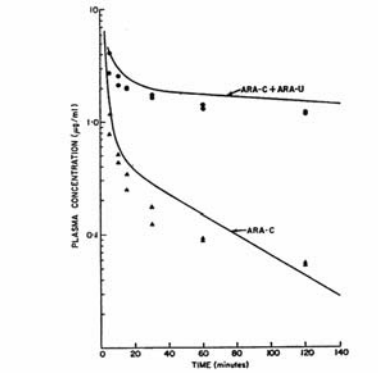
Compartmental Model for Ara-C Pharmacokinetics

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

MASS BALANCE EQUATION

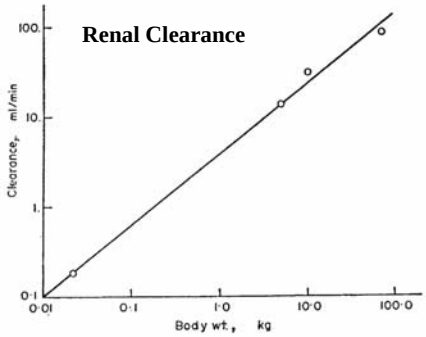
$$V_K \frac{dC_K}{dt} = Q_K C_B - Q_K C_K - CL_K C_B - \left(\frac{v_{max,K} C_K}{K_{m,K} + C_K} \right) V_K$$

where 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.



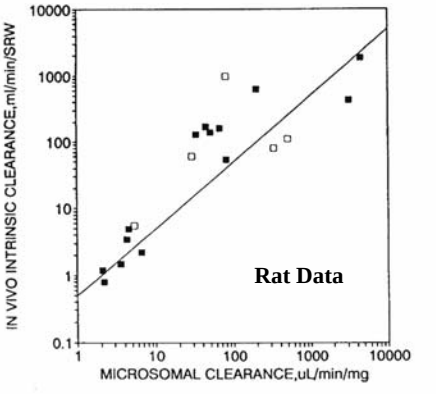
Dedrick RL et al, Biochem Pharmacol 21:1-16, 1972

Renal Clearance

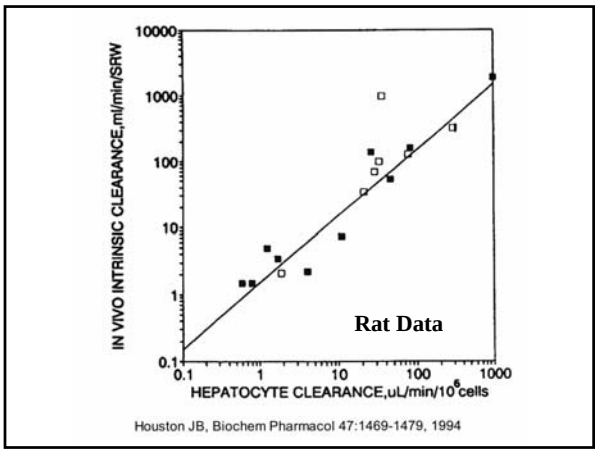


Kidney clearance of Ara-C and Ara-U vs body weight for mice, monkeys, dogs and humans

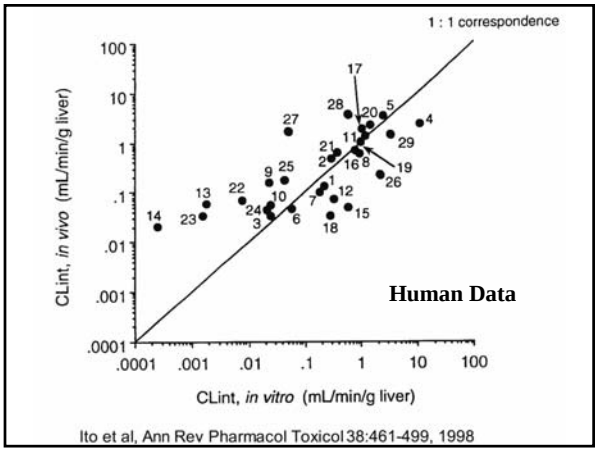
Dedrick RL et al, Biochem Pharmacol 22:2405-2417, 1973



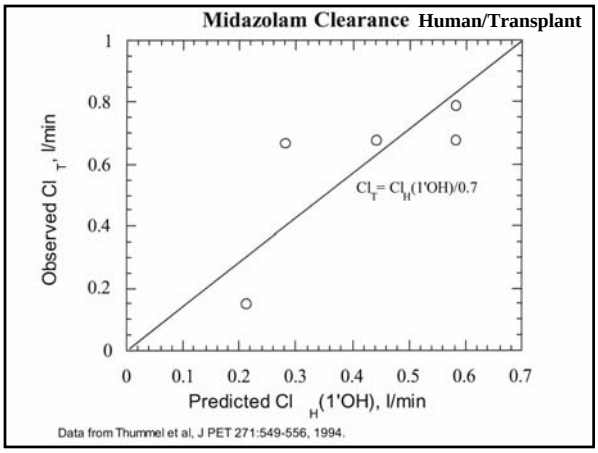
Houston JB, Biochem Pharmacol 47:1469-1479, 1994



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



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



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