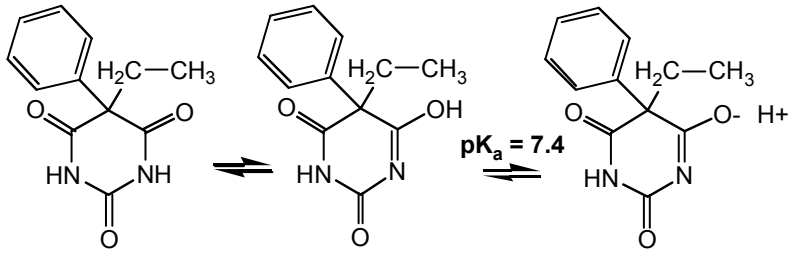
20.201 2005
Homework #2
9/14/05 **Due 9/21/04**

1) The following data were obtained from a dose-response study of three new drugs in a rat model for asthma. The response here is resolution of asthma symptoms.

	% Response (Ablation of Asthma Symptoms)		
Dose, g/kg	**Drug A**	**Drug B**	**Drug C**
1.00E-10	0	0	0
1.00E-08	3.96		
3.00E-08	29.3	2.80	2.0
1.00E-07	46.8	13.0	10.1
3.00E-07	68.2	28.0	25.0
1.00E-06	80.9	56.0	40.1
3.00E-06	90.4	74.7	50.0
1.00E-05	100	85.9	55.0
3.00E-05		95.3	57.1
1.00E-04	100	100.0	57.0
3.00E-04		96.7	57.0

a) For drug congeners A, B and C, plot the dose-response data and calculate the EC_{50} for the three drugs. Explain how you calculated these values. Define EC_{50}.
b) What is the relative order of potency for the three drugs? Explain your answer.
c) What is the relative order of efficacy for the three drugs? Explain your answer.
d) If the curves for A and B are the therapeutic and toxic responses, respectively, calculate the therapeutic index for this drug. Comment on the magnitude of the index and what implications this would have for FDA approval of the drug.

2) Phenobarbital is widely used to treat seizures. The drug is a weak acid by virtue of the reactions shown below.



a) What are the concentrations of ionized and unionized forms at pH 2 and pH 8.5 for a 1 μM total concentration of the drug?
b) Will there be significant absorption of phenobarbital directly from the stomach? Why or why not?
c) Explain how alkalinization of the urine could cause an increase in the rate of excretion of phenobarbital?

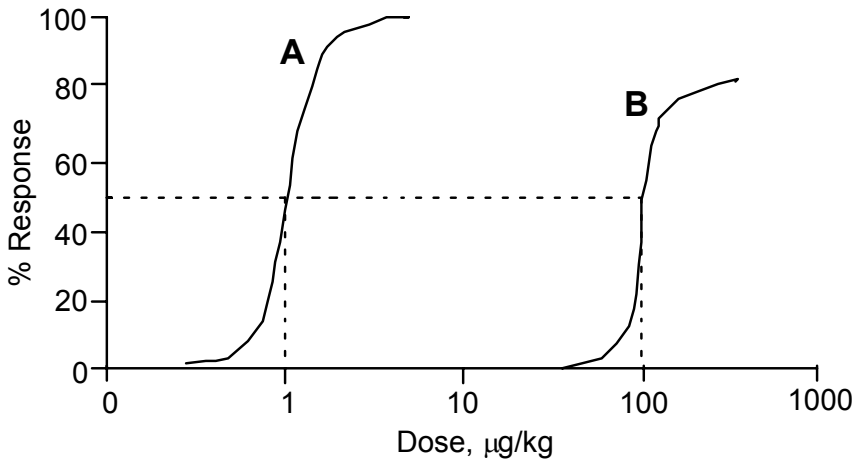
3) A new drug is an aromatic amine (i.e., base) with a pK_a of 5.

a) What is the ratio of ionized (*i.e.*, charged) to non-ionized forms of the drug at pH 2? At pH 7?

b) Will there be significant absorption of the drug from the stomach (i.e., through gastric epithelium)? Why or why not?

c) At equilibrium, what is the ratio of the concentration of uncharged drug in a buffer at pH 9 on one side of a lipid membrane to the concentration of uncharged drug in a buffer at pH 2 on the other side of the membrane? Assume that the drug is transported by simple diffusion.

4) The following questions address the dose-response graph shown below.



a) If A and B are anticancer drugs, which one is more potent and which one is more efficacious? Why? Describe an example of the measurement you might use to assess the "response" of an anticancer drug.

b) If A and B are toxins and the response is death of rats exposed to the toxin, what are the LD_{50}'s for A and B? Define the term, " LD_{50}."

c) Assume that curves A and B are the therapeutic and toxic dose-response curves for a new antiarrythmic drug (treats cardiac arrythmias). What is the therapeutic index (TI) for the drug? Define TI and give examples of "good" and "bad" TI's.