



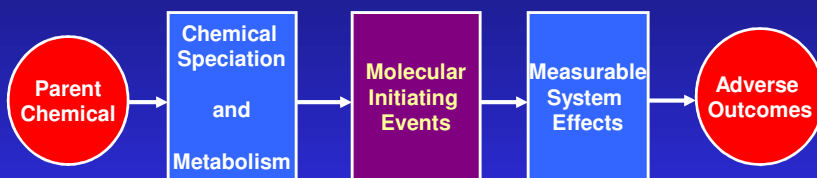
Narcosis as a Reference

Gilman Veith

McKim Conference on Predictive Toxicology

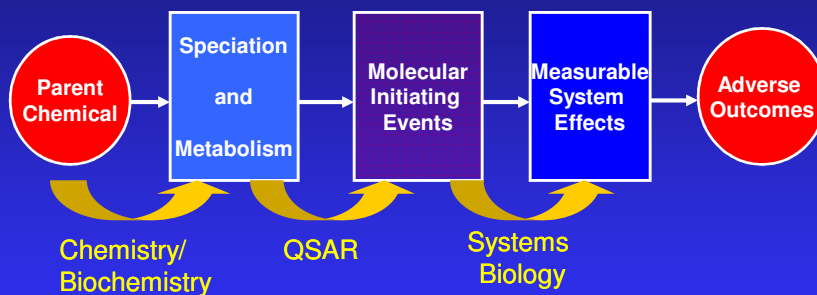
The Inn of Lake Superior
Duluth, Minnesota
September 25-27, 2007

Conceptual Framework

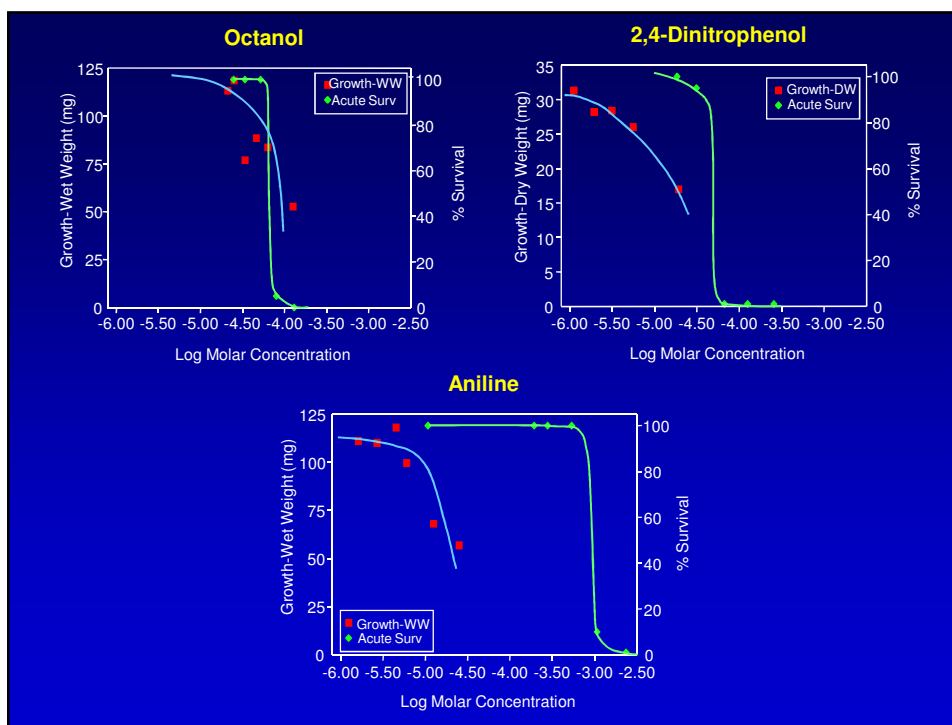


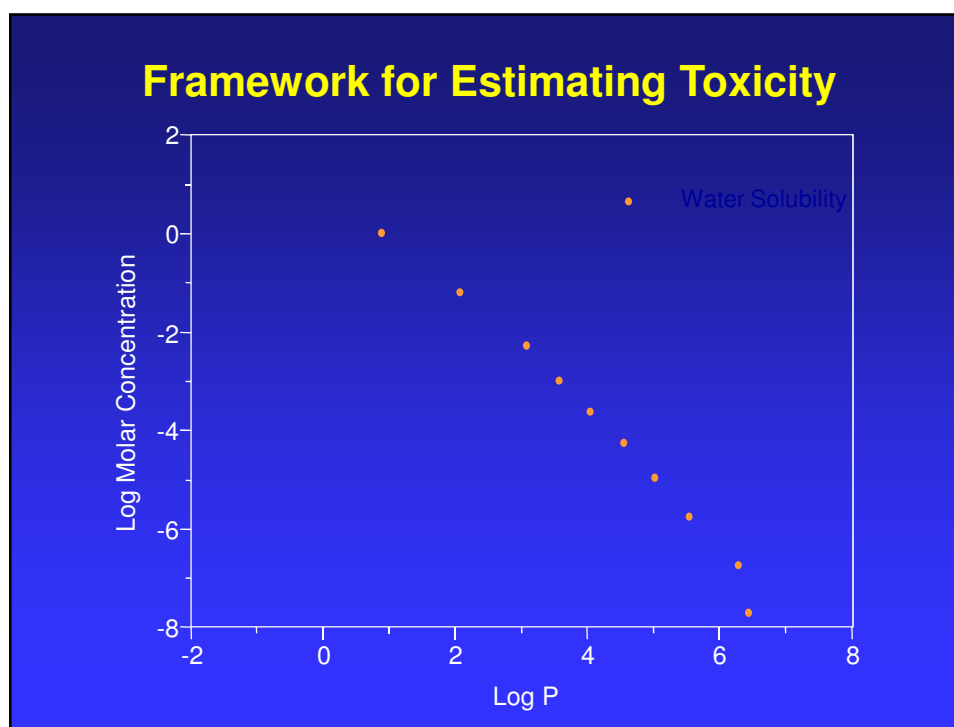
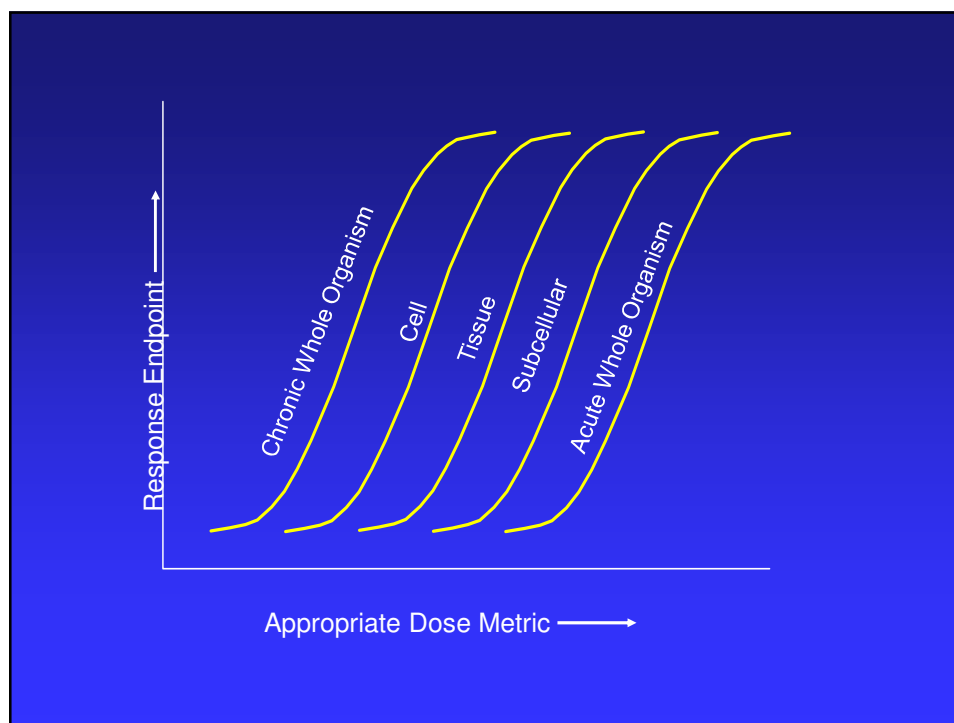
Rather than developing statistical models of complex endpoints, key molecular initiating events become the "well-defined" endpoints for QSAR.

IQF Framework for QSAR

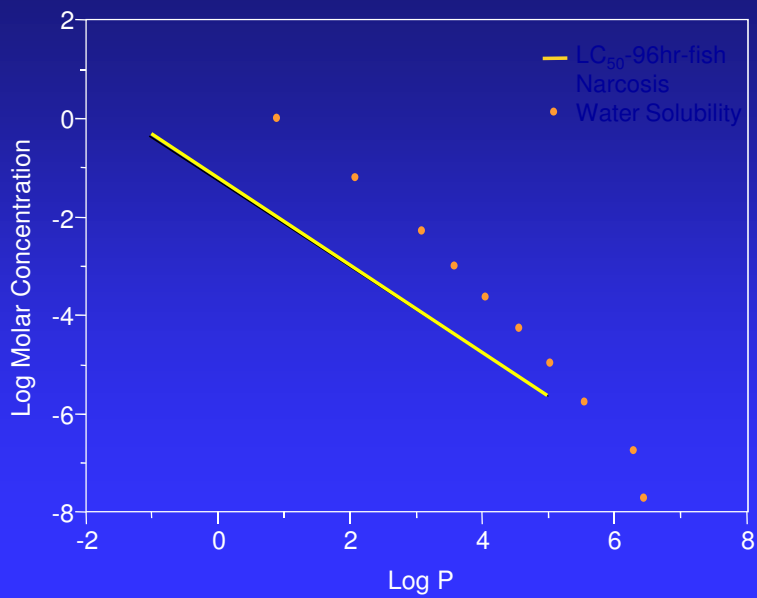


1. Identify Plausible Molecular Initiating Events
2. Design Database for Abiotic Binding Affinity/Rates
3. Explore Linkages in Pathways to Downstream Effects
4. Develop QSARs to Predict Initiating Event from Structure

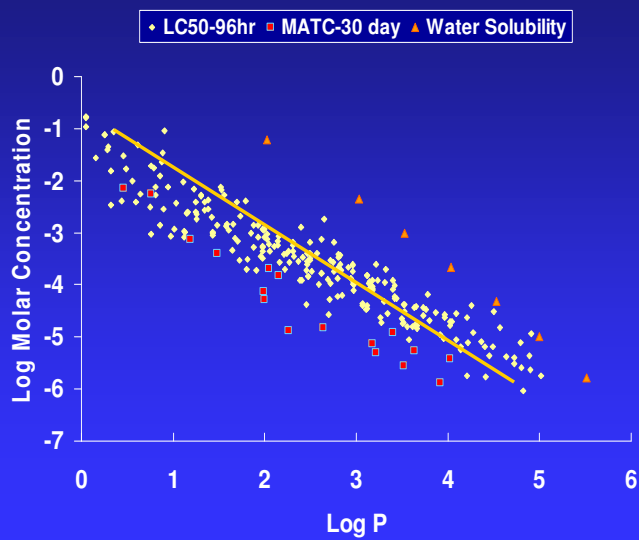


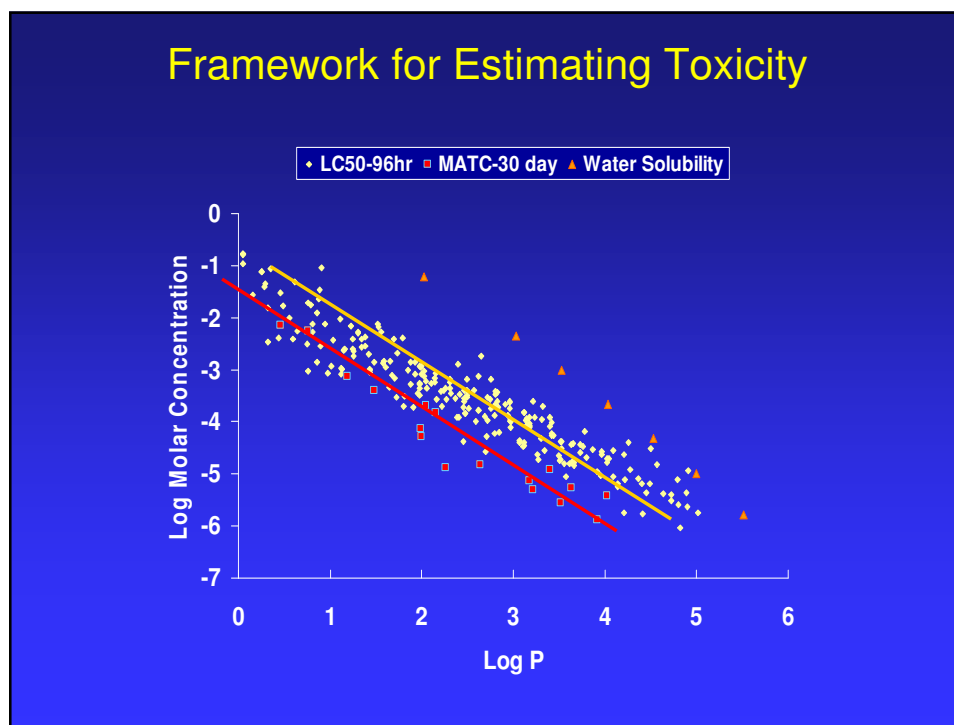
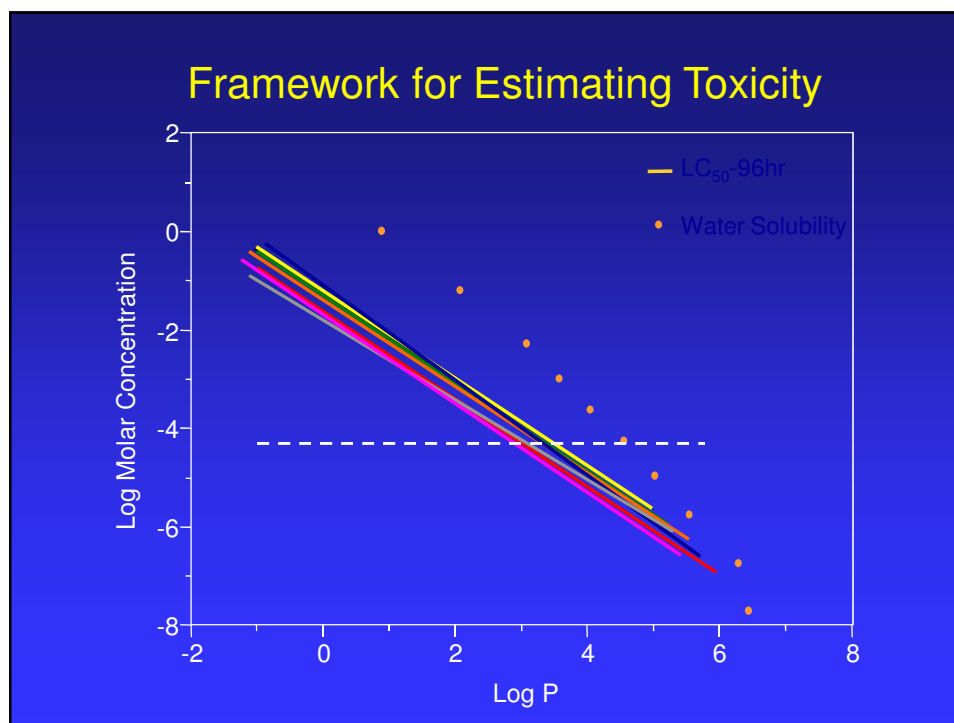


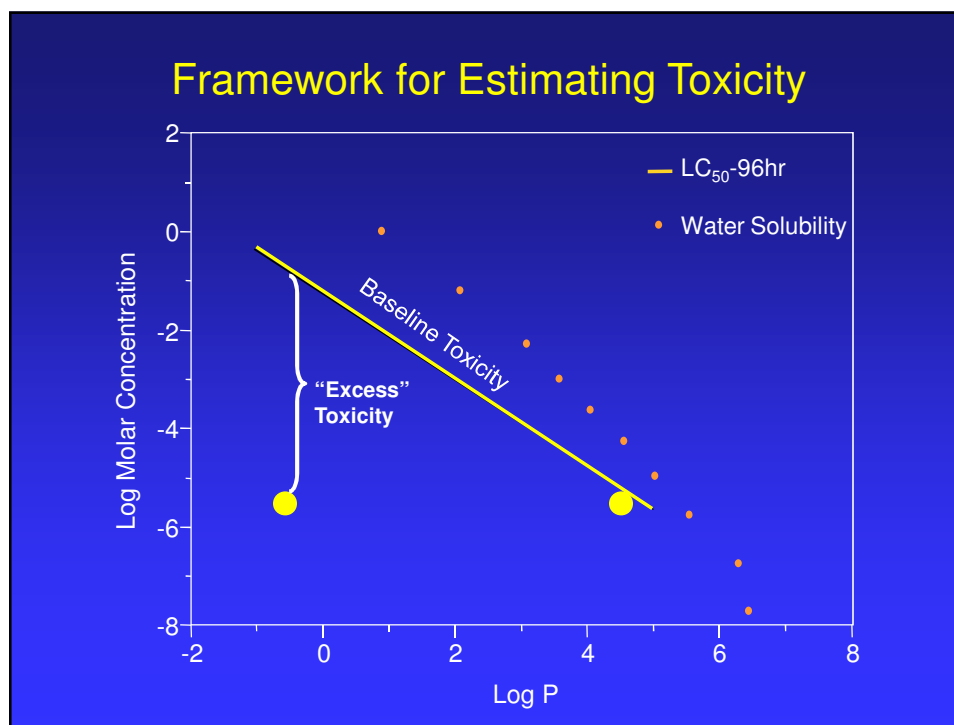
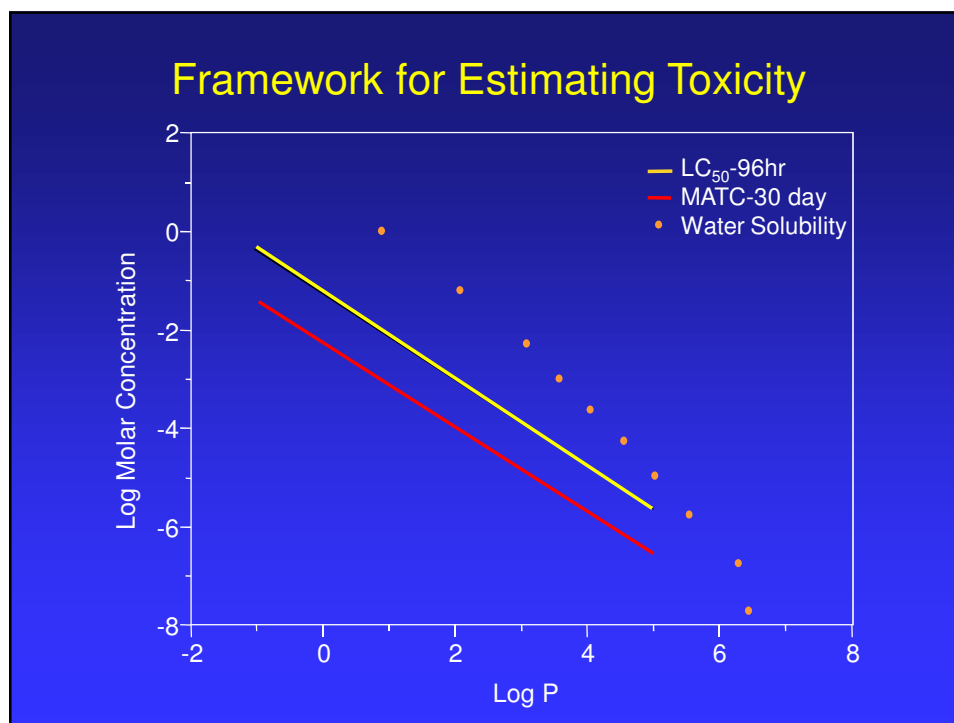
Framework for Estimating Toxicity

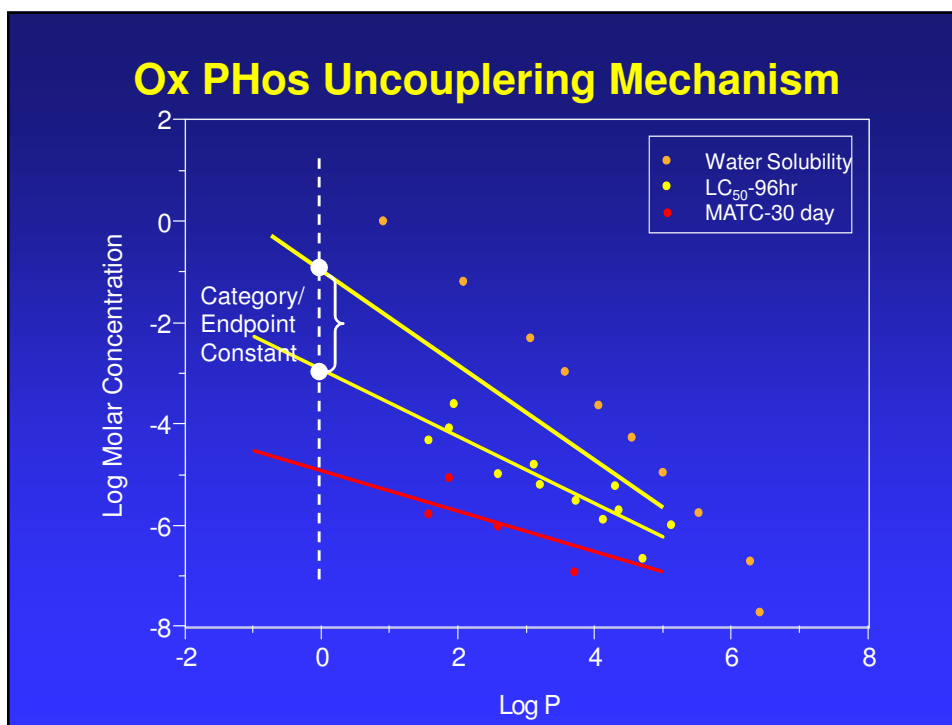
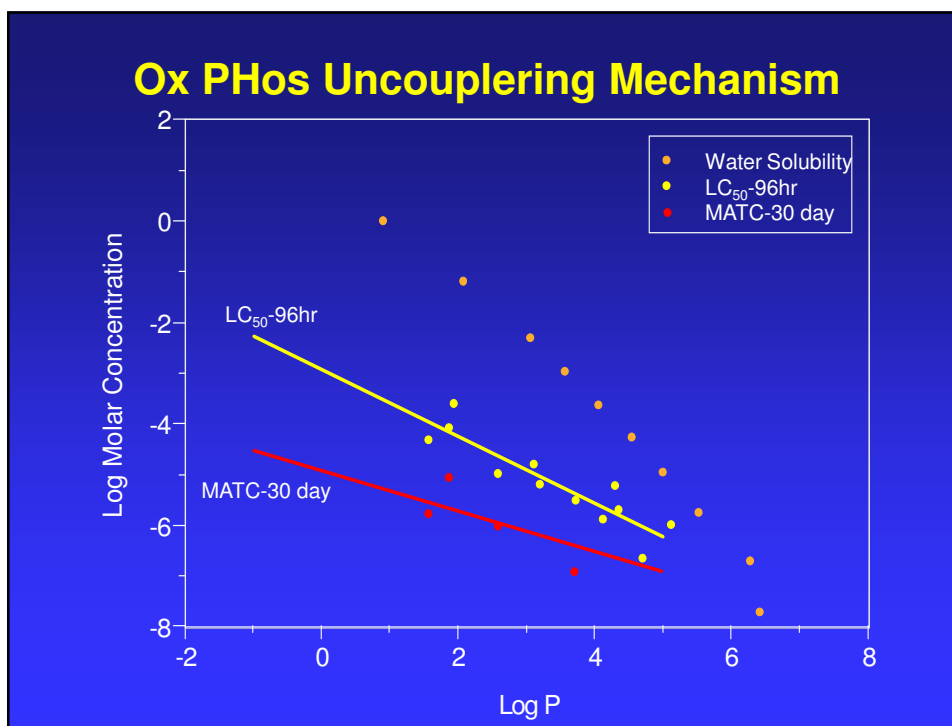


Framework for Estimating Toxicity

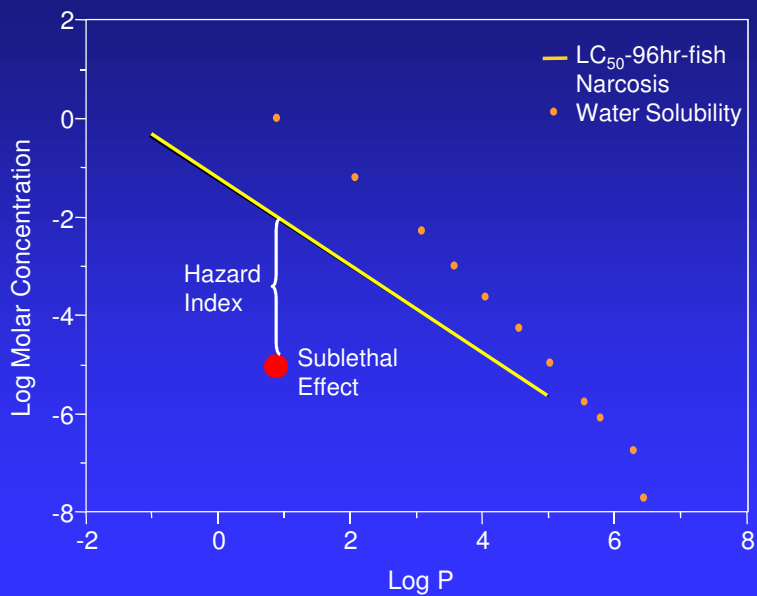




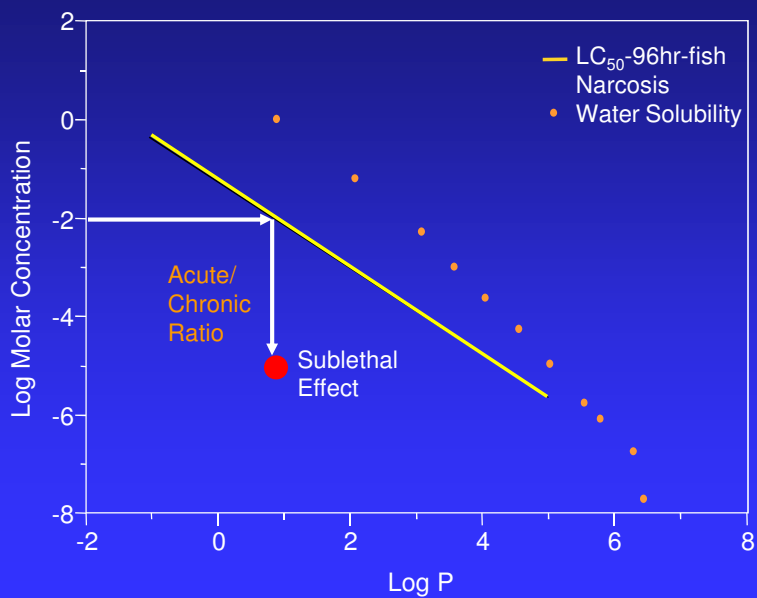


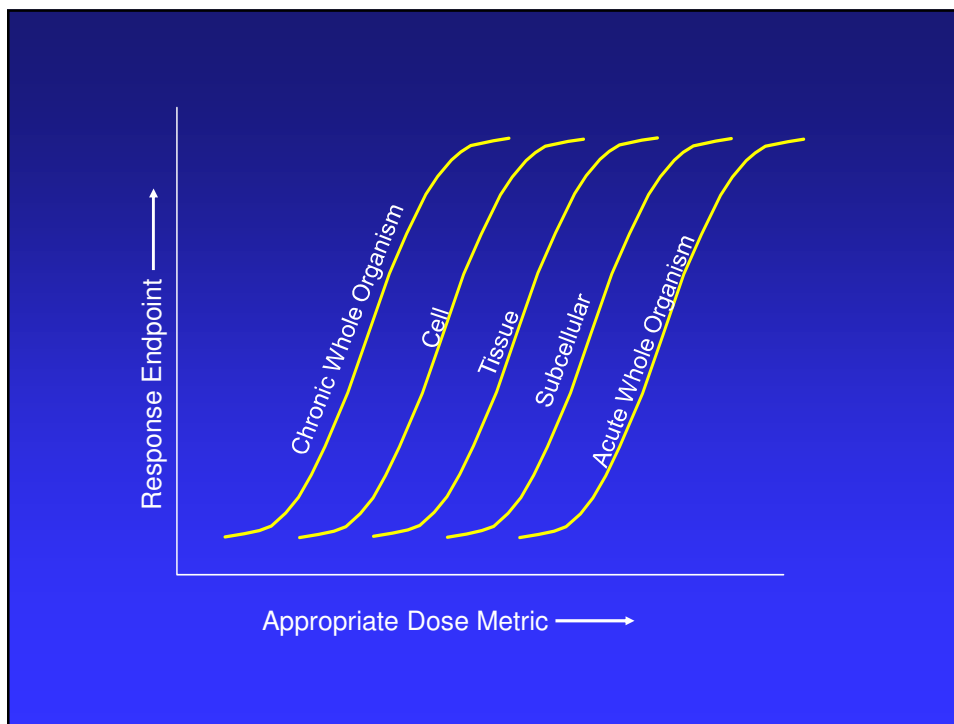


Framework for Estimating Toxicity

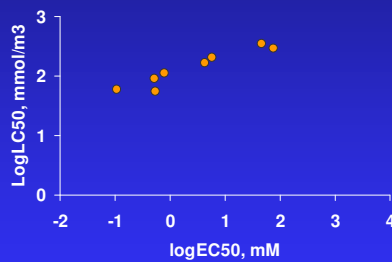
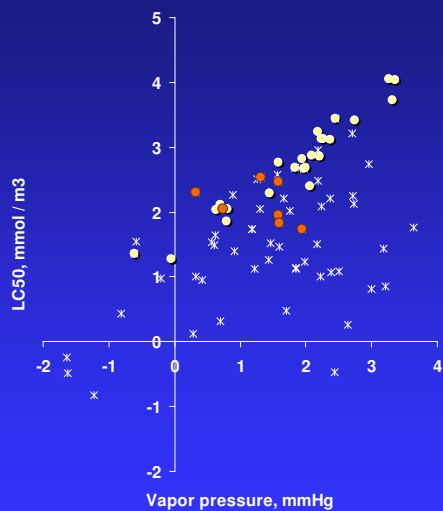


Framework for Estimating Toxicity

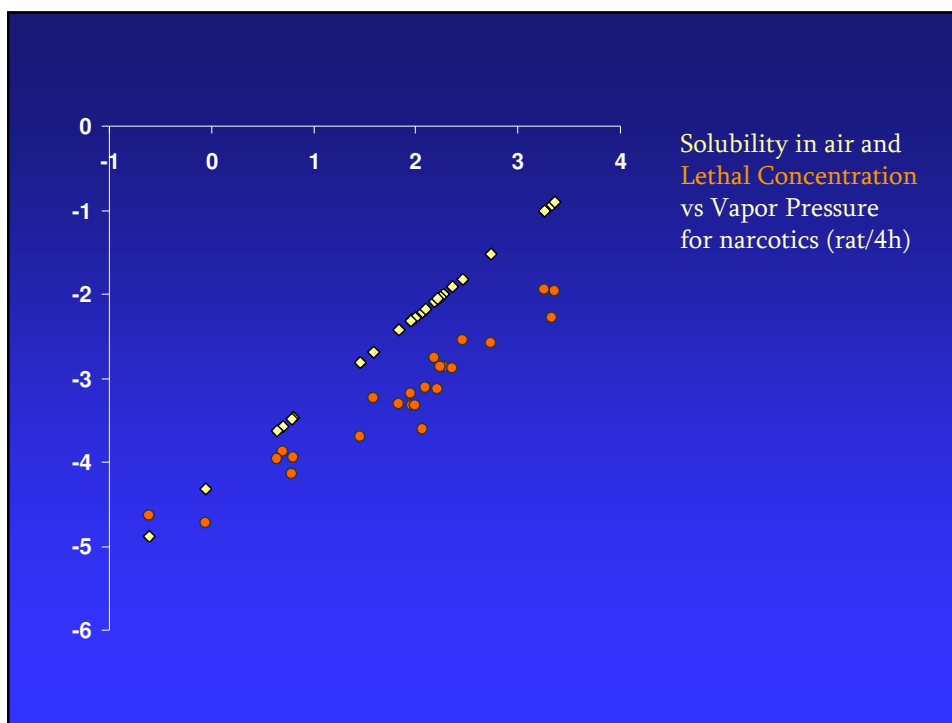




For **ACRYLATES & METHACRYLATES** there is no relationship with Vapor Pressure but significant correlation with GSH reactivity



LC50 vs GSH reactivity
for acrylates and methacrylates



Baseline Toxicity

- Fish and mammal inhalation baseline toxicity are not directly comparable because the external media are different
- However, blood thermodynamic activity for LC50(nar) should be the same in fish and mammal
- At steady-state, the activity in air/water equals the activity in blood by definition :

$$\alpha = C \times \gamma$$

α – activity; C- concentration; γ -activity coefficient

Baseline Toxicity

- The thermodynamic activity at any concentration can be estimated by dividing by the solubility in the medium
- activity for narcosis in fish = $LC50(\text{fish})/\text{water solubility}$
activity for narcosis in rat = $LC50(\text{rat})/\text{air solubility}$
- if activity for narcosis in fish and rat were equal, the plot of $LC50$ versus solubility in exposure medium should be the same

Log $LC50$ for fish or rat vs Solubility in water or air

