

# QSAR-based Prediction of Inhalation Toxicity

*Incorporating elements of dosimetry and reactivity to predict biological response*

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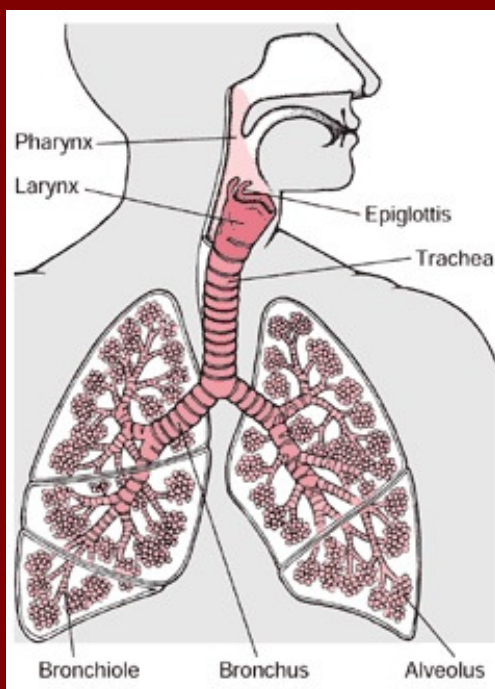
## Human Airway

*Chemical disposition  
(free vapor)-*

- *VP*
- *Sol<sub>H2O</sub>*
- *Chemical Reactivity*

*Biological Response -*

- *Protein adduct -  
immune surveillance*
  - *Asthma, T-cell mediated hypersensitivity*
  - *Irritation/inflammation /tissue necrosis*



## Factors affecting pulmonary response

Chem Name	Water Solubility	Chemical Reactivity	Pulmonary Toxicity
Acetaldehyde	High	Moderate	Upper airways
Ammonia	High	High	Upper airways
Phosgene Isocyanates	Low	High	Lower terminal airways
Carbon monoxide	Low	Low	none



## The QSAR Inhalation Toxicity Database

- Although inhalation toxicity data have been compiled in selected open access databases, the entries are limited and have seldom been subjected to rigorous peer review.
- Thus, although these databases may suffice for general reference purposes, the data is frequently ambiguous and of questionable quality.
- As a result, models of inhalation toxicity derived from these databases have largely been unsuccessful and doubts have been cast regarding the validity of QSAR approaches to inhalation toxicology.

## The Inhalation Toxicity Database

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- The inhalation toxicity database (ITDB) is an effort to compile high quality inhalation data published in the open literature and government reports as well as publicly available unpublished toxicity reports using strict Q/A standards.
- ITDB has a goal of eventually becoming an international and widely distributed resource for high quality inhalation toxicity data that can be used to better characterize inhalation toxicity with minimal animal testing.

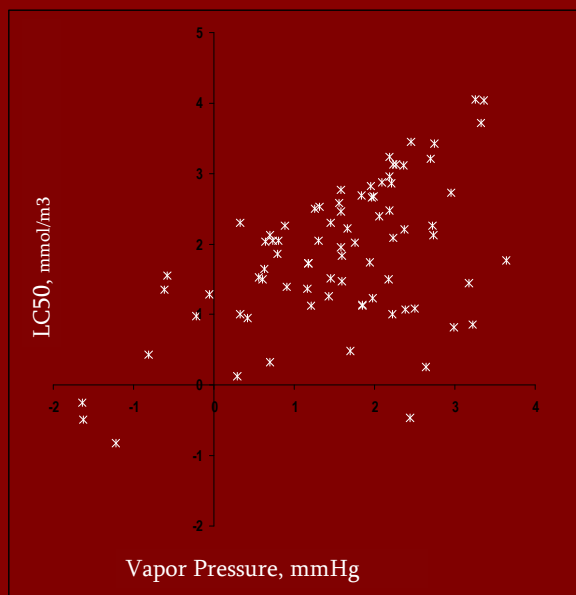
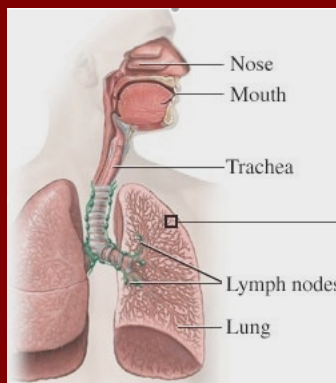
## Current Status of the ITDB

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- We have embarked on compiling an exhaustive mammalian inhalation toxicity database using strict standards of peer review to insure only high-quality studies are included.
- Currently focus on acute (4 hr) inhalation by rats
  - About 200 unique chemicals, 86 – tested for acute toxicity in rat/4h
  - Limited short-term mouse data
  - Expanding to include other species as well as repeat exposure and chronic inhalation data
- Preliminary analyses of the database.....

# Modeling Assumptions

- Obstructive disorders
  - Low vapor pressure
  - High water solubility
  - High chemical reactivity
  
- Restrictive disorders
  - Low vapor pressure
  - Low water solubility
  - High chemical reactivity
    - MoA - specific disease
  
- Non-specific, narcotic-like effects
  - Low vapor pressure
  - Low water solubility
  - Low chemical reactivity



LC50/rat/4h vs Vapor Pressure

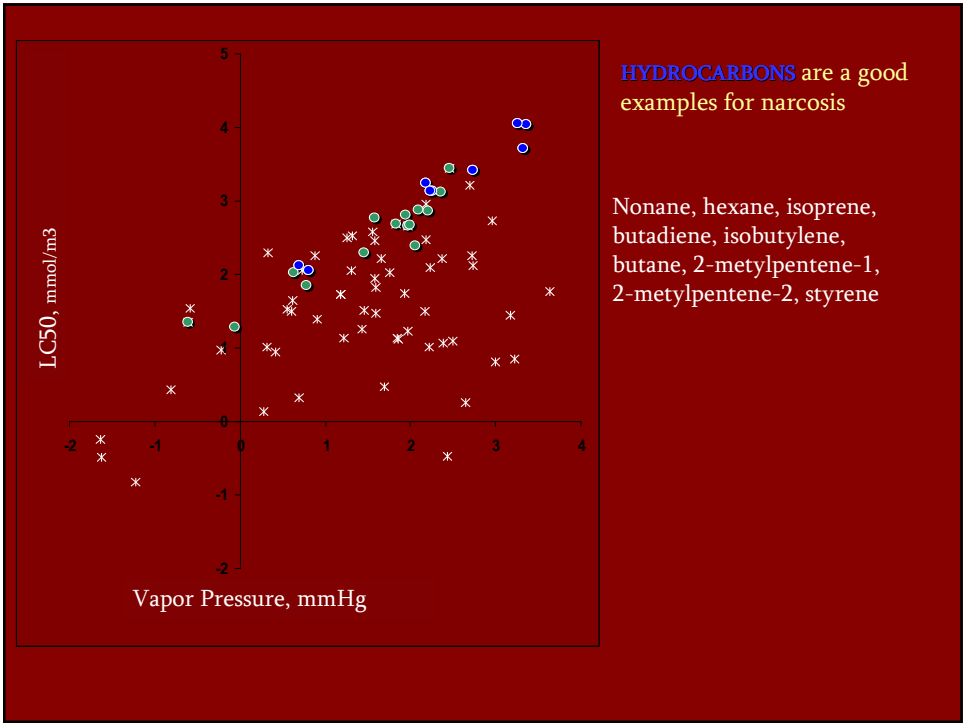
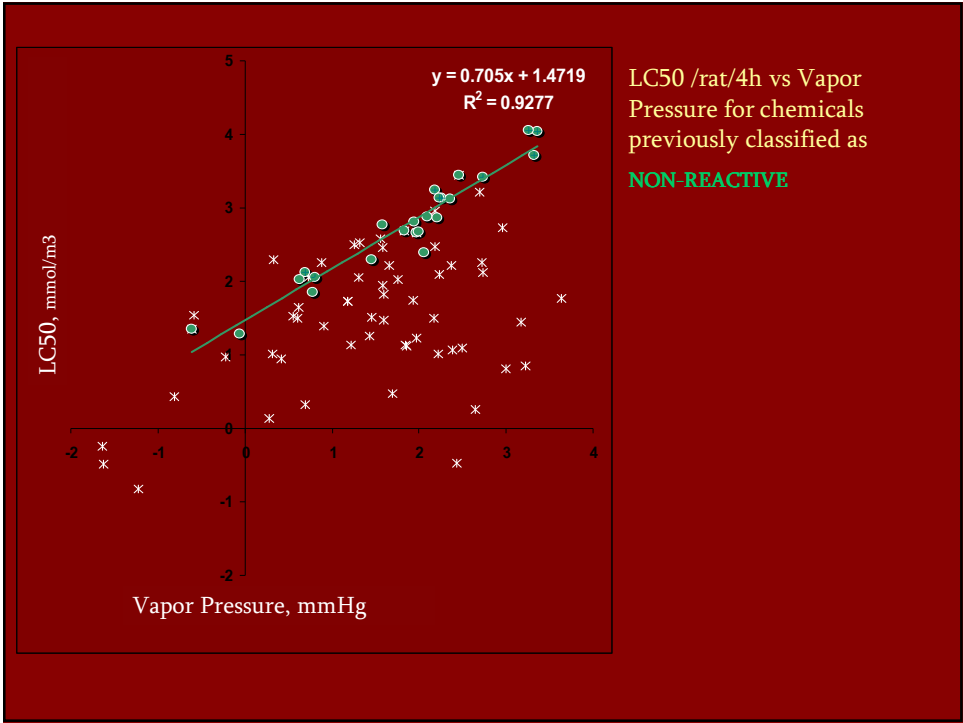
Data was compiled from the literature.

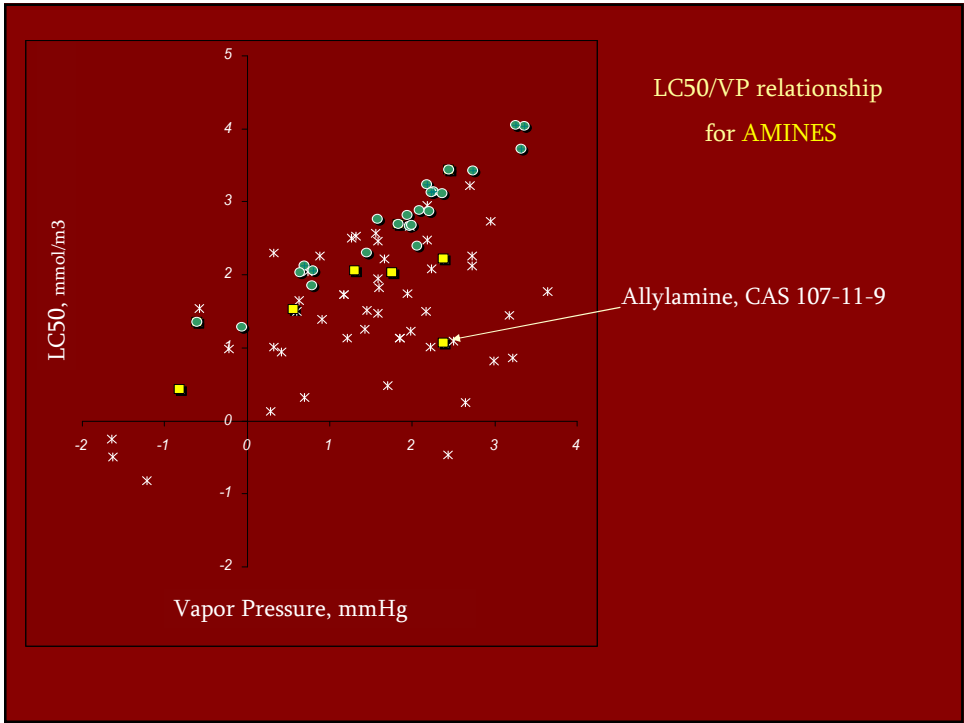
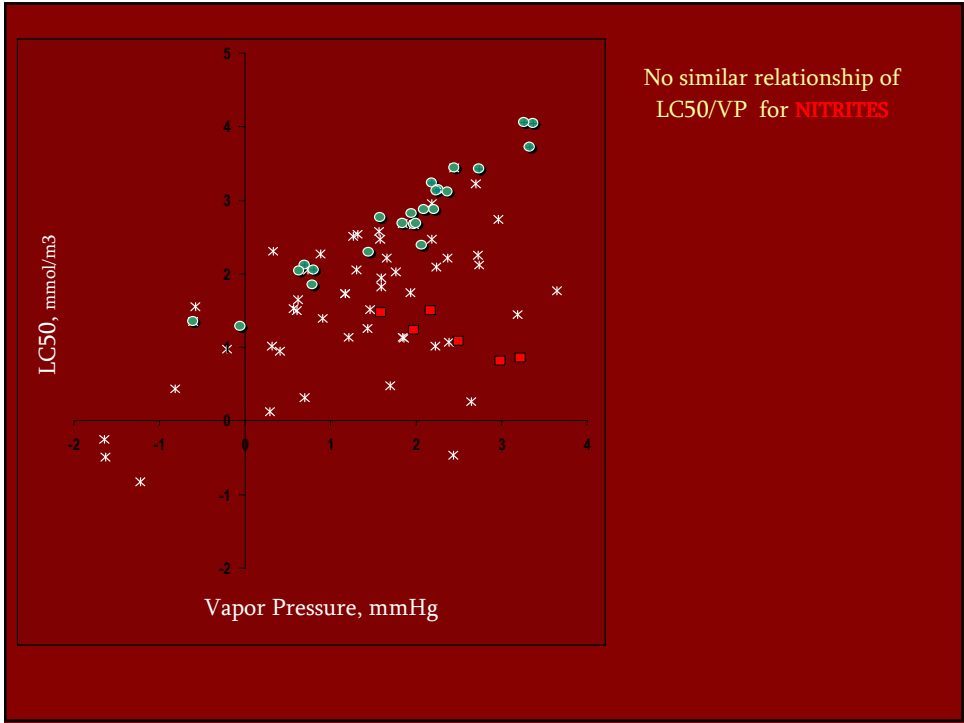
- From mid 50s to present
- All chemicals tested as vapors \*\*
- Consistent exposure conditions \*\*\*
- Different rat strains

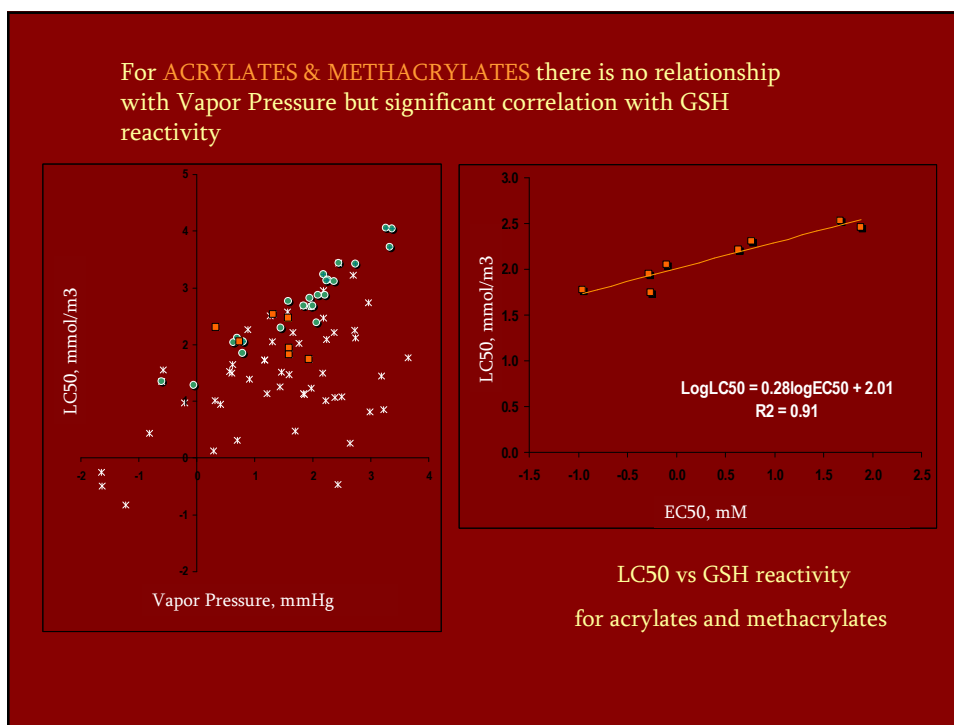
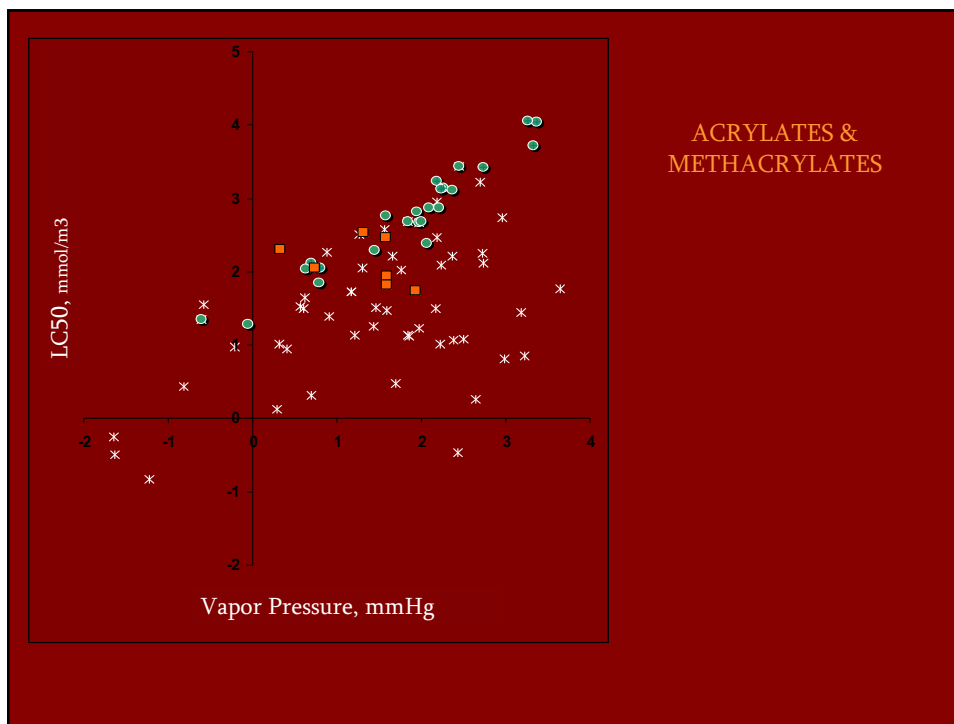
\* Guidelines somewhat vary with time

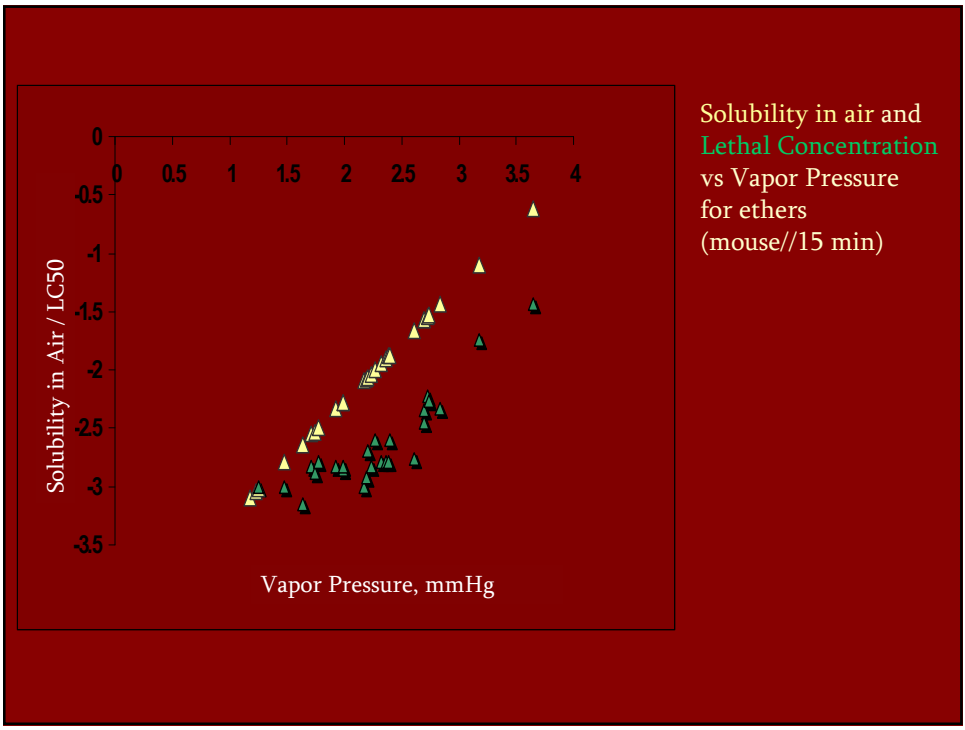
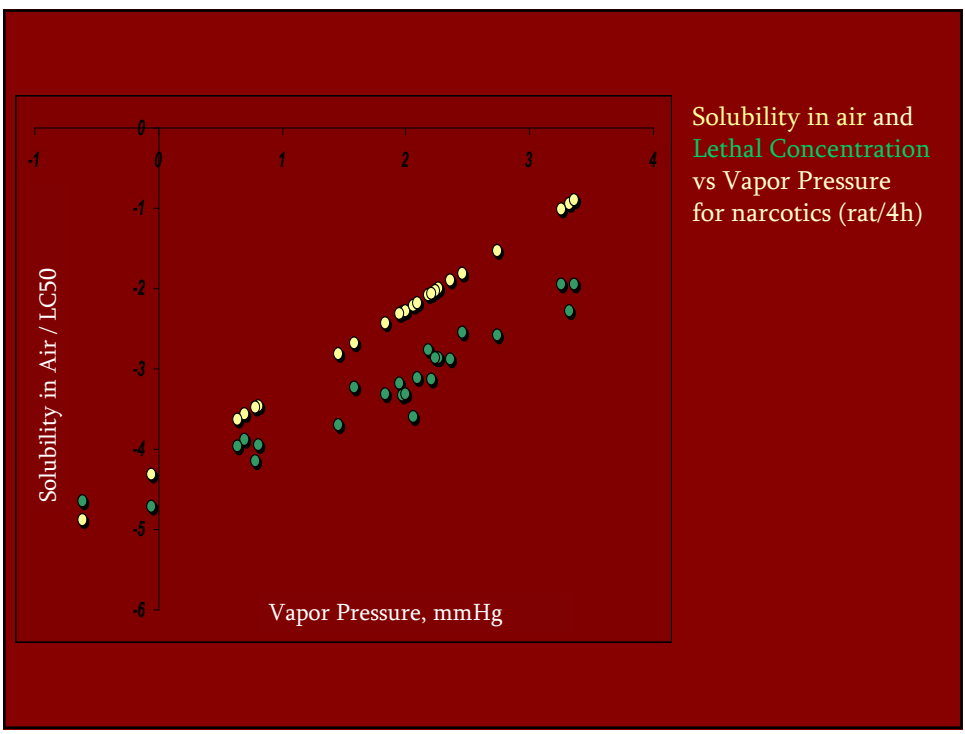
\*\* Specified (aimed) in the experiment but sometimes might not be truth

\*\*\* Exposure time constant, number of animals and observation periods vary











## Baseline Toxicity

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

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

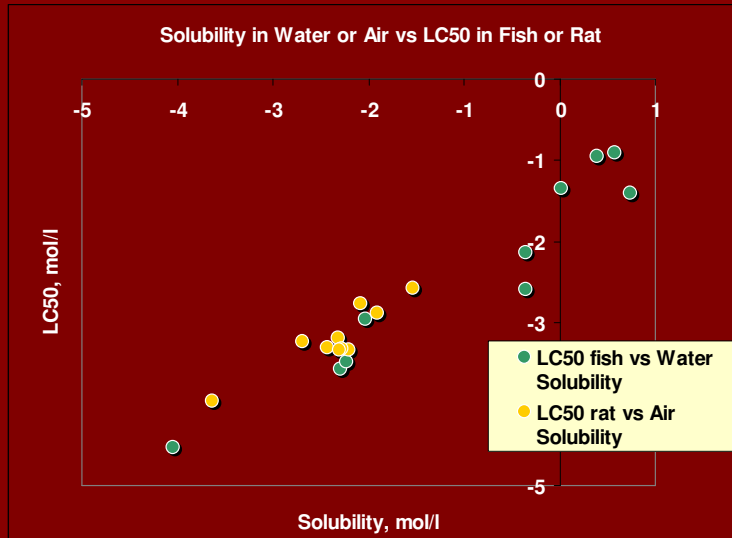
$\alpha$  – activity; C- concentration;  $\gamma$ -activity coefficient

## Baseline Toxicity

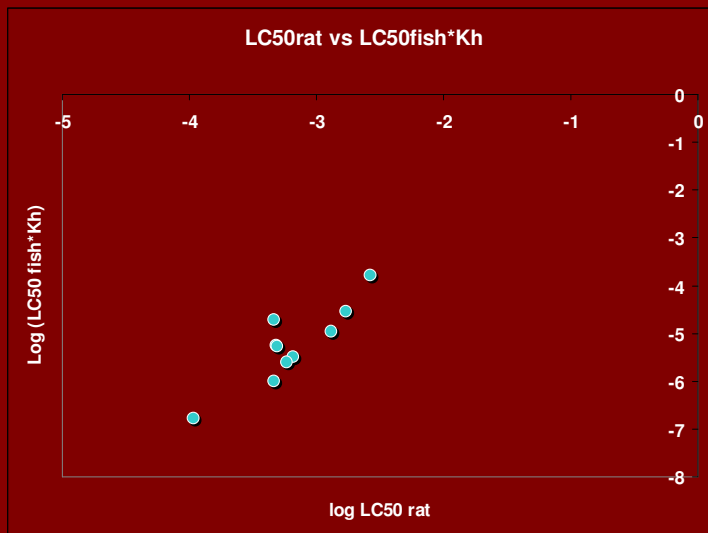
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- The thermodynamic activity at any concentration can be estimated by dividing by the solubility in the medium
- activity for narcosis in fish = LC50(fish)/water solubility  
activity for narcosis in rat = LC50 (rat)/air solubility
- if activity for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

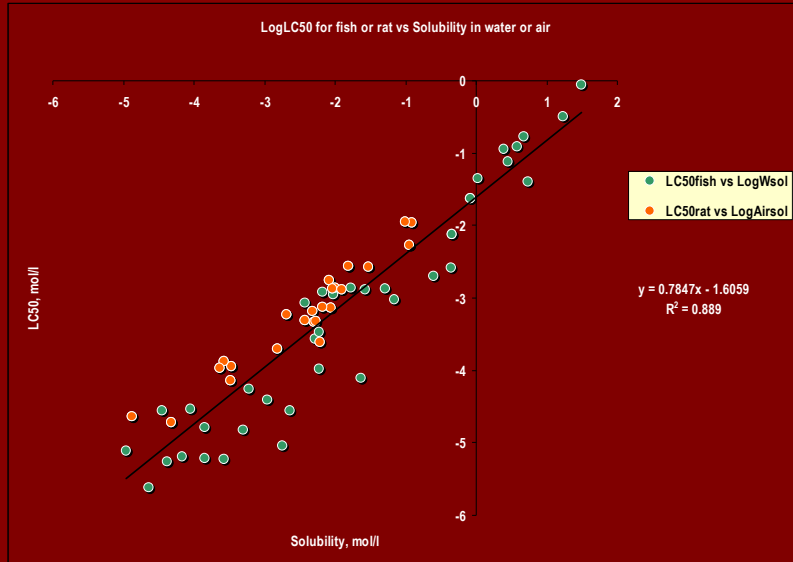
### Solubility in Water or Air vs LC50 in Fish or Rat (combined)



### LC50<sub>rat</sub> vs LC50<sub>fish</sub>\*Kh



## LogLC50 for fish or rat vs Solubility in water or air



## Concentration response curves for all mixture components

