## Neurotoxic Hazards – Context

- Specific vs non-specific
  - Pesticides designed to be neurotoxic
  - All the rest
- Acute vs persistent
  - Reversible ‘pharmacological’ actions
  - Holes in the brain
- Life stage susceptibility
  - Sensitive developmental periods
  - Aging

## Modeling Acute Neurotoxic Hazards

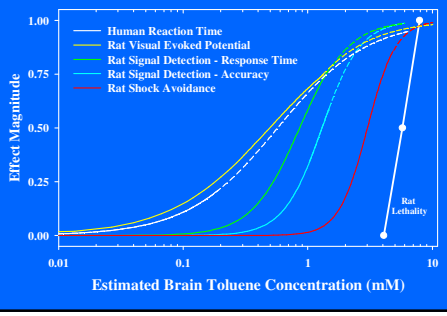
It’s as smple as A, B, C…

A. Identify molecular target site(s) of action
B. Identify factors affecting efficacy and potency at the target site(s)
C. Link effects at target site(s) to adverse outcome(s)

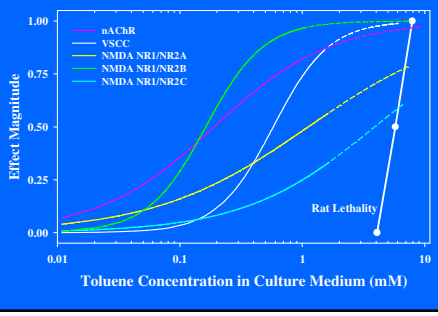
# How can *in vivo* and *in vitro* dose-response information be used to determine a toxicity pathway?

1. Does a common maximal effect at lethality indicate a common MOA?
2. How does knowledge of membrane targets (i.e., ion channels) help identify a toxicity pathway?
3. Can dose-response information point to predictive channel(s)?
4. What endpoint should be modeled?

**Effects of Inhaled Toluene *In Vivo***




**Effects of Inhaled Toluene *In Vitro***




# Factors predicting potency of solvents and anesthetic drugs

## Lipophilicity
(Meyer-Overton)

Relates applied dose (MAC) to lipophilicity (oil:gas partition)

Probably a kinetic factor that determines the amount of the chemical reaching the target membrane

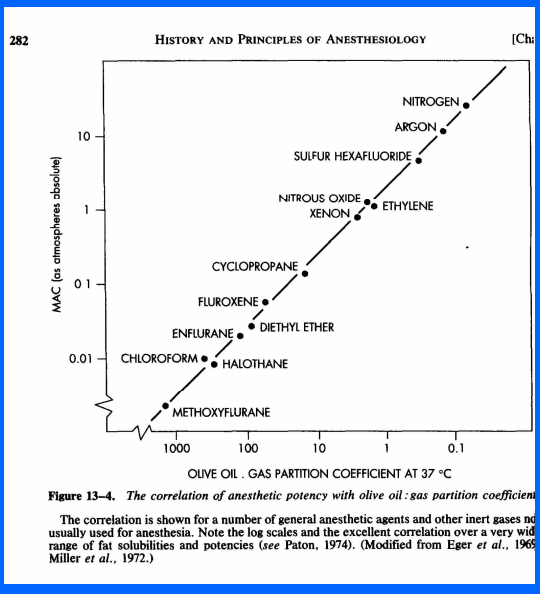



**Figure 13–4.** *The correlation of anesthetic potency with olive oil : gas partition coefficient*

The correlation is shown for a number of general anesthetic agents and other inert gases no usually used for anesthesia. Note the log scales and the excellent correlation over a very wid range of fat solubilities and potencies (*see* Paton, 1974). (Modified from Eger *et al.*, 1965 Miller *et al.*, 1972.)

## Sensitivity of Ion Channel Function to Selected Solvents and Pharmacological Agents

| Compound | Ion Channel | | | | |
|---|---|---|---|---|---|
| **Solvents** | **NMDA Receptor** | **nAChR** | **GABA Receptor** | **Glycine Receptor** | **VSCC*** |
| Toluene | Inhibits | Inhibits | Potentiates | Potentiates | Inhibits/Potentiates |
| Trichloroethylene | ND | ND | Potentiates | Potentiates | Inhibits/Potentiates |
| Perchloroethylene | ND | Inhibits | ND | ND | Inhibits/Potentiates |
| 1,1,1-Trichloroethan | Inhibits | ND | Potentiates | Potentiates | Inhibits |
| Ethanol | Inhibits | Inhibits/Potentiates | Potentiates | Potentiates | Inhibits |
| Halothane | Inhibits | Inhibits | Potentiates | Potentiates | Inhibits |
| **Pharmacological Agents** | **NMDA Receptor** | **nAChR** | **GABA Receptor** | **Glycine Receptor** | **VSCC*** |
| MK-801/Dizocipline | Antagonist | Antagonist | -- | -- | -- |
| Memantine | Antagonist | Antagonist | -- | -- | -- |
| NMDA | Agonist | -- | -- | -- | -- |
| Mecamylamine | -- | Antagonist | -- | -- | -- |
| Nicotine | Potentiates | Agonist | -- | Agonist | -- |
| Bicuculline | -- | Antagonist | Antagonist | -- | -- |
| Picrotoxin | -- | -- | Antagonist | Antagonist | -- |
| GABA | -- | -- | Agonist | -- | -- |
| Glycine | Agonist | -- | -- | Agonist | -- |
| Strychnine | -- | Antagonist | Antagonist | Antagonist | -- |

-- No Effect ND - Not Determined
*VSCC - Voltage Sensitive Calcium Channel

Bushnell et al., 2005

## Factors predicting potency of solvents and anesthetic drugs

### Molecular Size
'Alcohol cut-off'

Relates potency at GABA receptor to size of molecule (C number)

Probably a dynamic factor that suggests a receptor with finite size at the target membrane

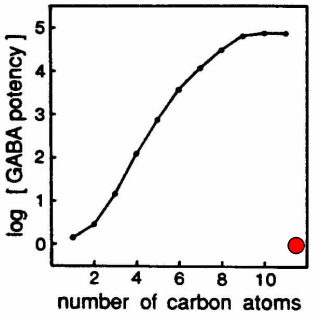



Fig. 3 Relationship between potencies for current enhancement and the numbers of carbon atoms of *n*-alcohols. With increase in the number of carbon atoms, the potency first increased and then leveled off, and at $C_{12}$ it disappeared. Potencies (in $M^{-1}$) are defined as reciprocals of the concentrations for enhancing the current to 133% of the control value

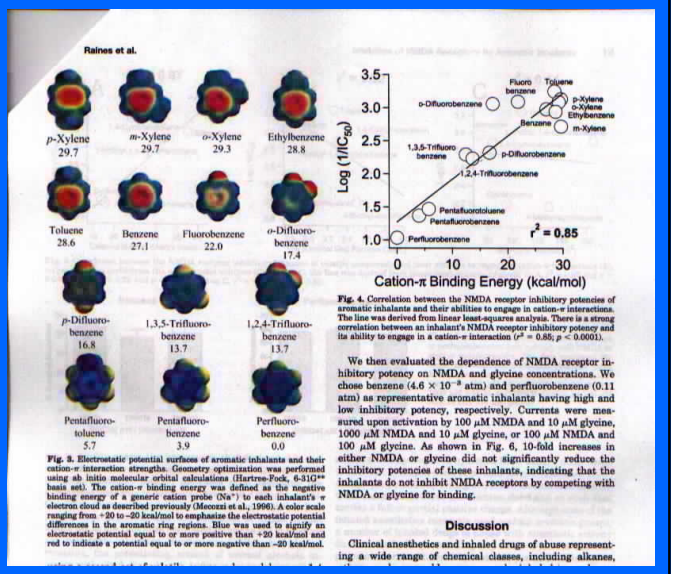
**Nakahiro et al., 1996**

## Factors predicting potency of solvents and anesthetic drugs

### Binding energy
(Raines)

Relates potency at NMDA receptor to cation-π binding energy

Probably a dynamic factor that determines the magnitude of the effect at the target site




Raines et al., 2004

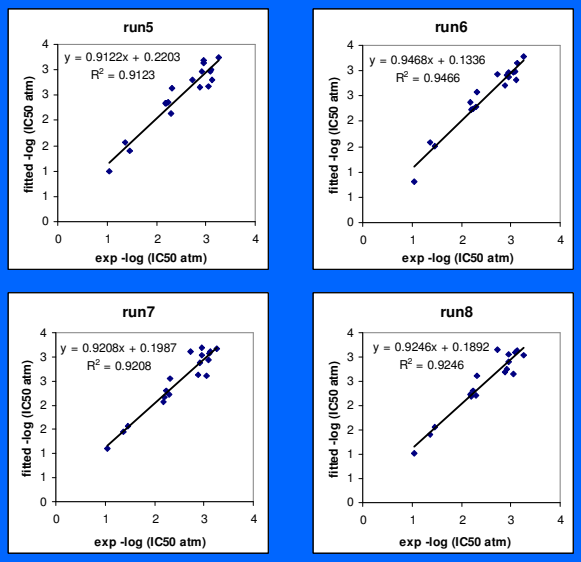
## Factors predicting potency of solvents and anesthetic drugs

**Genetic Algorithm-Based Descriptor Selector Algorithm**

Used Raine's data set of 18 chemicals for which IC50 values at the NMDA receptor were determined.

Exhaustive approach to determine which of 1500 descriptors could be added to the binding energy to maximize the *leave one out* $q^2$ value.

Very good correlations between measured and predicted IC50s involving 2 or 3 parameters of the 1500 in the pool.




Todd Martin, NRMRL

Can these factors be incorporated into a model?

$E_{GABA} \sim f(\log P, Cn, X)$

$E_{NMDA} \sim f(\log P, \pi, X)$

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$E_{in\ vivo} \sim F(E_{GABA}, E_{NMDA}, \ldots X)$