

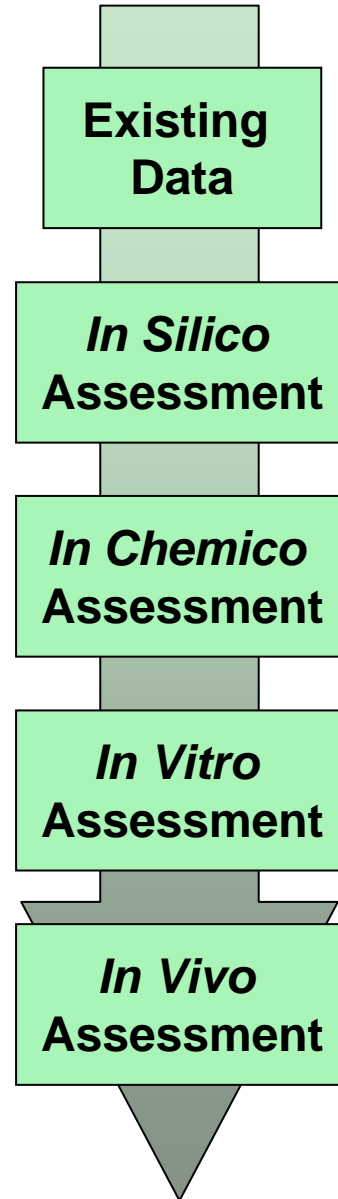
# **Biological Read-Across: Species-Species and Endpoint- Endpoint Extrapolation**

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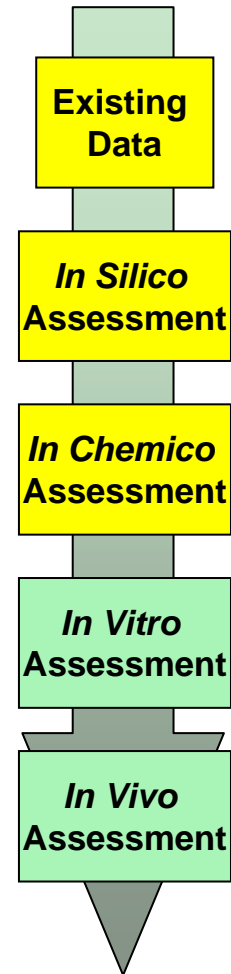
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# Integrated Testing Strategies (ITS)



# An Initial Stage of an ITS is the Use of *In Silico* and *In Chemico* Techniques

- Existing data
- Category formation
- Filling data gaps



# Category Formation

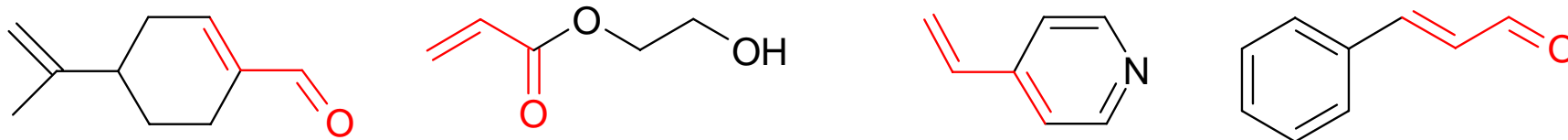
- **Developing groups of similar compounds**
- **Obtaining toxicological data and information**
- **Performing read-across to “interpolate” toxicological endpoints**

# Category Formation

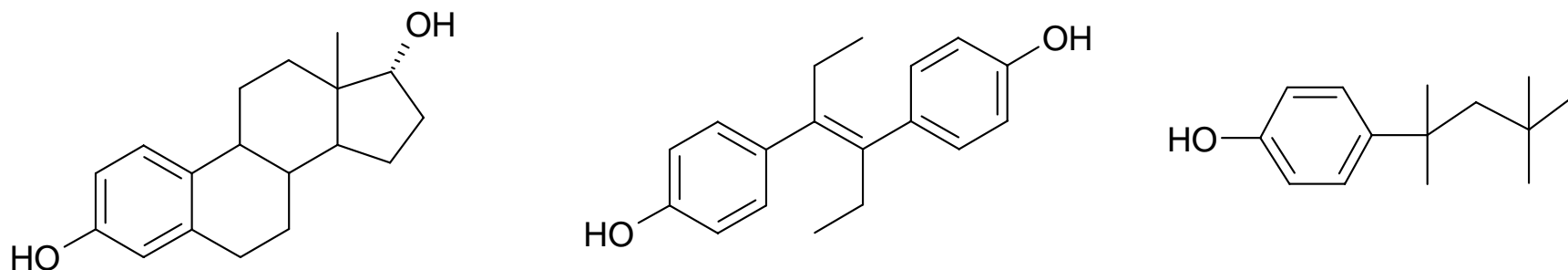
## Structural Analogues





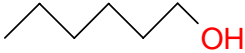
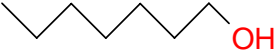
## Mechanistic Analogues



## Toxicologically Meaningful Analogues



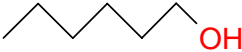
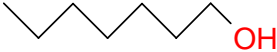


# Chemical Read-Across

							
<b>Toxicity</b>	●	→	○	●	→	○	<b>SAR / Read-Across</b>
<b>Toxicity</b>	●	→	○	○	←	●	<b>Interpolation</b>

# Biological Read-Across

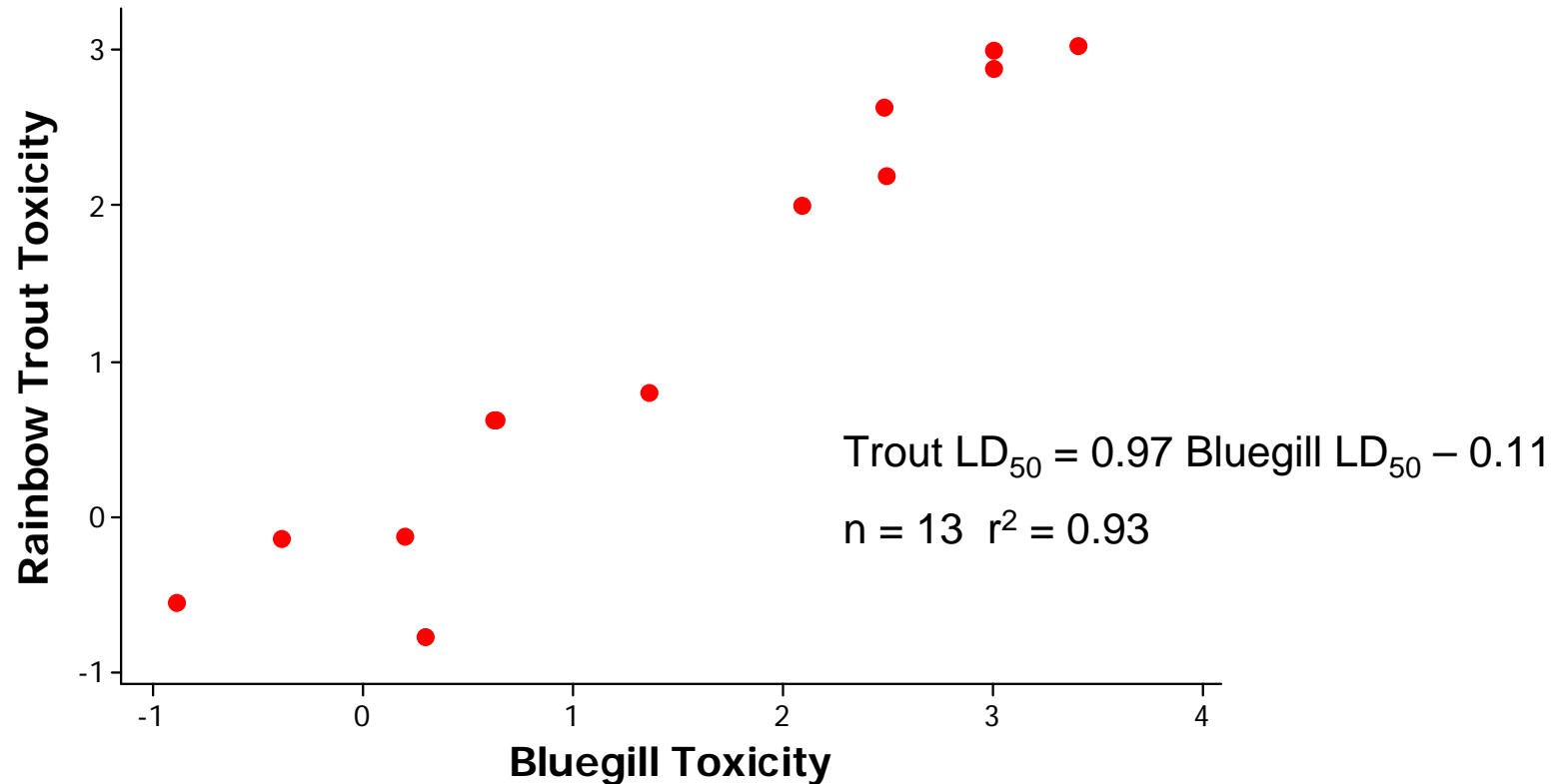
## *Read-Down*

	 OH	 OH	 OH	 OH
Species 1	●	●	●	●
Species 2	↓ ○	●	↓ ○	↓ ○
Species 3	↓ ○	↓ ○	↓ ○	●

Single Endpoint

# Inter-Species Relationships

## Fish to Fish – Miscellaneous Chemicals

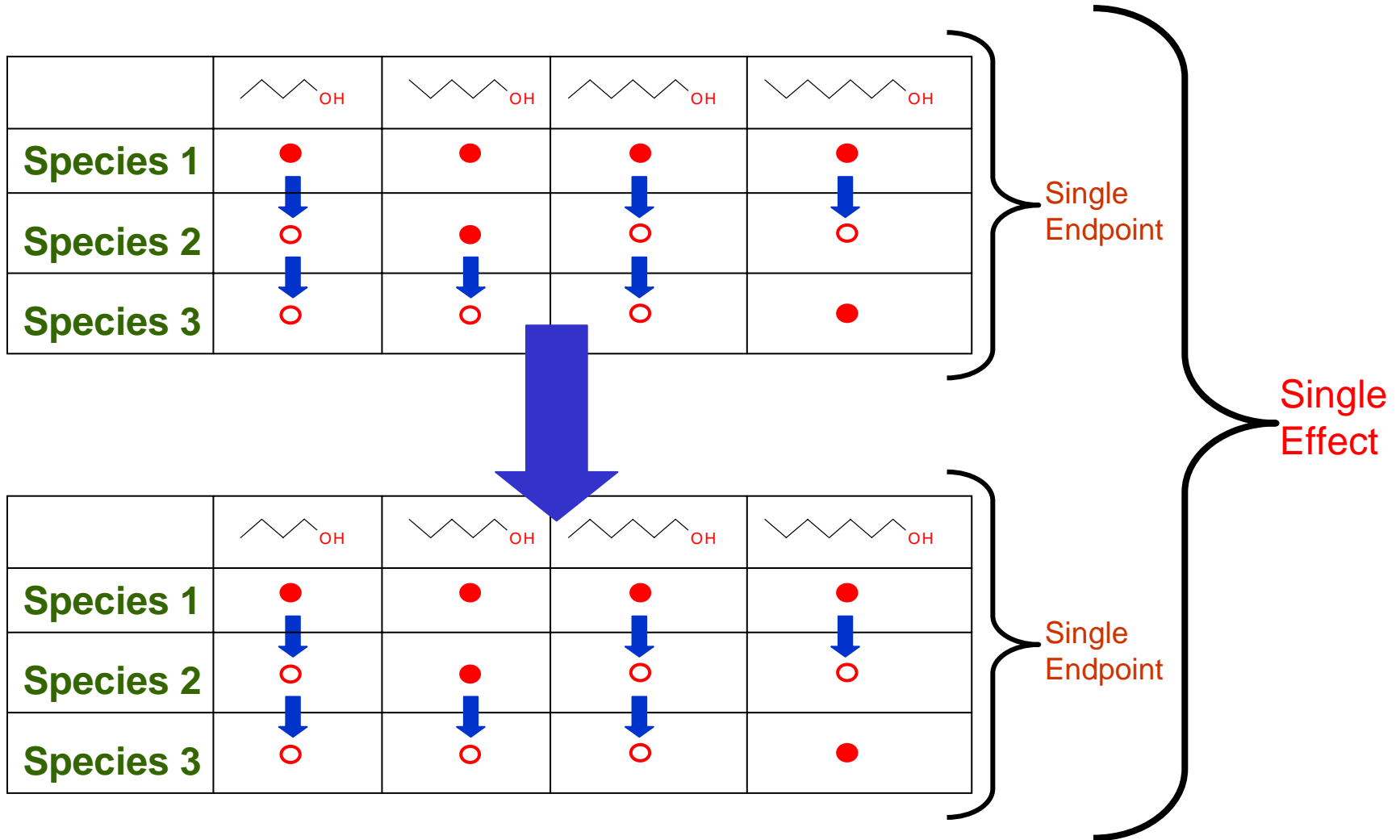


Data from: LeBlanc GA (1984) *Environ. Toxicol. Chem.* 3: 47-60

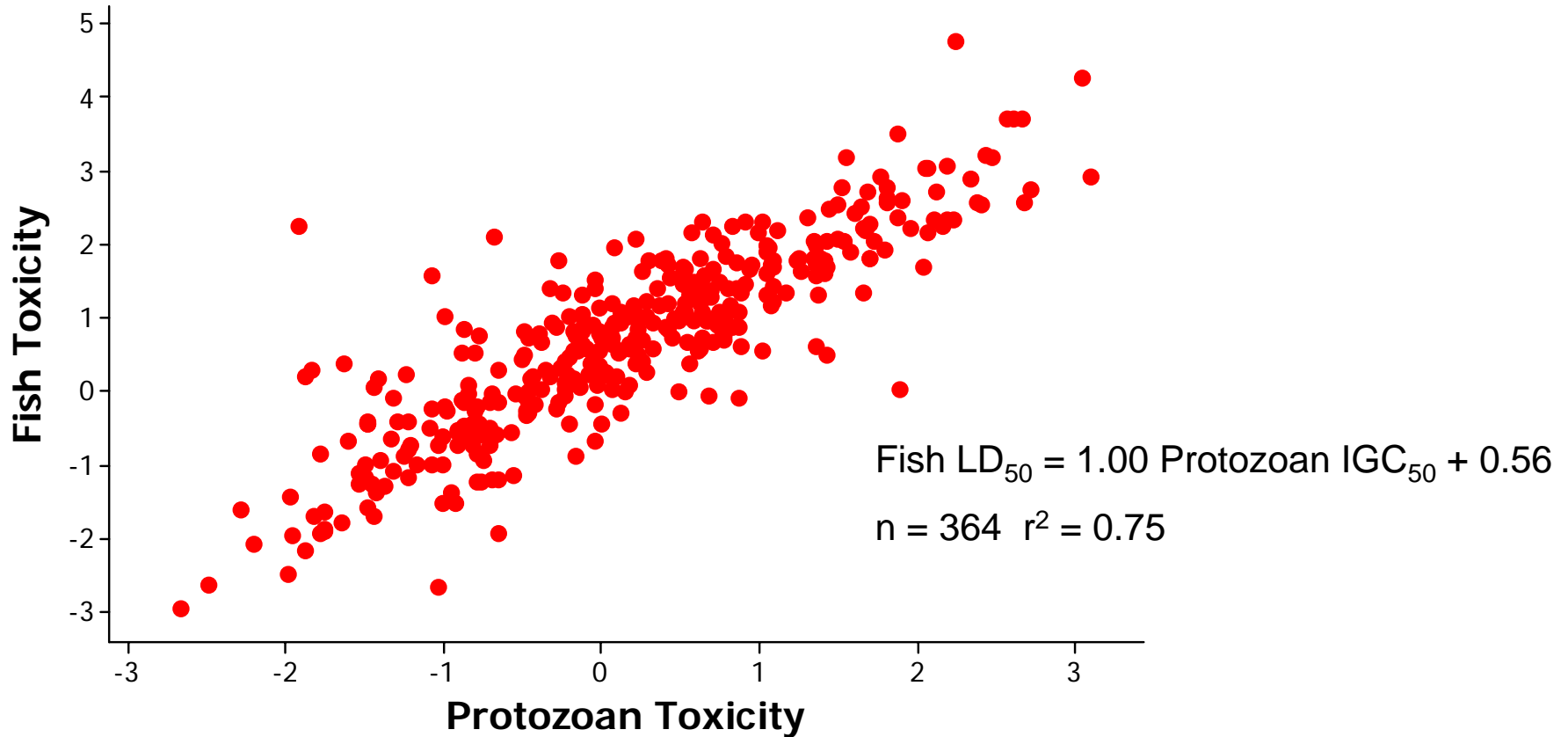


# Biological Read-Across

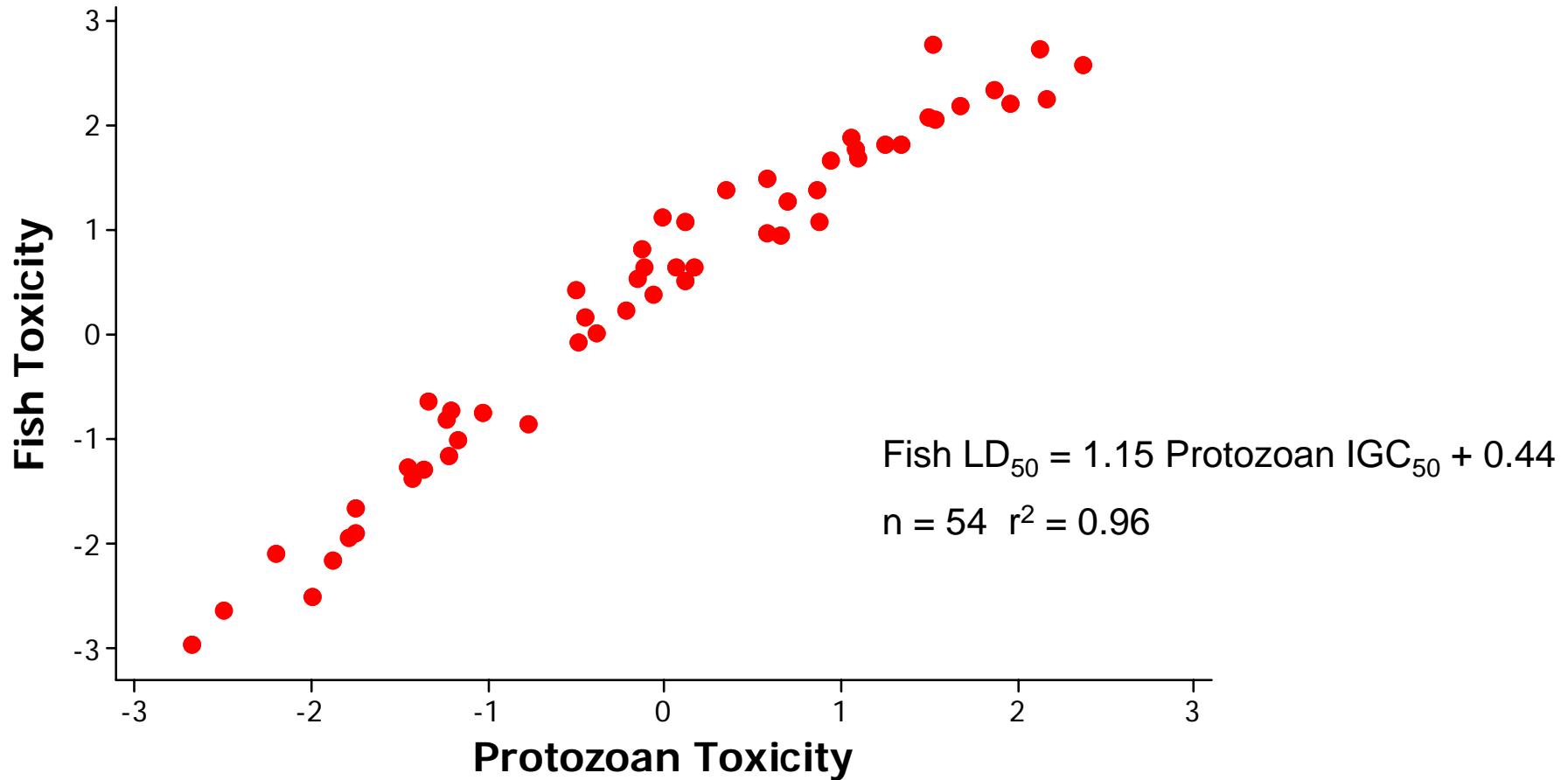
## *Trophic Level Read-Down*



# Fathead Minnow vs *Tetrahymena pyriformis* Toxicity



# Fathead Minnow vs *Tetrahymena pyriformis* Toxicity of Non-Polar Narcotics



Cronin MTD et al (1991) *Sci Tot Environ* 109-110: 431-439

# Between Taxa Extrapolations are Stronger Within a Mechanism

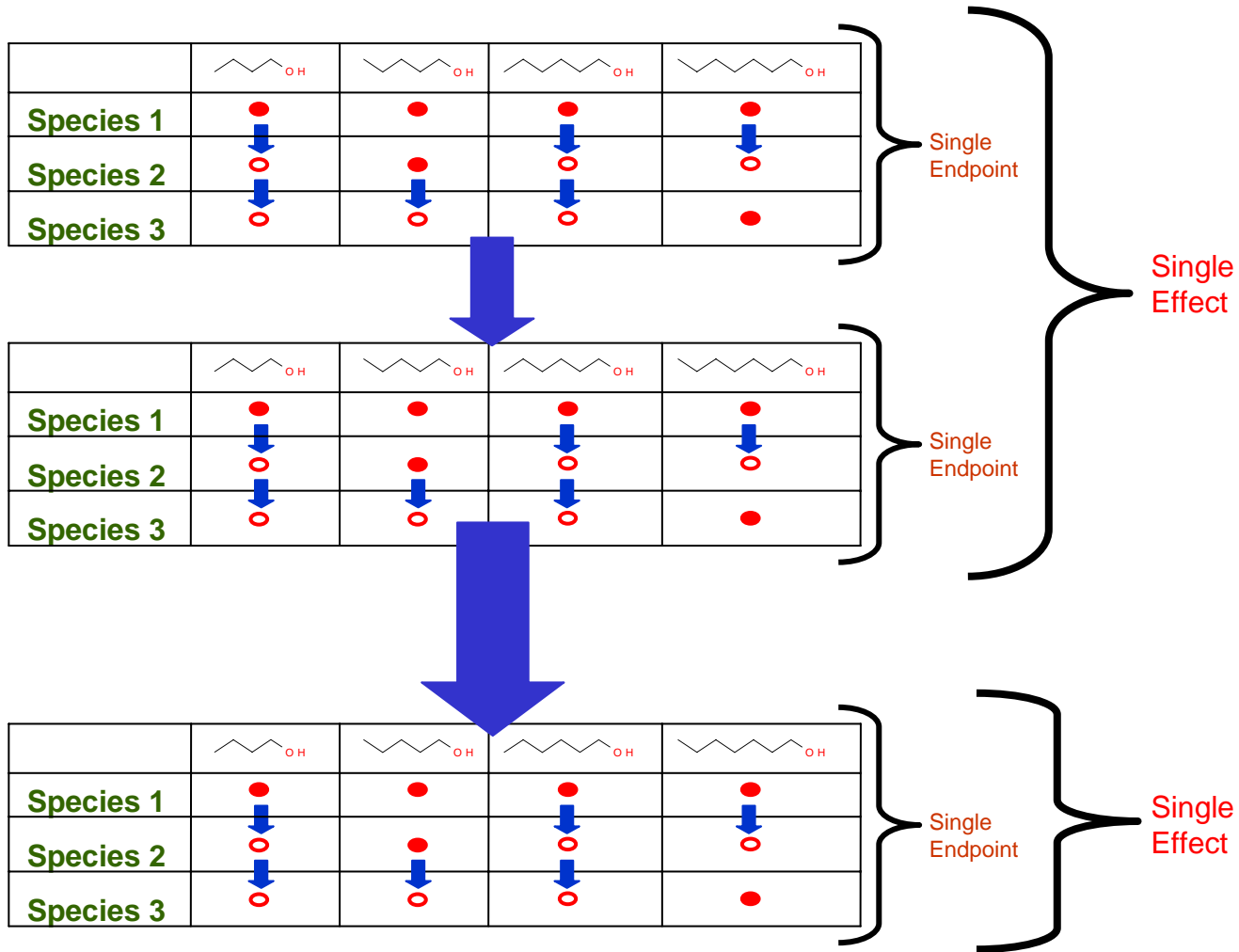
- Narcotic potency is often consistent across trophic levels, only differing by species sensitivity
- Reactive chemicals show more significant inter-species variability
- Species specific metabolism can be identified
  - Esterase in fish and not in *Tetrahymena*
- Form categories on mechanisms for biological read-across

# **Tools to Form Categories: Acute Aquatic Toxicity**

- **Verhaar rules and updates**
- **US EPA (Aster)**
- **Protein reactivity rules**
- **Metabolic groups**

# Biological Read-Across

## *Endpoint to Endpoint Read-Down*



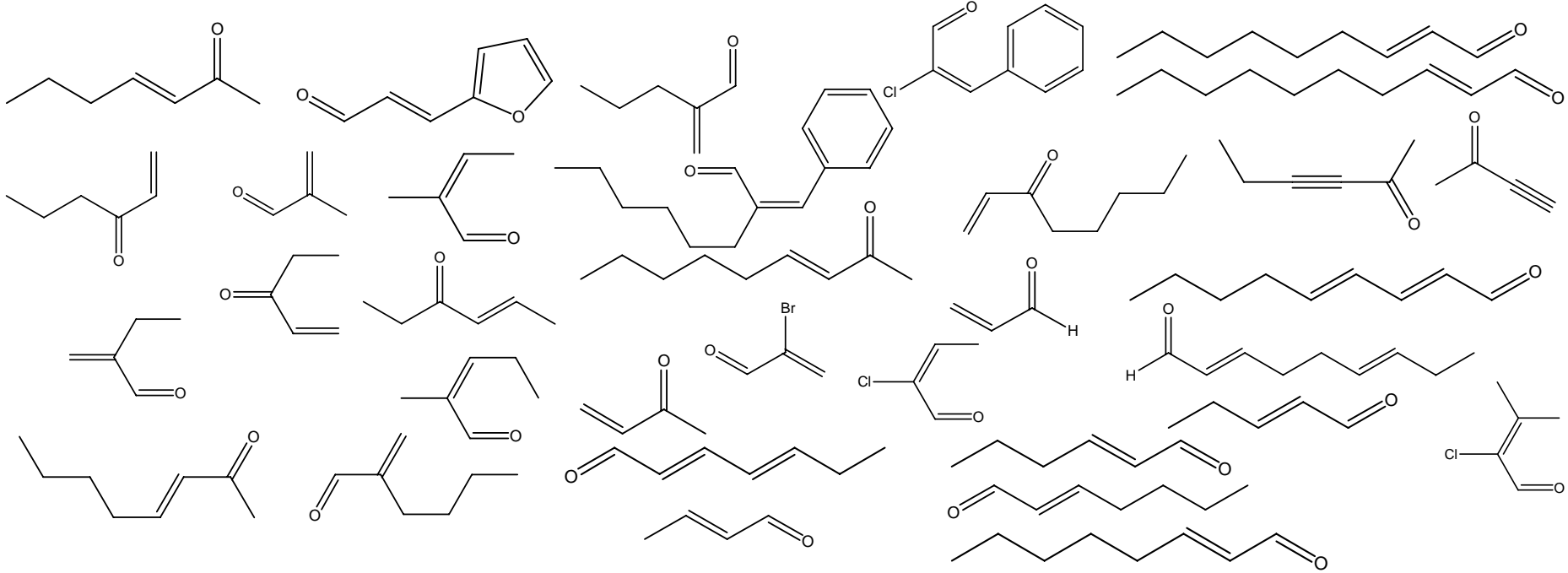
# **(Protein) Reactive Toxicity**

- **A number of toxic effects are a result of reactivity with biological macromolecules**
  - **Skin sensitisation, excess acute aquatic toxicity, mutagenicity**
- **Reactivity is the formation of a covalent bond with e.g. a protein or DNA**
- **Reactive toxicity has been a challenge to model (quantitatively) *in silico***

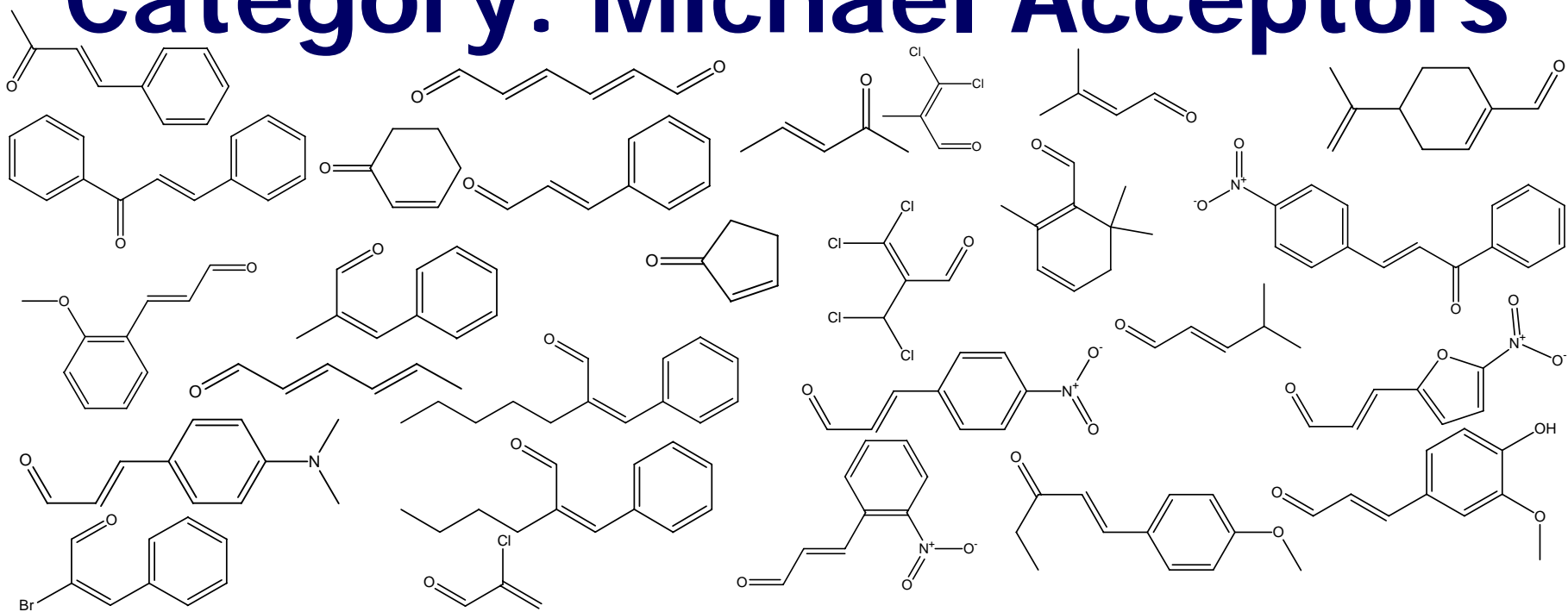
# Predicting Reactive Toxicity

- Reactivity can be associated with mechanistic organic chemistry
- Relative reactivity can be quantified by *in chemico* reactivity
- Domains of reactivity have been defined
  - SMARTS strings for five classic mechanisms
- Endpoints superimposed across a domain

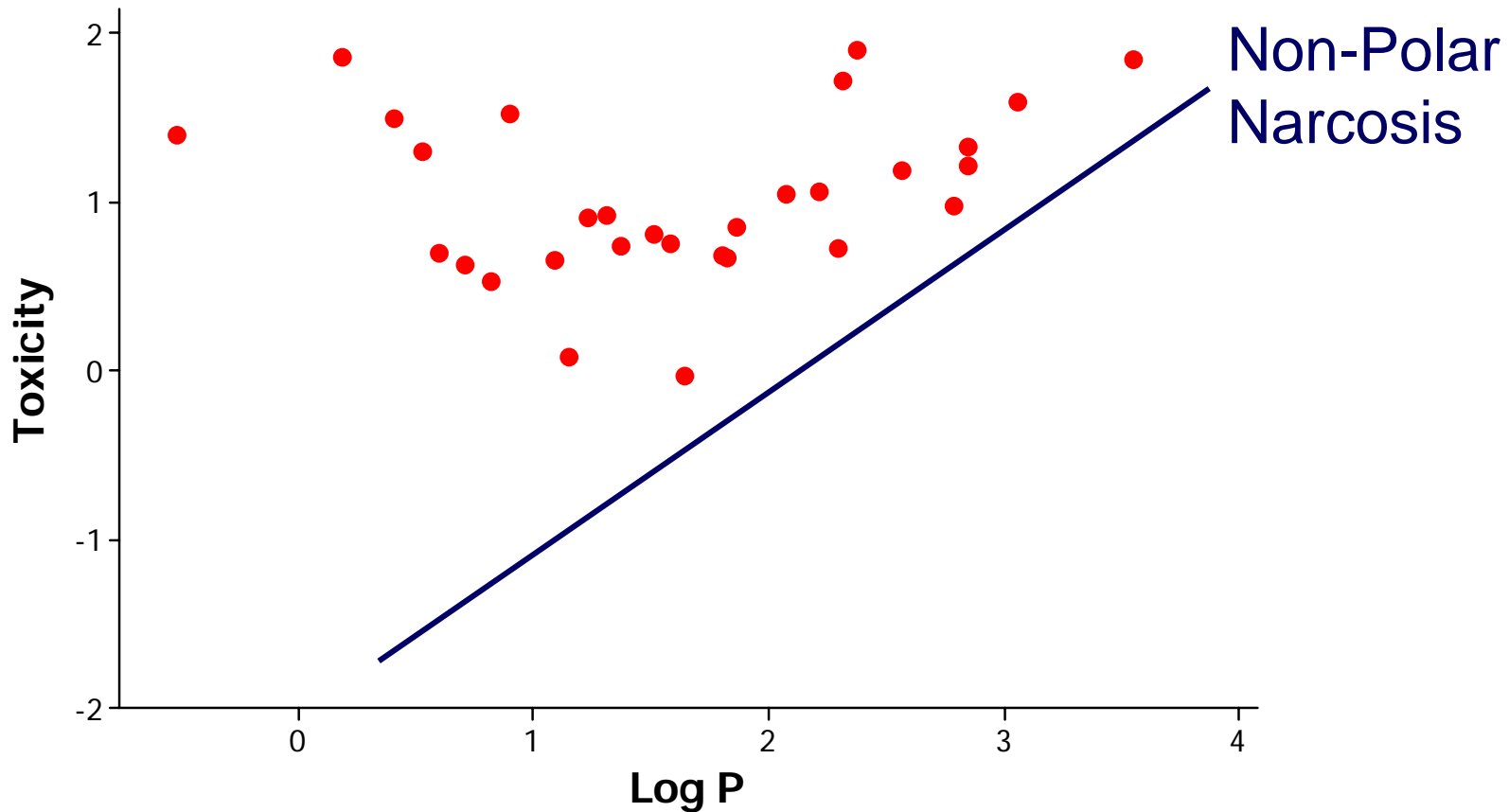




# Category: Michael Acceptors

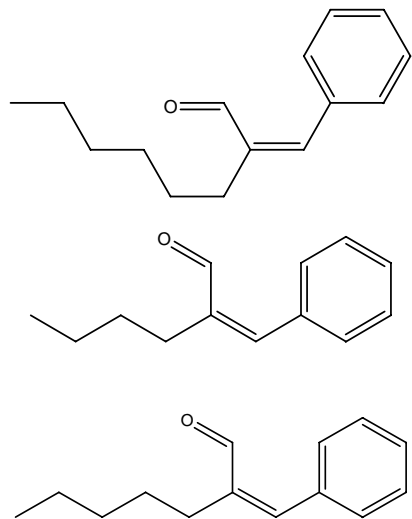


# Michael Acceptors Show Excess Acute Aquatic Toxicity

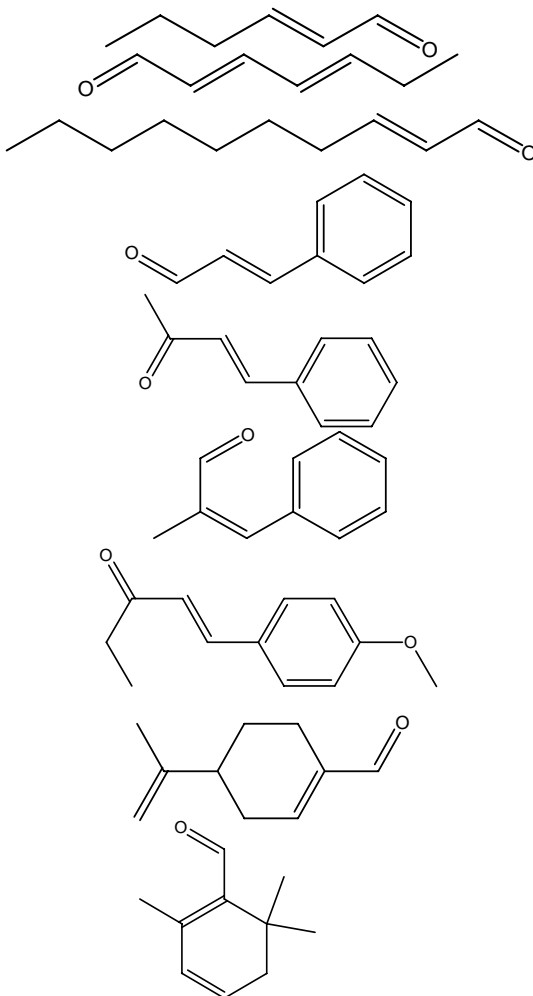


# Skin Sensitisers?

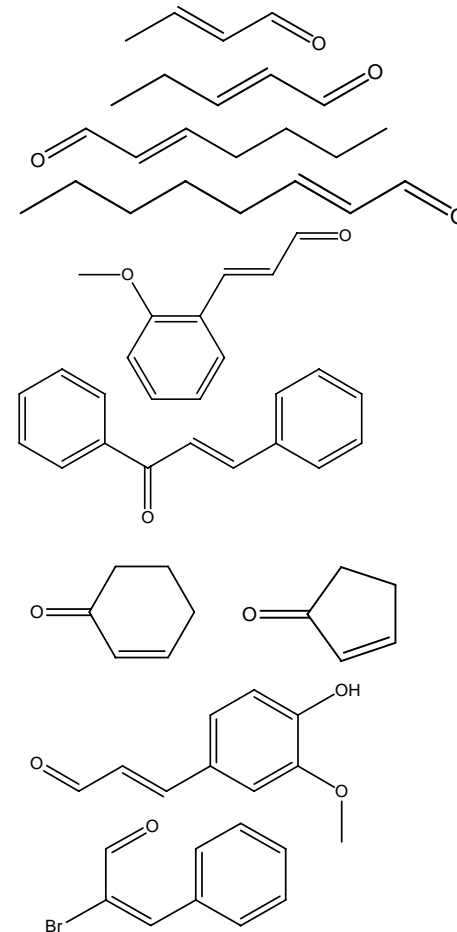
## LLNA Weak Sensitiser



## LLNA Moderate Sensitiser

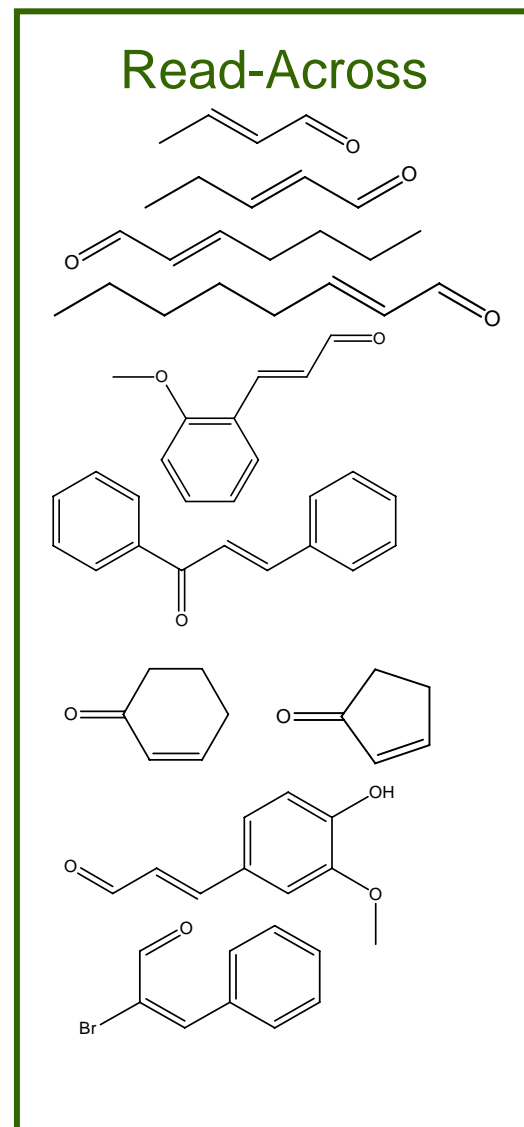


## Read-Across

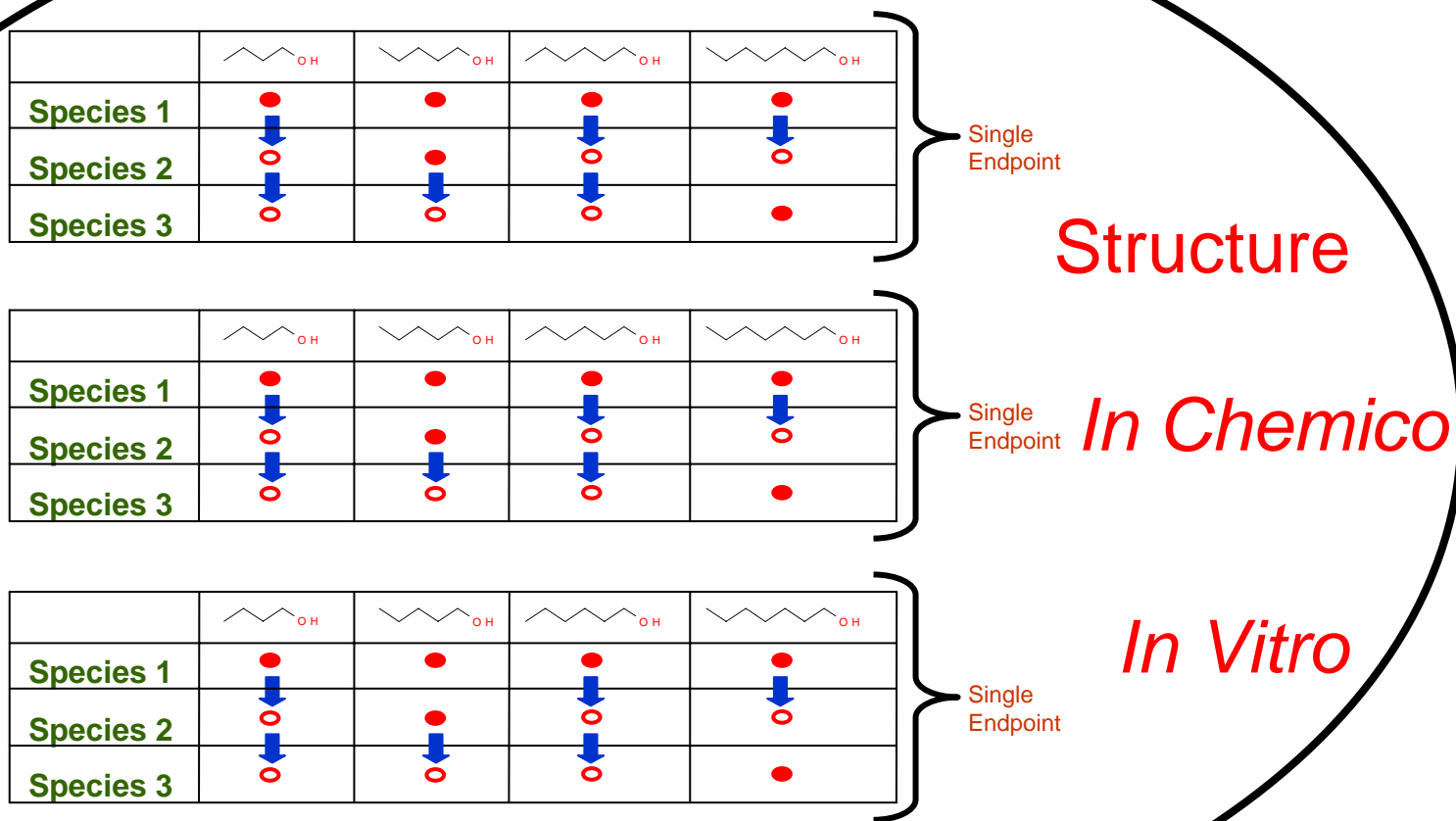


# Further Lines of Evidence: *In Chemico* Reactivity

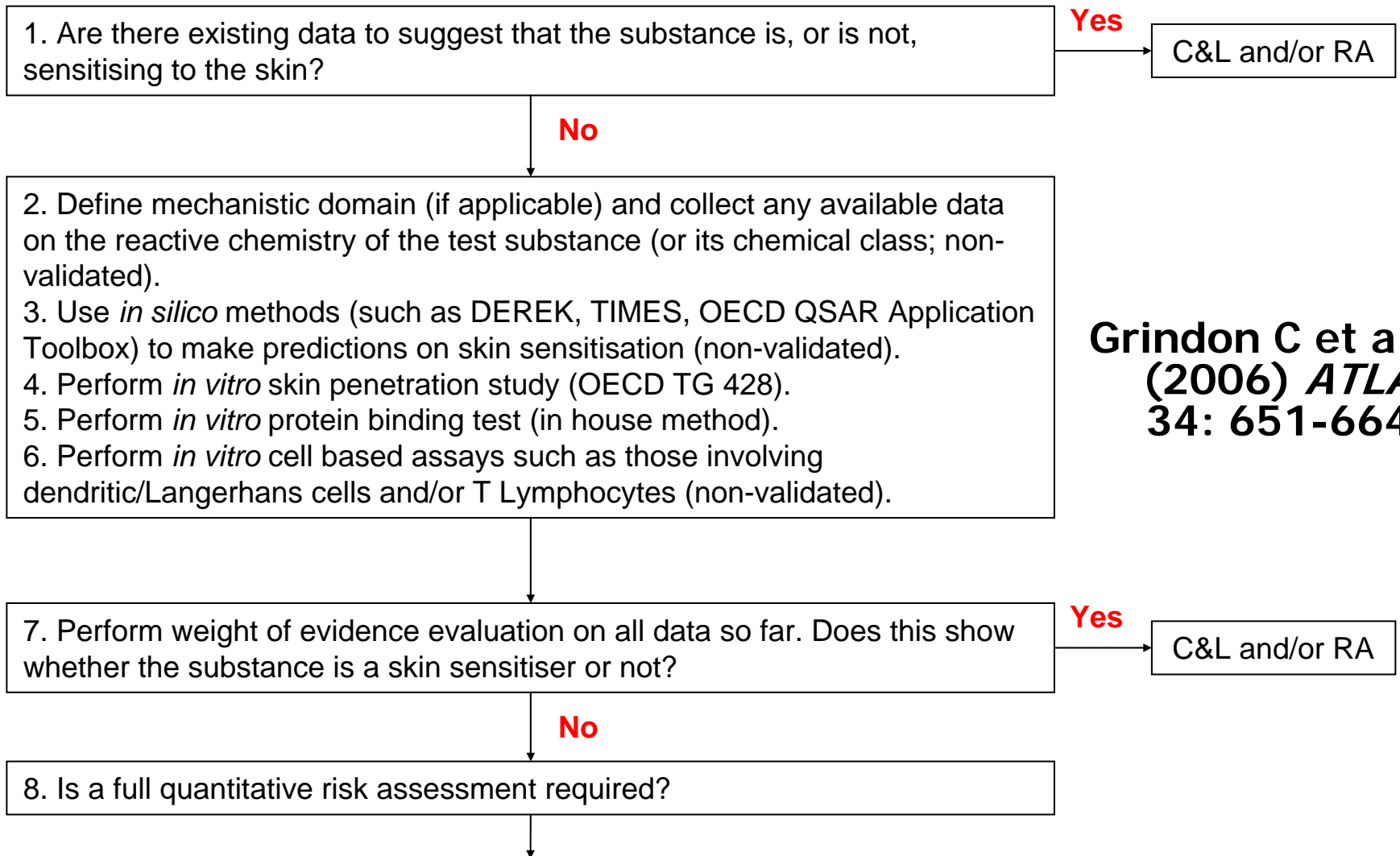
- Reactivity with a nucleophile e.g. glutathione is associated with sensitisation
- *In chemico* reactivity can be measured (and predicted)
- *In chemico* reactivity will extend the domain of the category and assist in read-across



# Category Formation: Filling an Incomplete Data Matrix by Weight of Evidence



# Integrated Testing Strategies



**Grindon C et al  
(2006) *ATLA*  
34: 651-664**

A special supplement of *ATLA* is available with details of these ITS

# Conclusions

- **Mechanisms of action can be used to form categories**
- **Categories allow for biological read-across**
  - **Species to species**
  - **Endpoint to endpoint**
- **Tools are available to assist in the formation of robust categories**
- **Categories can be implemented through ITS**

# Acknowledgements

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# References

- Aptula AO, Patlewicz G, Roberts DW, Schultz TW (2006) Non-enzymatic glutathione reactivity and in vitro toxicity: A non-animal approach to skin sensitization. *Toxicology in Vitro* 20: 239- 247.
- Cronin MTD, Dearden JC, Dobbs AJ (1991) QSAR studies of comparative toxicity in aquatic organisms. *Science of the Total Environment* 109/110:431-439.
- Ellison CM, Cronin MTD, Madden JC, Schultz TW (2008) Definition of the structural domain of the baseline non-polar narcosis model for *Tetrahymena pyriformis*. *SAR and QSAR in Environmental Research*. 19: In Press.
- Enoch SJ, Cronin MTD, Schultz TW, Madden JC (2008) Quantitative and mechanistic read across for predicting the skin sensitization potential of alkenes acting via Michael addition. *Chemical Research in Toxicology* 21: 513-520.
- Enoch SJ, Madden JC, Cronin MTD (2008) Identification of mechanisms of toxic action for skin sensitisation using a SMARTS pattern based approach. *SAR and QSAR in Environmental Research*. 19: 555-578.
- Gerberick F, Aleksic M, Basketter D, Casati S, Karlberg A-T, Kern P, Kimber I, Lepoittevin JP, Natsch A, Ovigne JM, Rovida C, Sakaguchi H, Schultz T (2008) Chemical reactivity measurement and the predictive identification of skin sensitizers. *Alternatives to Laboratory Animals* 36: 215-242.
- Grindon C, Combes R, Cronin MTD, Roberts DW, Garrod J (2006) Integrated decision-tree testing strategies for environmental toxicity with respect to the requirements of the EU REACH Legislation. *Alternatives to Laboratory Animals* 34: 651-664.
- Kahn I, Maran U, Benfenati E, Netzeva TI, Schultz TW, Cronin MTD (2007) Comparative quantitative structure–activity–activity relationships for toxicity to *Tetrahymena pyriformis* and *Pimephales promelas*. *Alternatives to Laboratory Animals* 35: 15-24.
- LeBlanc GA (1984) Interspecies relationships in acute toxicity of chemicals to aquatic organisms. *Environmental Toxicology and Chemistry* 3: 47-60.
- OECD (2007) Series on Testing and Assessment No. 80. Guidance on groupings of chemicals, September 26 (2007) (ENV/JM/MONO(2007)28).