The Local Models for Skin Sensitisation and Developmental Toxicity

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What is a Chemical Category?

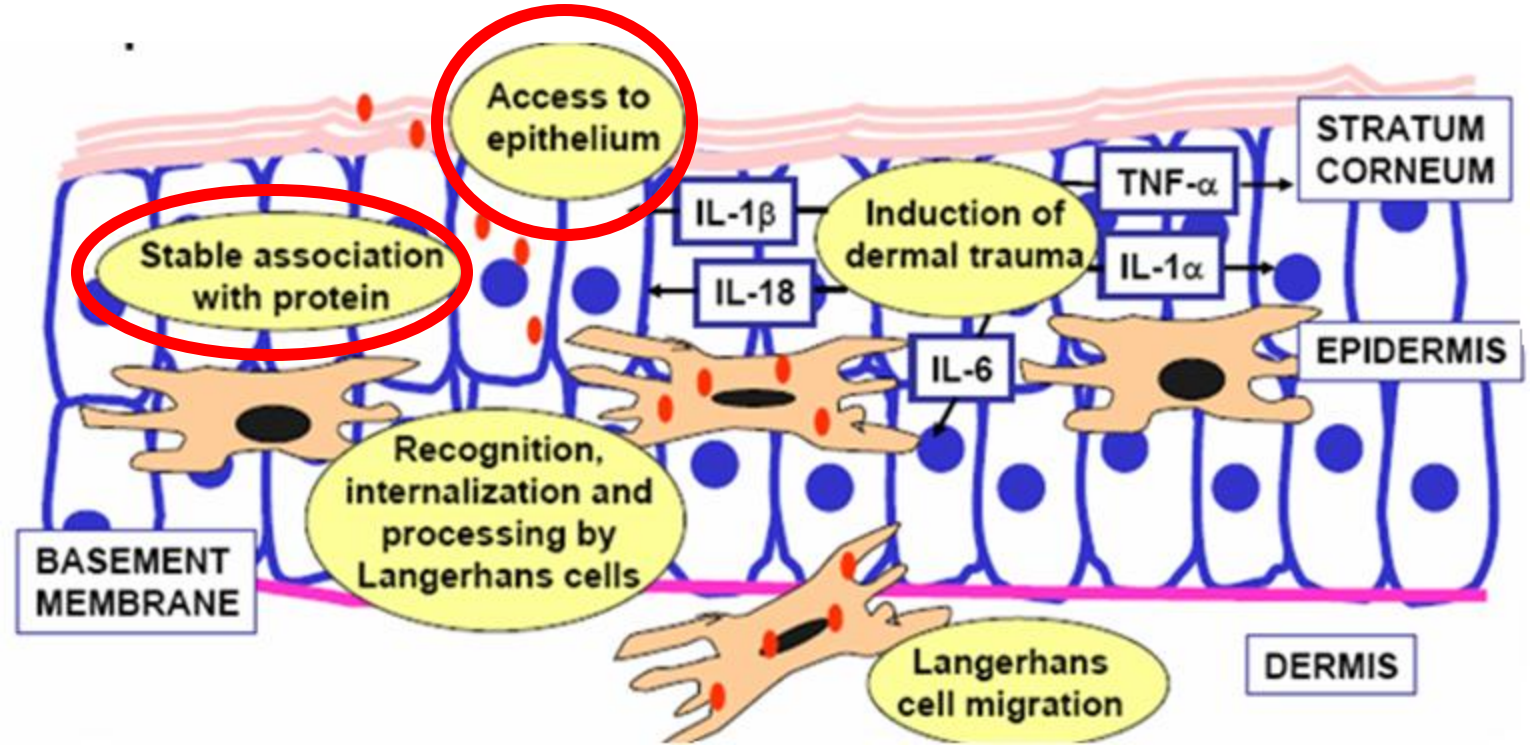
‘Group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity, these structural similarities may create a predictable pattern in any or all of the following parameters: physicochemical properties, environmental fate and environmental effects, and human health effects’[1]

[1] OECD, 2007 Guidance on grouping chemicals

Category Formation and Read-Across

- **Toxic mechanisms of action define categories**
- **Chemical similarity can be used to group chemicals into categories**
- **Quantitative and qualitative read-across**

Skin Sensitisation



Electrophilic Reaction Chemistry

- **Six key chemical reactions have been defined for protein reactivity[2]**
- **All known skin sensitising chemicals can be assigned to one of these mechanisms**
- **Five of these mechanisms are well defined in the literature**
- **SMARTS based rules have been developed[3]**

[2]Aptula and Roberts (2006) Chem Res Toxicol 19; 1097-1105
[3]Enoch et al (2008) SAR QSAR Environ Sci 19; 555-578

SMARTS Rules

	Acylation	Michael	Schiff base	S_N2	S_NAr	S_N1	Non
Acylation	24		1	1			
Michael		44					2
Schiff base			40				3
S_N2	2	2		47			
S_NAr					3		
S_N1							1
Non							22

SMARTS Rules

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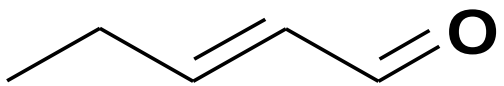

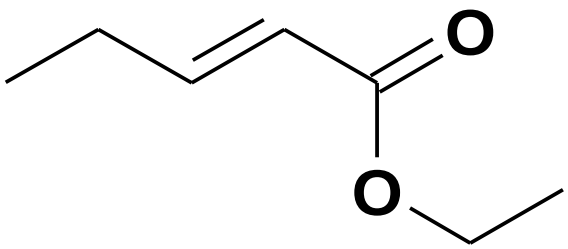

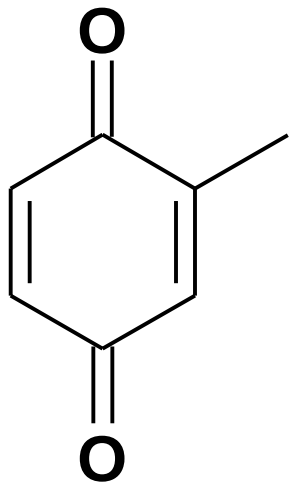

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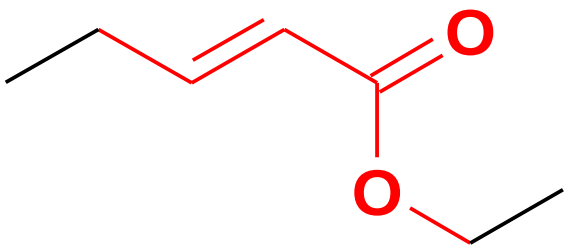
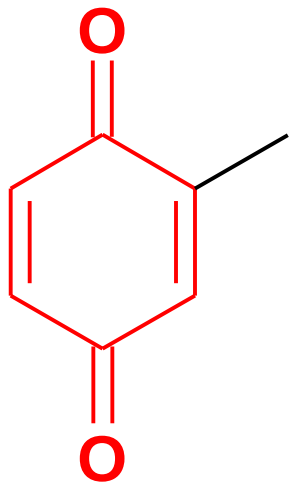
S_NAr					3		
S_N1							1
Non							22

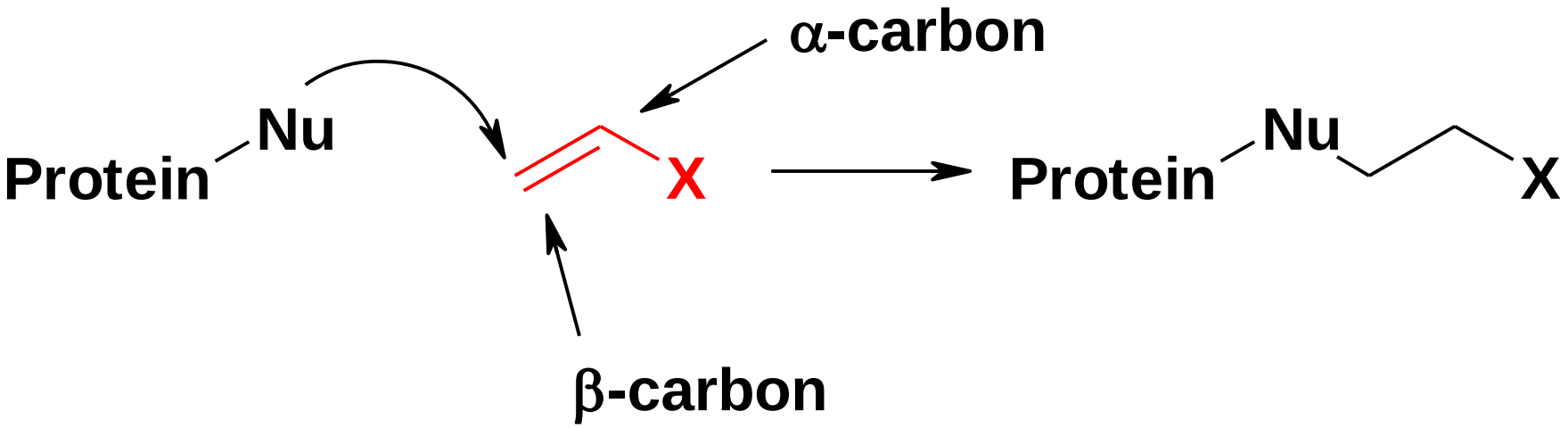
C=[CH][$([CH]=O),$(C(=O)OC)]

C1=CC(=O)C=CC(=O)C1



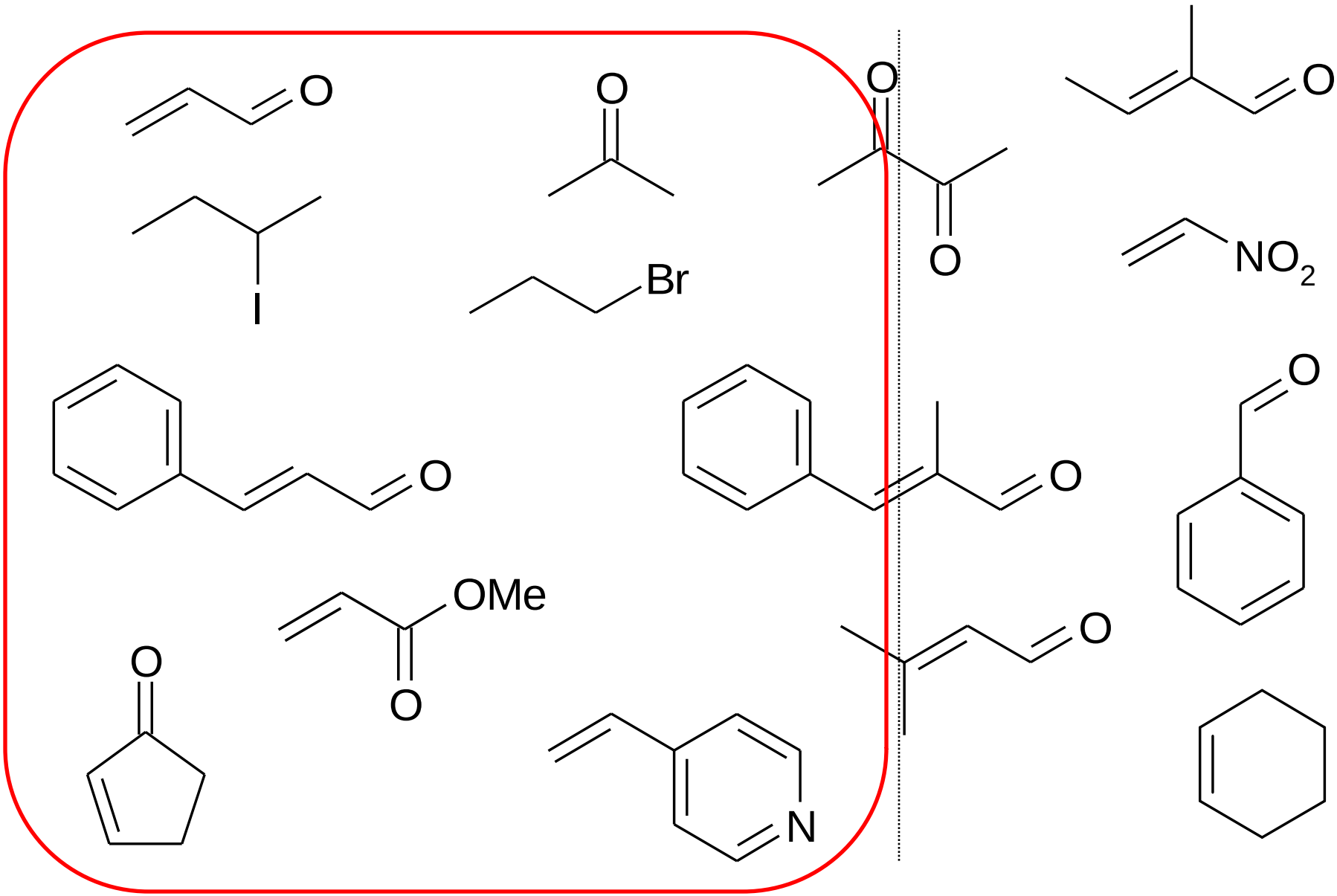


Mechanism of Michael-Type Addition

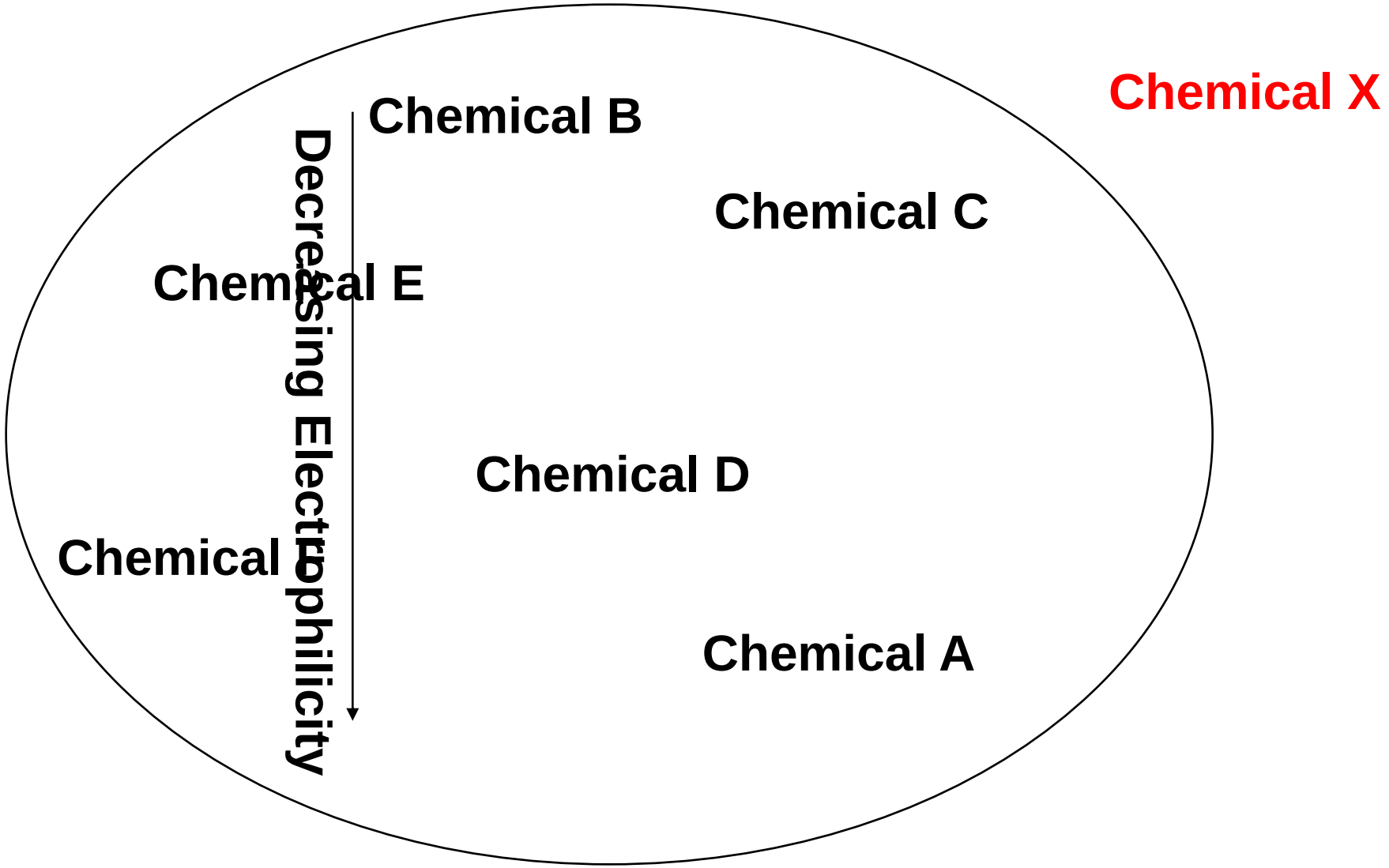


X = electron withdrawing substituent e.g. CO, CHO, NO_2, CO_2R.

Mechanistic Category Formation



Quantitative Read-Across

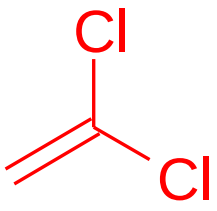


Methodology

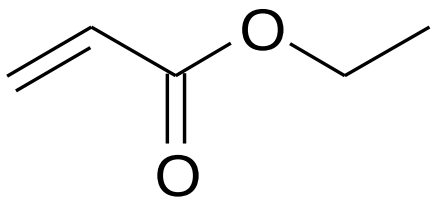
- **Use the electrophilicity index (ω) to model protein reactivity within a category**
- **Electrophilic index calculated from HOMO and LUMO using DFT**
- **Model the skin sensitising potential of 22 α, β-unsaturated alkenes[4]**

[4]Enoch et al (2008) Chem Res Toxicol 21; 513-520

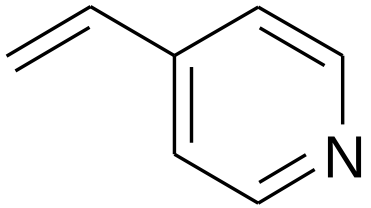
Quantitative Electrophilicity (ω) Ranking



pEC3 = NC, ω = 1.10



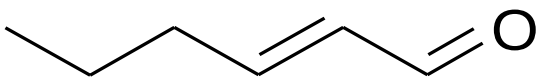
pEC3 = 0.55, ω = 1.49



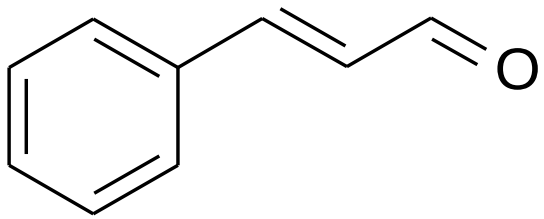
pEC3 = 1.82, ω = 1.55

Increasing electrophilicity (ω)

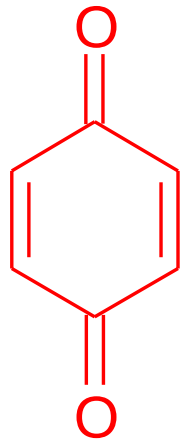
Increasing skin sensitising potential (pEC3)



pEC3 = 1.25, ω = 1.61

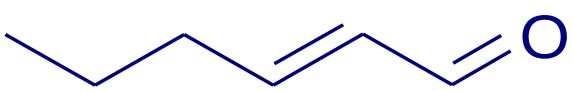


pEC3 = 1.64, ω = 2.10



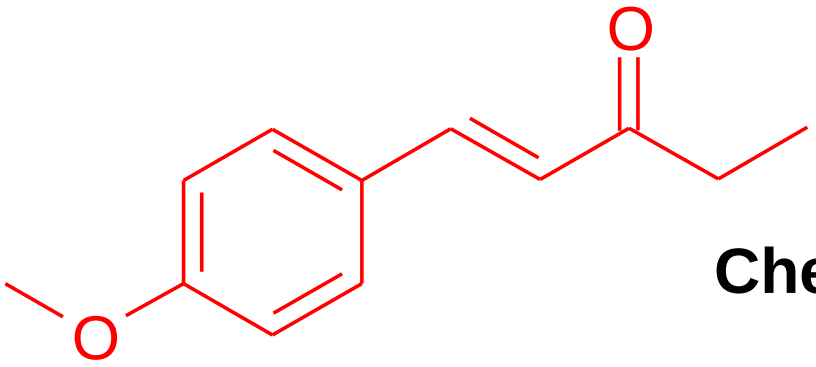
pEC3 = 4.04, ω = 3.90

Quantitative Read-Across Predictions



Chemical A:

ω = 1.61, EC3 = 5.5, pEC3 = 1.25

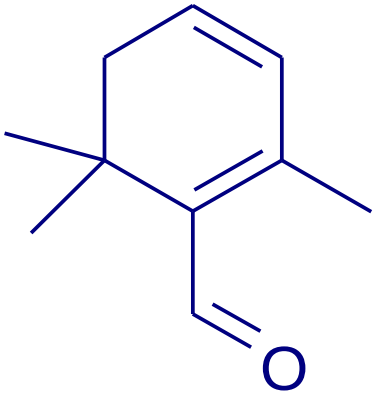


Chemical X:

ω = 1.73

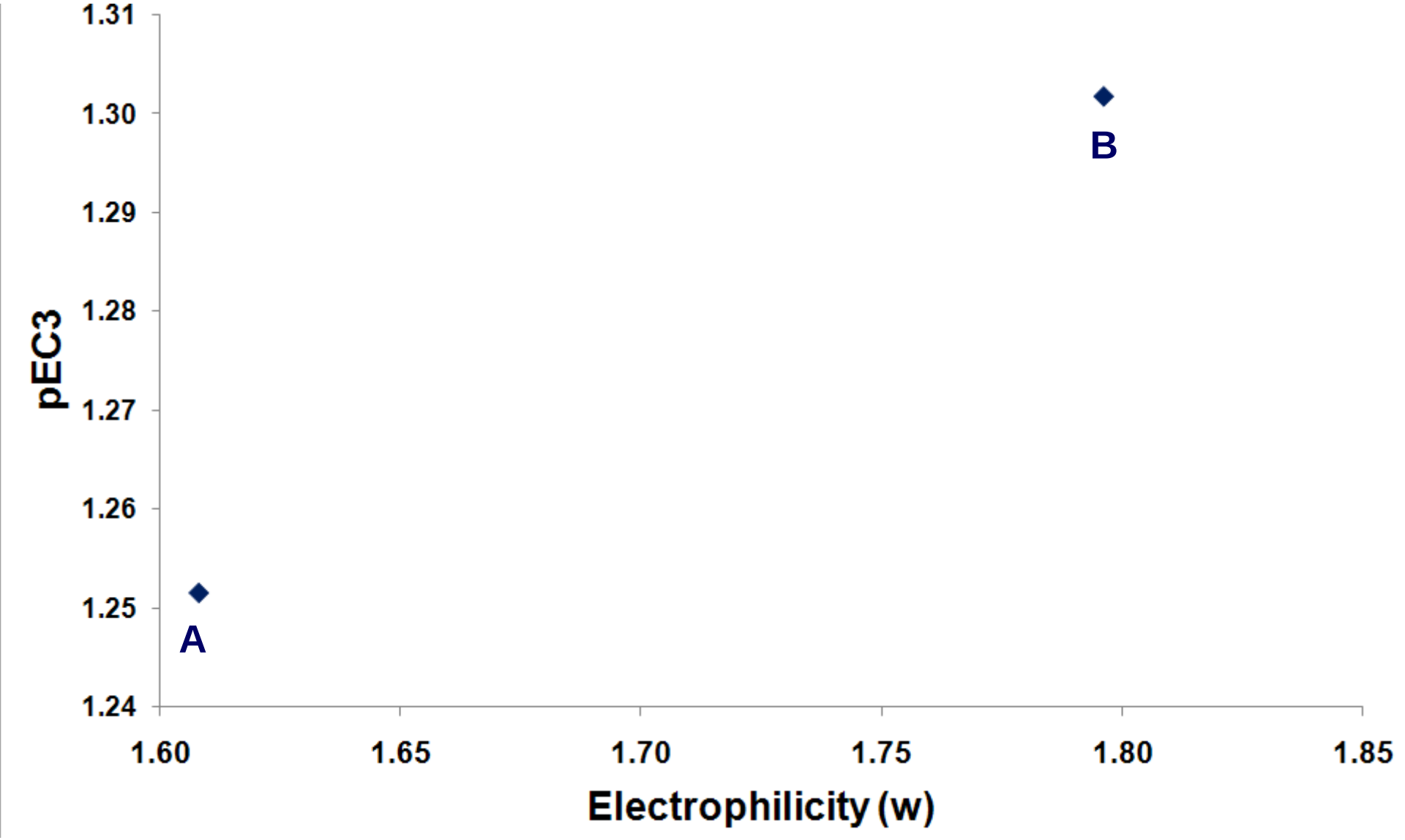
Pred. pEC3 = 1.29 (1.31)

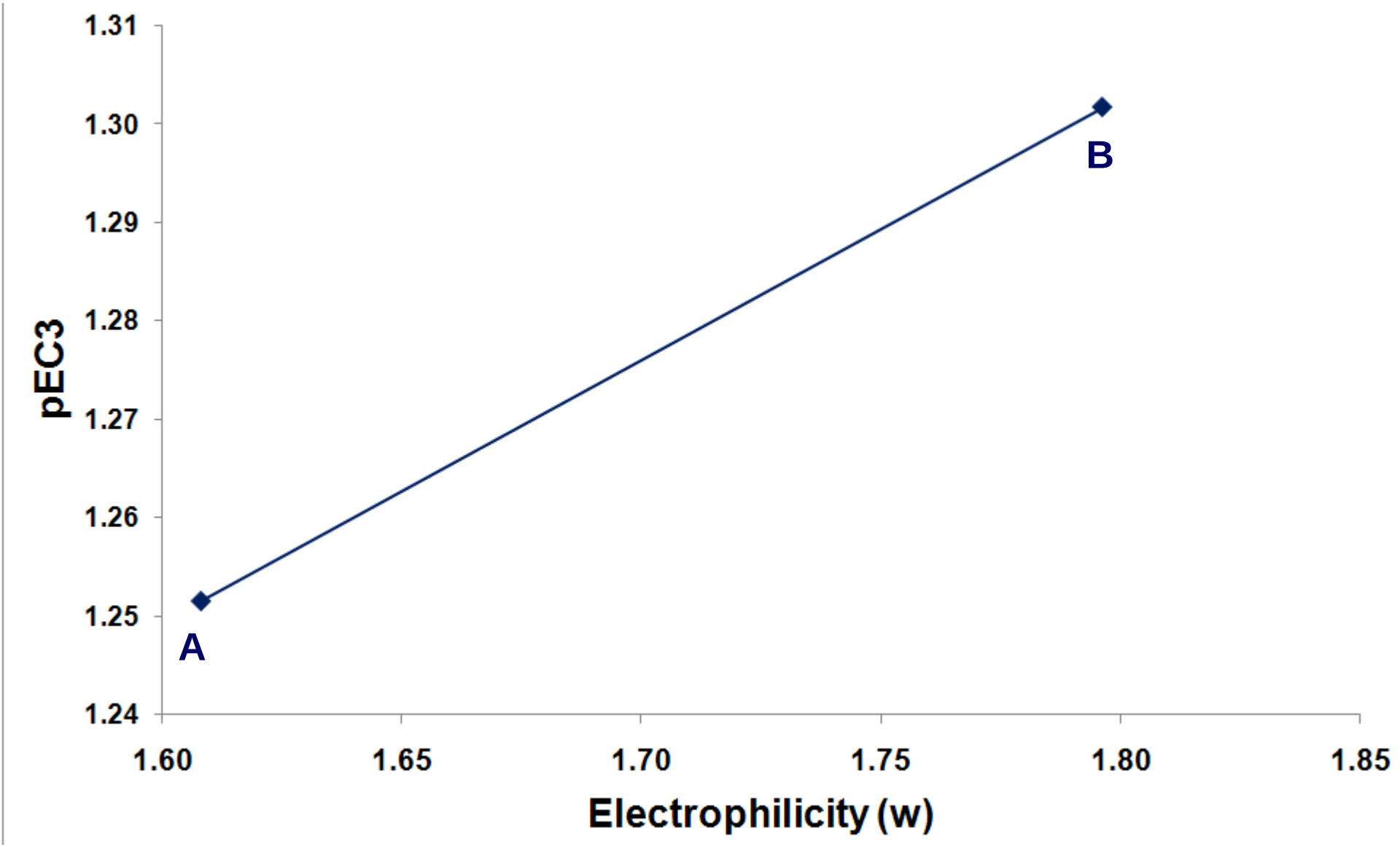
Pred. EC3 = 9.87 (9.30)

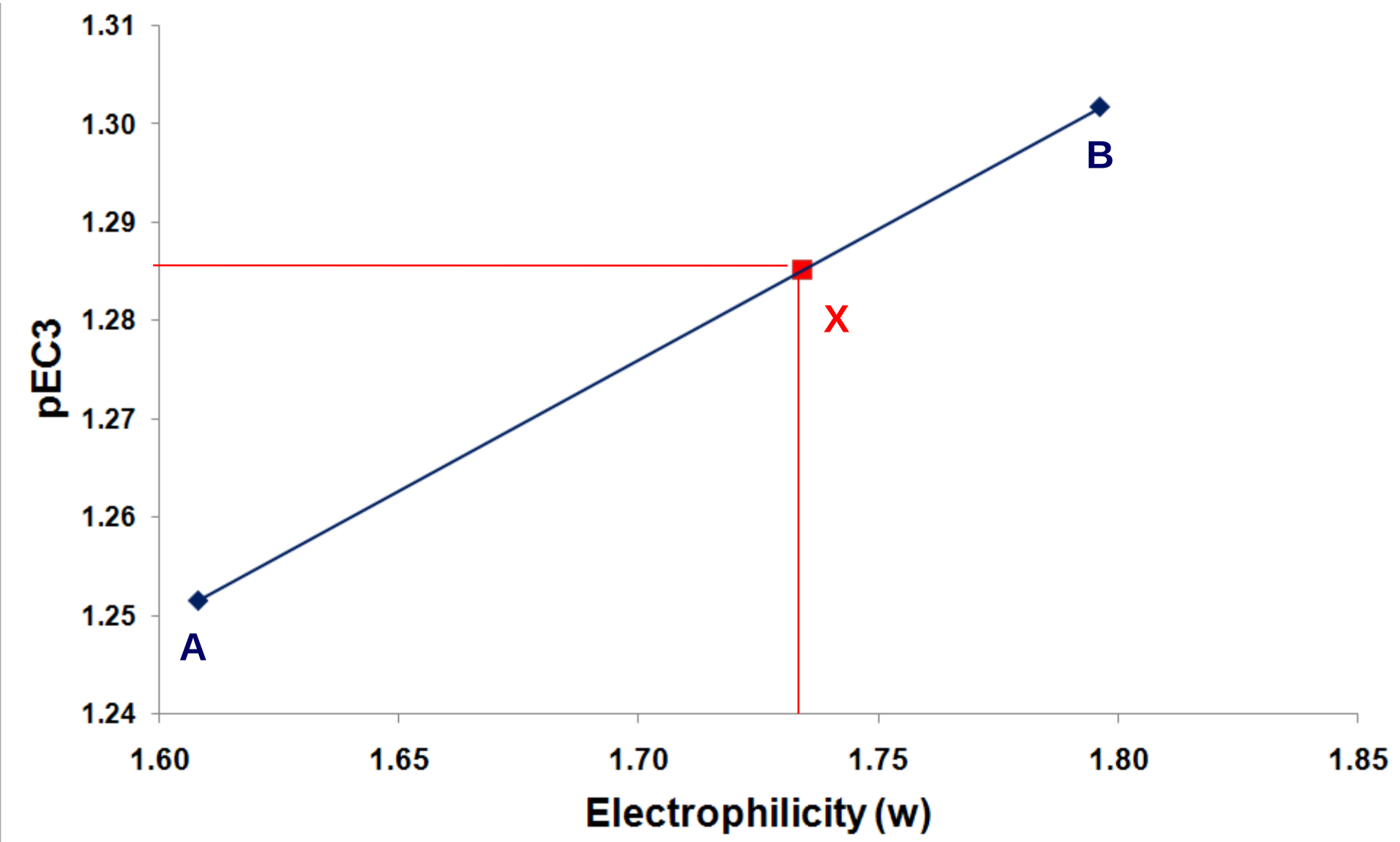


Chemical B:

ω = 1.80, EC3 = 7.5, pEC3 = 1.30


1.31
1.30
1.29
1.28
1.27
1.26
1.25
1.24
pEC3
A
B
1.60
1.65
1.70
1.75
1.80
1.85
Electrophilicity (w)


1.31
1.30
1.29
1.28
1.27
1.26
1.25
1.24
pEC3
A
B
1.60
1.65
1.70
1.75
1.80
1.85
Electrophilicity (w)


1.31
1.30
1.29
1.28
1.27
1.26
1.25
1.24
pEC3
A
B
X
1.60
1.65
1.70
1.75
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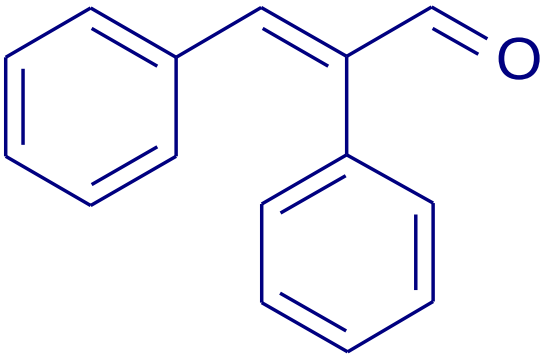
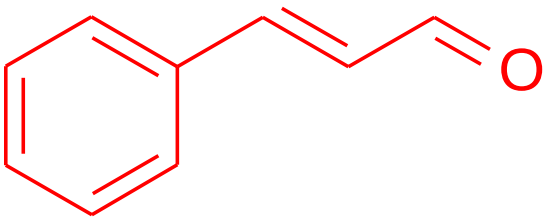
1.85
Electrophilicity (w)

Quantitative Read-Across Predictions



β-phenyl cinnamic aldehyde:

ω = 2.04, EC3 = 2.5, pEC3 = 1.92

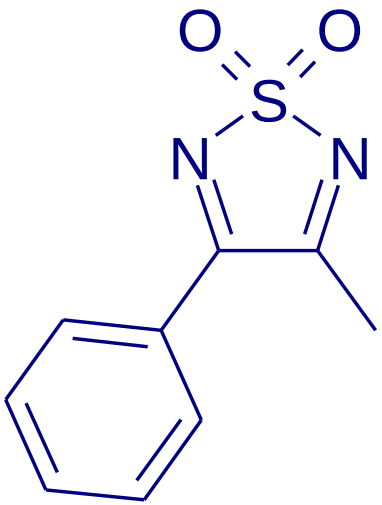


Cinnamic aldehyde:

ω = 2.10

Pred. pEC3 = 1.93 (1.64)

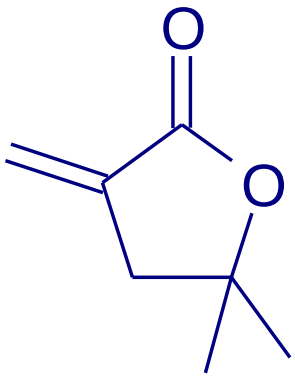
Pred. EC3 = 1.54 (3.00)



MPT:

ω = 3.21, EC3 = 1.4, pEC3 = 2.17

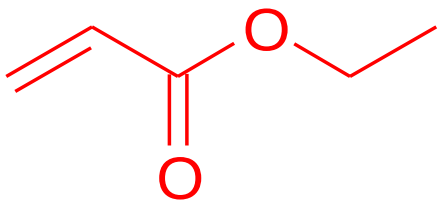
Quantitative Read-Across Predictions



5,5-dimethyl-3-methylene-dihydro-2(3H)-furanone:

ω = 1.49, EC3 = 1.8, pEC3 = 1.85

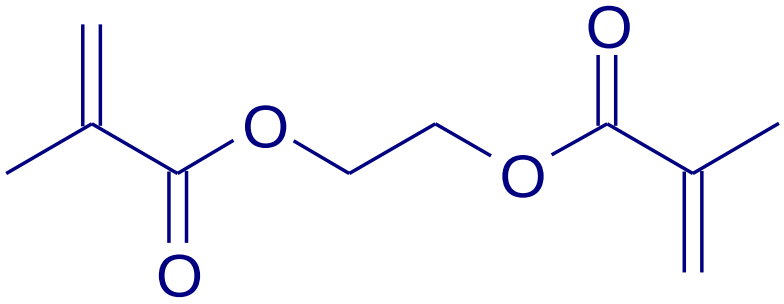
Ethyl acrylate:



ω = 1.49

Pred. pEC3 = 1.40 (0.55)

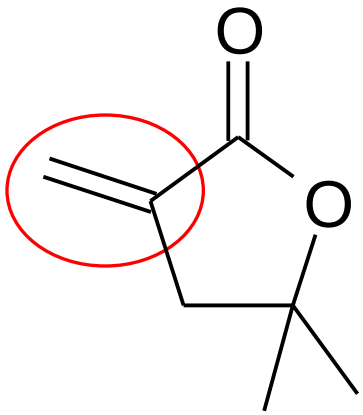
Pred. EC3 = 4.13 (28.0)



Ethylene glycol dimethacrylate:

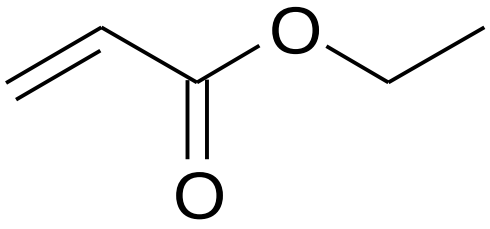
ω = 1.51, EC3 = 28.0, pEC3 = 0.85

5,5-Dimethyl-3-methylene-dihydro-2(3H)-furanone and ethyl acrylate



pEC3 = 1.85 (EC3 = 1.8), ω = 1.49

Ring strain release = entropy gain



pEC3 = 0.55 (EC3 = 28.0), ω = 1.49

Conclusions

- **Chemistry driven categories provide a strong basis for toxicity prediction**
- **Mechanistic read across provides good predictions for the toxicity of chemicals where electrophilic reactivity dominates**
- **The electrophilic index (ω) is able to model electrophilic reactivity within these categories**

Developmental Toxicity

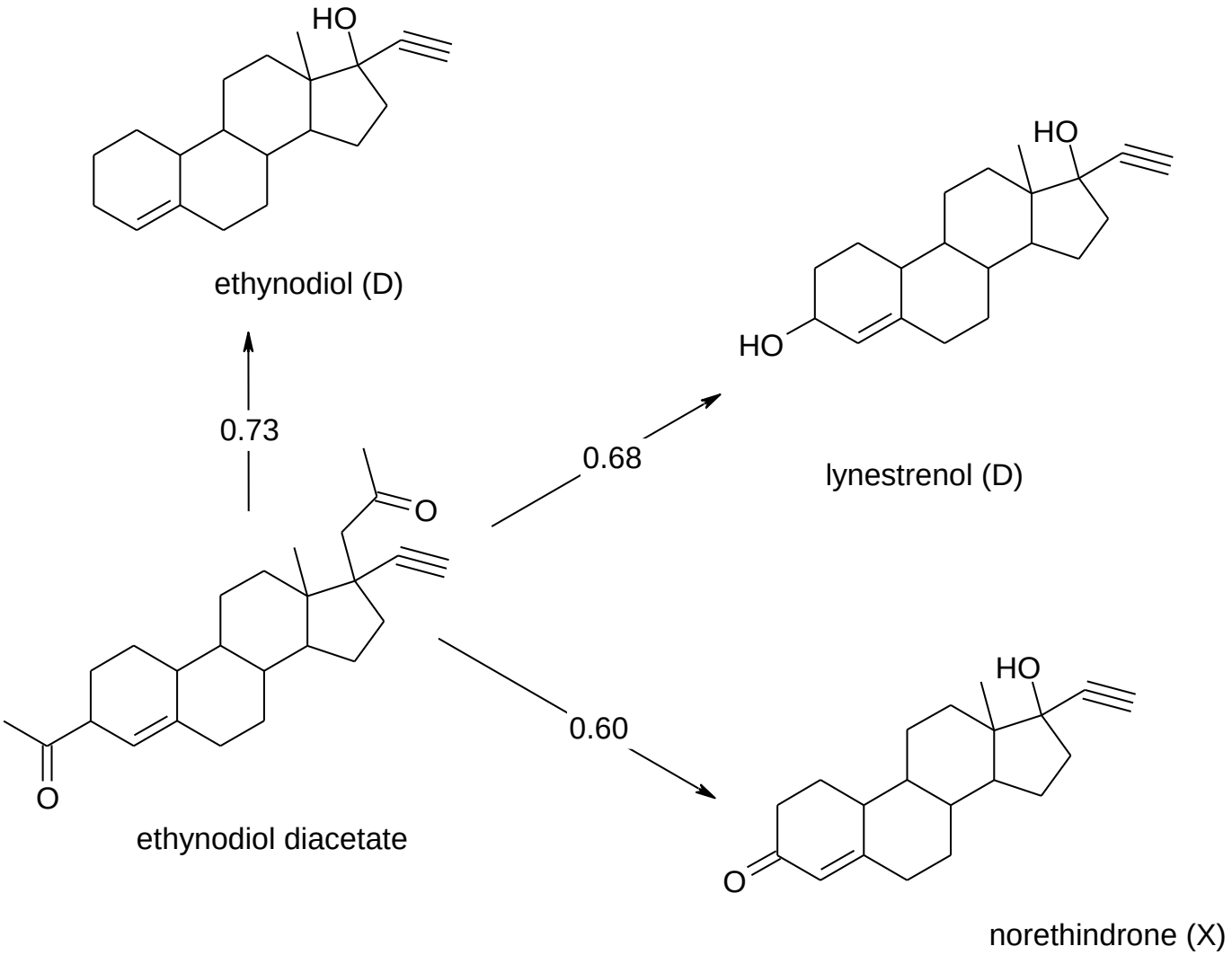
Similarity Category Formation

- 290 chemicals mainly drugs
- 57 query and 233 database chemicals
- Teratogenicity activity taken from FDA classes
- 2D similarity using atom environment and fingerprint similarity methods used
- All freely available in the Toxmatch software

FDA Classes

- **A: Control studies in women indicate no risk**
- **B: Control studies in animals indicate no risk**
- **C: Either animal studies indicate risk or there are no controlled animal or human studies**
- **D: Positive evidence of human risk**
- **X: Positive human and animal risk**

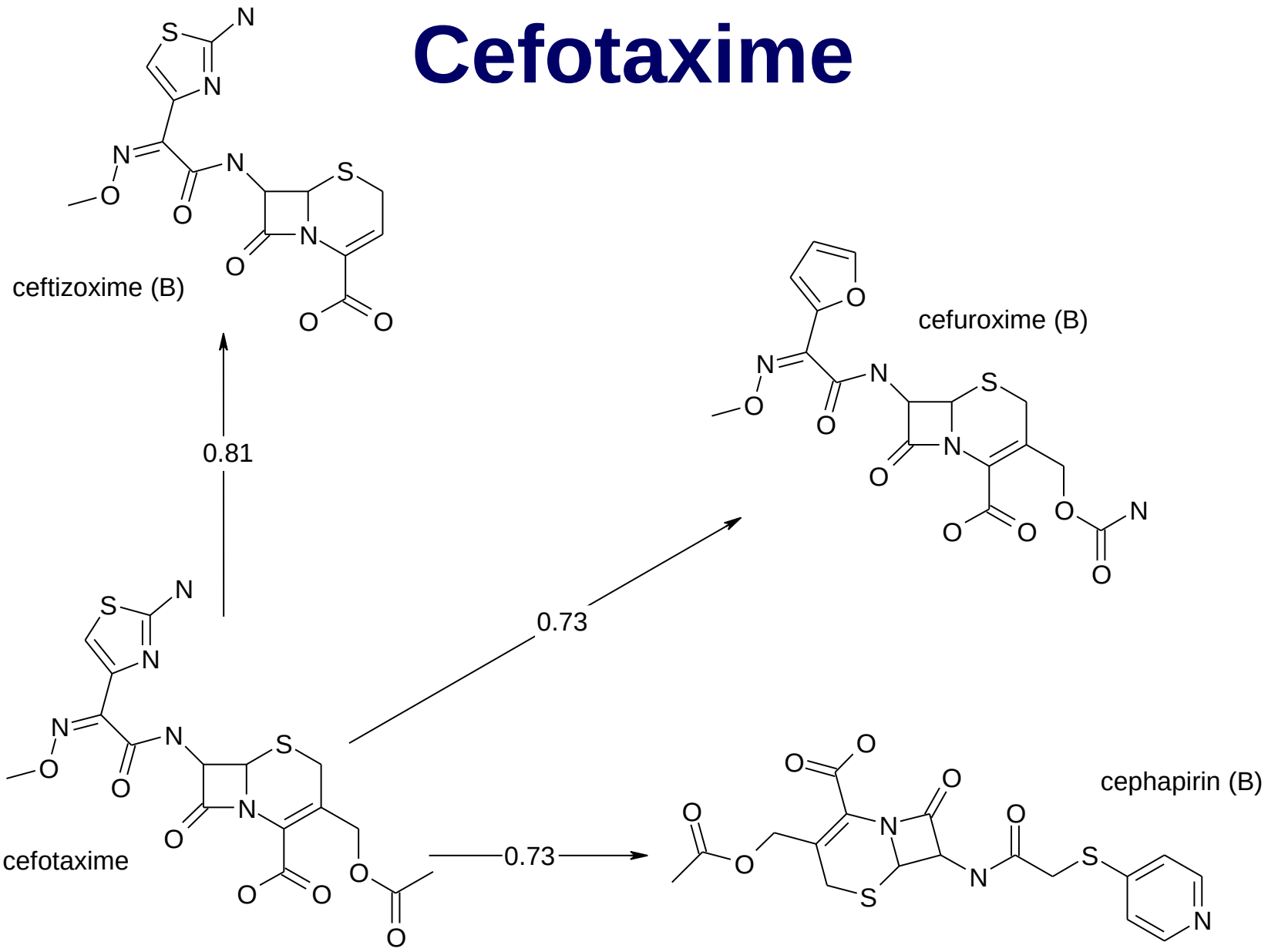
Ethynodiol diacetate



Read-across prediction (atom environment similarity): D / X

Actual classification: D

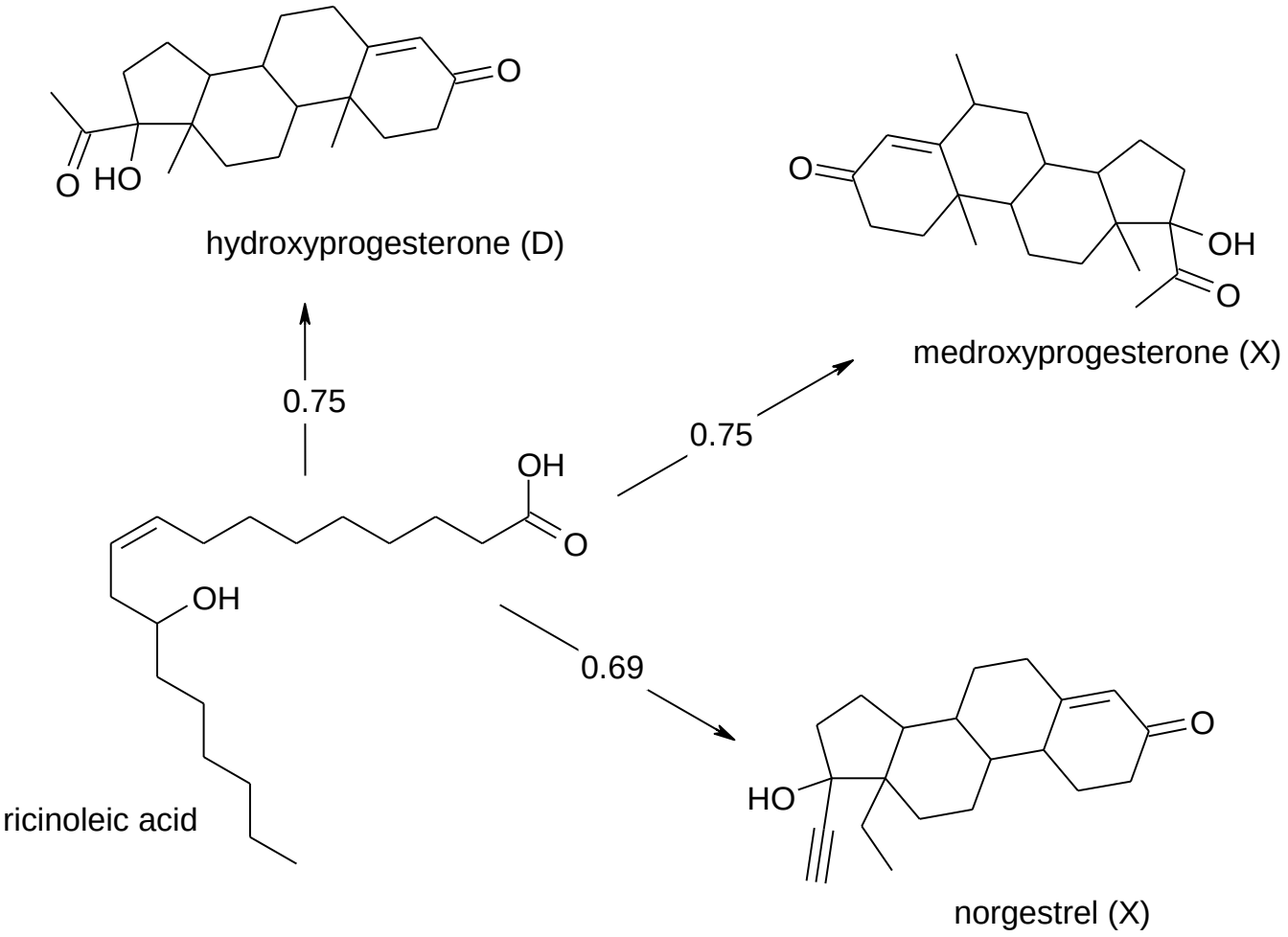
Cefotaxime



Read-across prediction (fingerprint similarity): B

Actual classification: B

Ricinoleic acid



Read-across prediction (fingerprint similarity): X
Actual classification: B

Conclusions

- **Multiple 2D similarity methods used to develop categories containing structural analogues**
- **Expert judgement is required**
- **Qualitative read-across gives good predictions within categories**

Local Model Conclusions

- **SMARTS based rules allow protein reactive chemicals to be assigned to mechanistic categories**
- **2D similarity methods can identify analogues enabling category formation**
- **Read-across can provide transparent predictions within these categories**