Defining Protein Reactivity Through Electrophilic Chemistry to Allow for Chemical Grouping and Read-Across

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Introduction

• *In silico* methods to predict the toxicity of chemicals include the use of (quantitative) structure-activity relationships (Q)SARs. They require only a molecular structure to make a prediction.

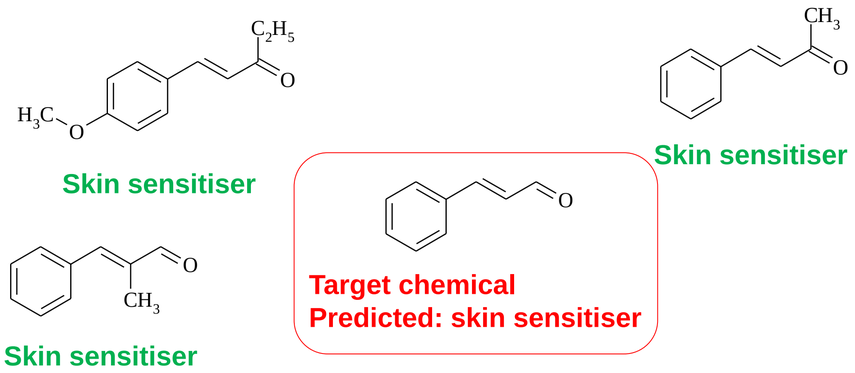
• The formation of categories of chemicals is a powerful technique to group compounds together on the basis of similar molecular features.

• Once a group of chemicals have been grouped together, read across of unknown activity can be attempted.

• Many toxic effects, e.g. skin and respiratory sensitisation, rely on the covalent binding of the chemical with proteins as the initiating event.

• The OECD QSAR Toolbox can be used to form categories on the basis of "profiles" of chemical associated with a mechanism of action or effect.

Example of Category Formation: Skin Sensitisation



•The skin sensitisation potential of the target chemical is not known
• A category was formed using the OECD Toolbox on the basis of the polarised alkene group
• All members of the category are skin sensitisers, therefore read-across suggests the target will be a skin sensitiser

Aims

• To review the current status of structural alerts related to covalent protein binding.

• To develop a comprehensive profiler for direct acting covalent protein binding for the OECD QSAR Toolbox, on the basis of mechanistic organic chemistry.

Methods

Data

• A thorough analysis of the literature and available expert systems was performed to determine the current status of alerts related to covalent protein binding.

Development of a comprehensive profiler for covalent protein binding

• The existing alerts were rationalised in terms of mechanistic reaction chemistry to provide a complete set of alerts.

• The alerts are only deemed appropriate if they were supported by published meta evidence supporting the chemistry.

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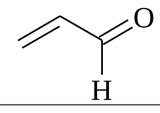
Current Structural Alerts for Protein Binding

A Structural Alert is a Molecular Fragment Associated with Activity

• Alerts should have a mechanistic basis
• A polarised aldehyde is a structural alert



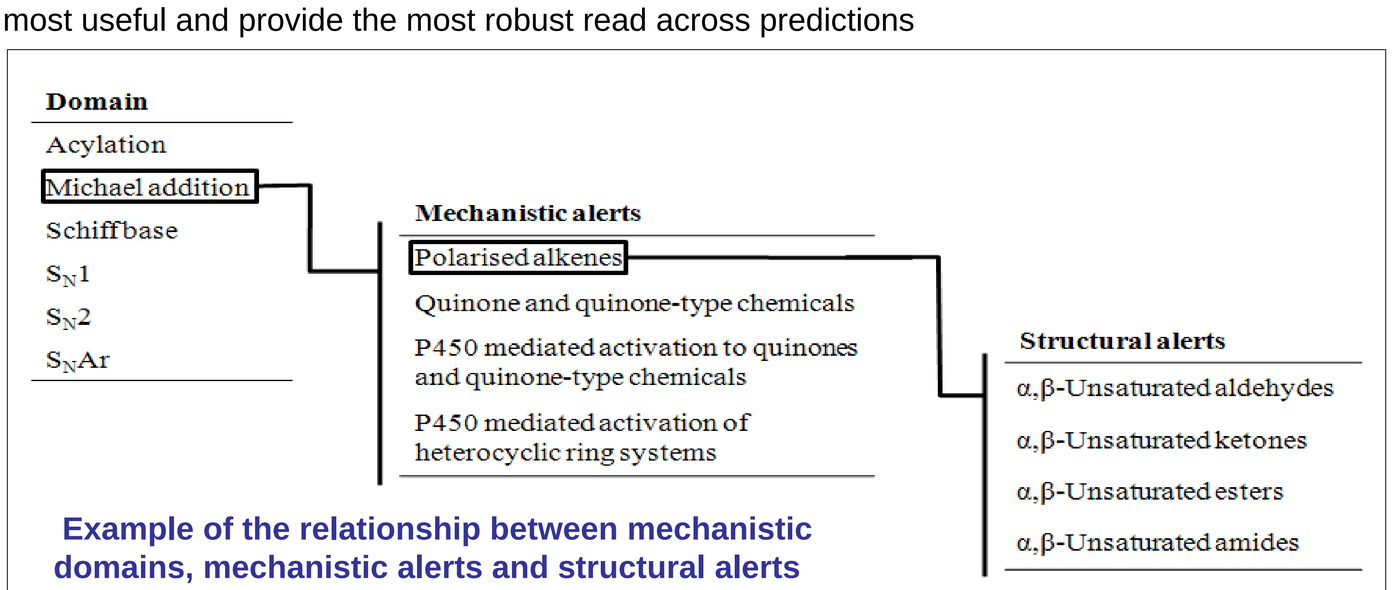
• Polarised alkenes are able to undergo Michael addition reactions

• A review of the literature found a number of alerts for protein binding.
• The alerts are summarised below and cover different approaches from using statistical techniques to human expert knowledge.

Publicly Available Structural Alerts for Applicable to Covalent Protein Binding

• Four datasets related to skin sensitisation (References 1-4)
• A dataset related to respiratory sensitisation (5)
• A dataset related to skin irritation (6)
• Four datasets related to excess acute aquatic toxicity (7-10)
• A dataset related to *in chemico* glutathione reactivity (11)

• The alerts were organised into profiling levels relating levels of mechanistic detail together.
• This allows three levels of profiling to be undertaken in the OECD QSAR Toolbox.
• The more focussed the profiling level the more closely related the chemicals in the resulting category
• Categories developed at the 'Mechanistic alert' and 'Structural alert' level are likely to be the most useful and provide the most robust read across predictions



Example of the relationship between mechanistic domains, mechanistic alerts and structural alerts

A Profiler of Protein Binding for the OECD QSAR Toolbox

• A total of103 structural alerts for protein binding have been developed, assigned to the mechanistic domains as shown below.
• These give a broader coverage of protein binding alerts than single set of alerts previously.

Mechanistic Domains

• This new set of structural alerts can be assigned to previously suggested mechanistic domains:

Michael: 35 alerts Acylation: 17 alerts S_NAr: 4 alerts S_N2: 43 alerts Schiff base : 4 alerts

• Several alerts have the possibility of more than a single mechanism depending on the substitution pattern around the reactive fragment

Conclusions

• A broad set of 103 new structural alerts for protein binding have been developed.
• All alerts are supported by meta data from the literature.
• These structural alerts are available in version 2.1 (and higher) of the OECD QSAR Toolbox.

References

1. Enoch, S. J. et al (2008) SAR and QSAR in Environmental Research, 19, p555-578
2. Zinke, S. et al (2002) ATLA, 30, p285-2989
3. Gerner, I. et al (2004) ATLA, 32, p487-509
4. Dimitrov, S. D. et al (2005) International Journal of Toxicology, 24, p189-204
5. Enoch, S. J. et al (2010) Chemical Research in Toxicology, 23, p1547-1555
6. Hulzebos, E. et al (2005) QSAR & Combinatorial Science, 24, p332-342
7. Verhaar, H. J. M. et al (1992) Chemosphere, 25, p471-491
8. Hermens, J. L. M. (1990) Environmental Health Perspectives, 87, p219-225
9. von der Ohe, P. C. et al (2005) Chemical Research in Toxicology, 18, p536-555
10. Nendza, M. et al (2007) SAR and QSAR in Environmental Research, 18, p155-168
11. Schultz, T. W. et al (2007) Chemical Research in Toxicology, 20, p1359-1363