Strategies for Intelligent Toxicity Testing: Integration of *In Silico* and Chemical Reactivity Information

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Introduction

Utilisation of non-test data for risk assessment of chemicals is an attractive prospect. *In silico* and *in chemico* data can be formalised into Integrated Testing Strategies (ITS) to reduce animal testing. *In chemico* data are obtained from abiotic chemical reactivity assays[3]. *In silico* approaches include the use of existing data and (quantitative) structure-activity relationships ((Q)SARs). Defining categories (groups) of chemicals allows for prediction of activity via read-across (the analogue approach). *In chemico* assays provide valuable data for "reactive" toxicity endpoints, i.e. where the formation of covalent bonds with biological macromolecules is required to elicit a response. This information has enabled identification of mechanisms of action which can be utilised in category formation. Approaches to ITS have been published for acute environmental effects[4] and skin sensitisation[5]. This provides a framework for the generation of usable tools to enable efficient risk assessment from non-test data. This study focuses on the development of such strategies.

Aims

- The aims of this study were to develop strategies to predict (i) acute environmental toxicity and (ii) skin sensitisation potential from a knowledge of chemical structure.

Methods

- Data were obtained from the literature for skin sensitisation in the local lymph node assay[2] and for acute aquatic effects to *Tetrahymena pyriformis*[6].
- Data for reactivity of compounds were obtained from an *in chemico* assay[7].
- Within the well-characterised chemical mechanistic domain (Michael-type nucleophilic addition) structural fragments were defined. Compounds falling within this domain were identified and are seen to be associated with skin sensitisation and excess acute aquatic toxicity.
- Available data and a knowledge of mechanistic organic chemistry were combined to enable qualitative and quantitative predictions of toxicity.

Results and Discussion

Data were compiled for structurally similar compounds identified as falling within the Michael mechanistic domain. Table 1 shows how such data can be utilised to qualitatively predict excess acute aquatic toxicity. Table 2 shows how quantitative prediction of skin sensitisation potential is possible when information on physico-chemical parameters correlated with potency are available (further details given in Enoch et al 2008)[1]. In this example the electrophilicity index, ω, is known to correlate with skin sensitisation potential (measured as EC3 values).

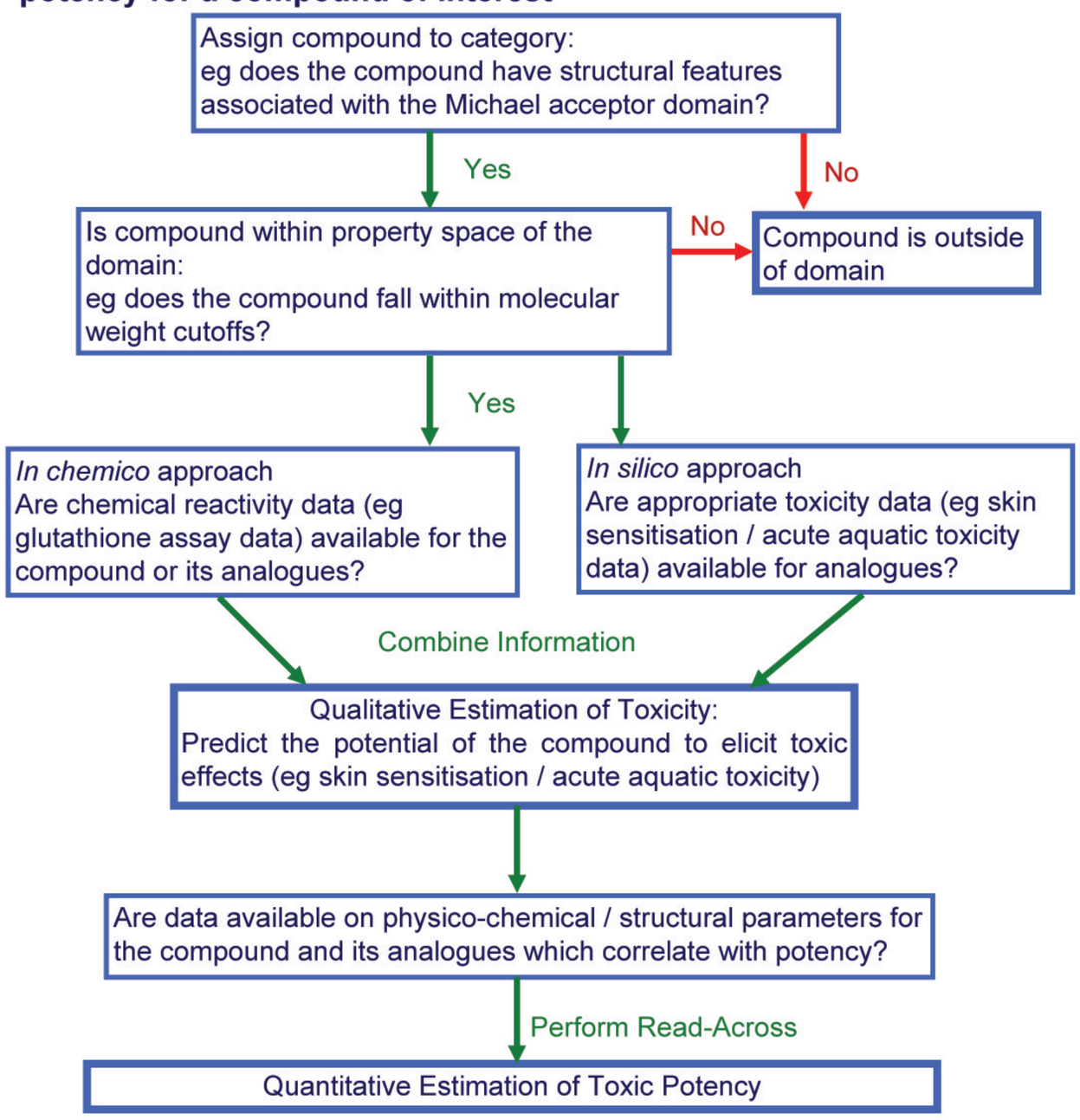
Table 1.Qualitiative prediction of excess acute toxicity

Compound	Reactivity in glutathione assay (RC50 (mM))	T. Pyriformis assay
3-buten-2-one	0.090	Excess toxicity - known
3-penten-2-one	0.11	Excess toxicity - known
3-octen-2-one	0.46	Excess toxicity – known
4-hexen-3-one	0.34	Excess toxicity – *predicted*

Table 2. Quantitative prediction of skin sensitisation

Compound	Electrophilicity (ω)	EC3 value
Safranal	1.796	7.5 – known
Diethyl maleate	1.804	*8.74 – predicted*
α-amyl cinnamic aldehyde	1.839	11 – known

Figure 1. Decision tree for qualitative and quantitative prediction of potency for a compound of interest



Conclusions

- For certain sub-classes of molecules qualitative prediction of toxicity or quantitative estimation of potency is possible utilising *in silico* data, supported by *in chemico* reactivity information. A strategy for such predictions is summarised in Figure 1 above.
- Where a known relationship exists between measured or calculable physico-chemical parameters and the activity of the compound, *in silico* read-across techniques can be employed to make a quantitative prediction of toxicity[1].

References

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