Overview of the status of predictive computer models

Expert Meeting: identification of pre- and pro-haptens

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Overview

- Non-testing approaches
- Skin sensitisation – biological understanding
- (Q)SAR models
- Read-across approaches
- Expert systems
  - Knowledge based
  - Statistical based
  - Hybrid
- IATA
  - IATA models

Continuum of non-testing approaches

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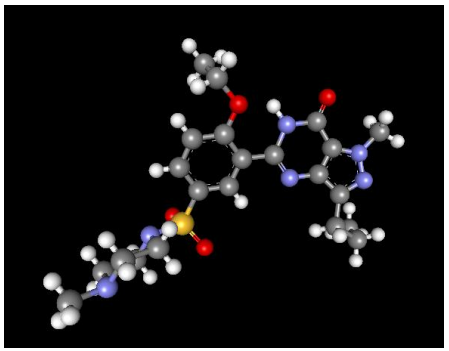
Activity = Function



Properties of a chemical and how it will interact with a defined system are inherent in its molecular structure

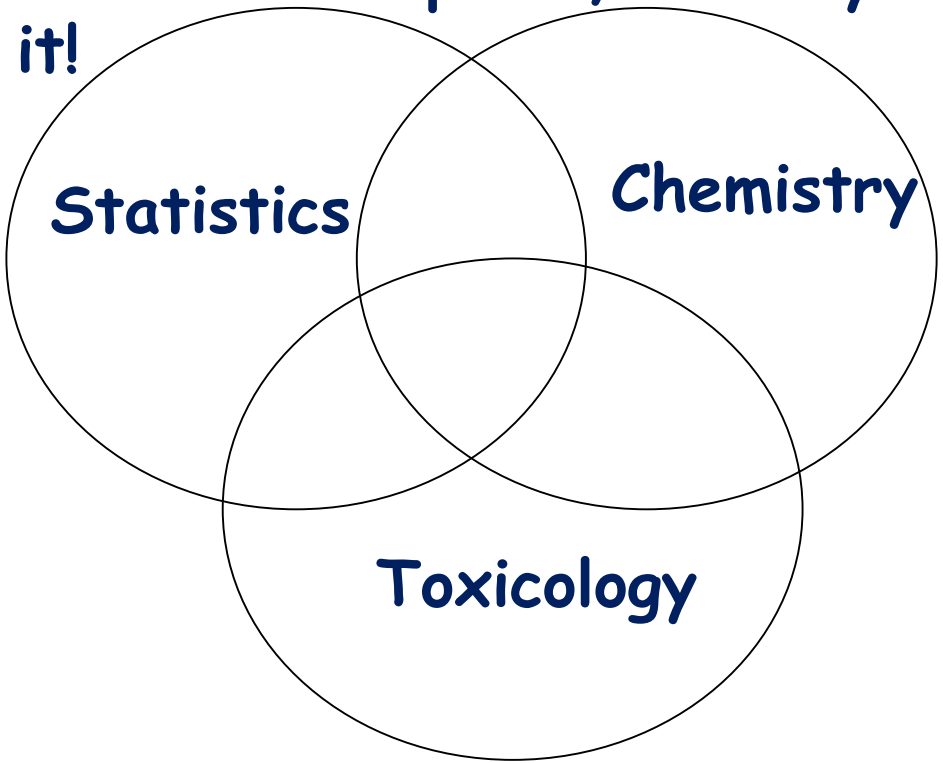
Chemical grouping → (Q)SARs

Less Formalised in structure

More Formalised in structure

Non-testing approaches

- Multi-disciplinary approach of integrating chemistry and toxicology using statistical approaches..
- Requires data as inputs (calculated and/measured descriptors, toxicity data) and lots of it!



Skin sensitisation AOP (OECD, 2012)

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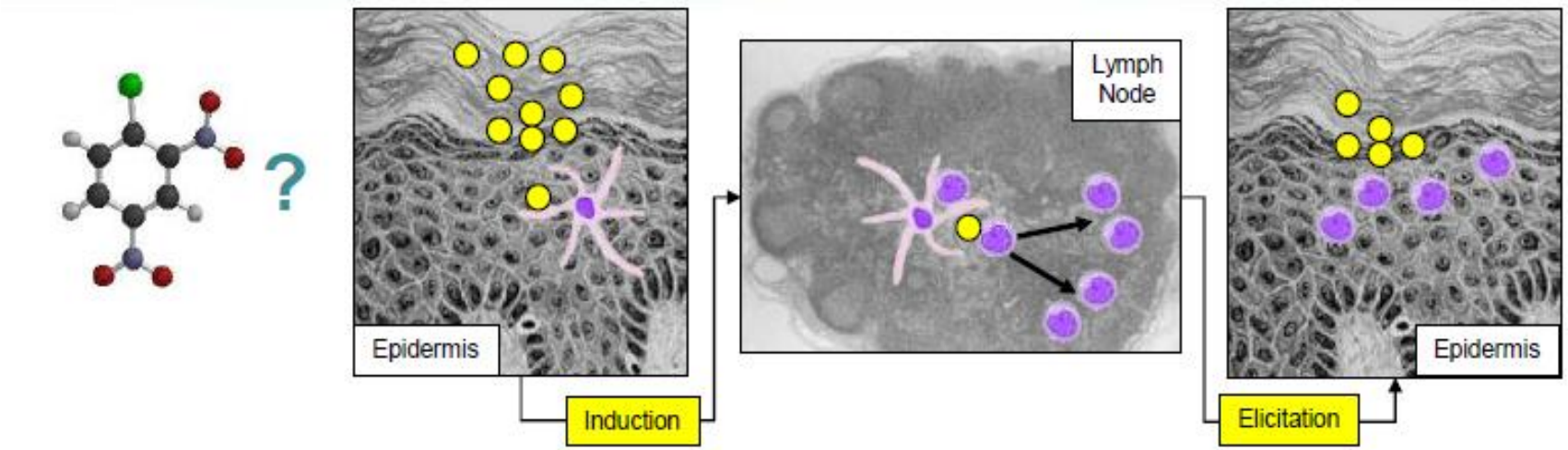
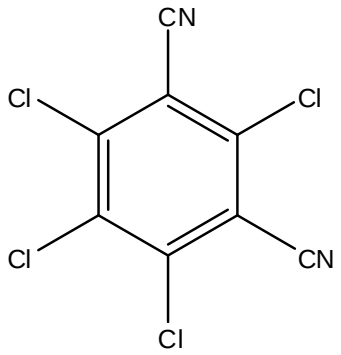


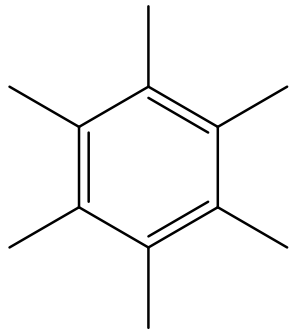
Chemical Structure & Properties	Molecular Initiating Event	Cellular Response	Organ Response	Organism Response
1. Skin Penetration				
2. Electrophilic substance: directly or via auto-oxidation or metabolism	3-4. Haptenation: covalent modification of epidermal proteins	5-6. Activation of epidermal keratinocytes & Dendritic cells	7. Presentation of haptenated protein by Dendritic cell resulting in activation & proliferation of specific T cells	8-10. Allergic Contact Dermatitis: Epidermal inflammation following re-exposure to substance due to T cell-mediated cell death
	Key Event 1	**Key Event 2 + 3**	**Key Event 4**	**Adverse Outcome**

Physico-chemical Basis of Skin Sensitisation

- Skin sensitisation potential is dependent on electrophilic reactivity of the skin sensitiser or a derivative (produced by metabolism or oxidation)



Reactive

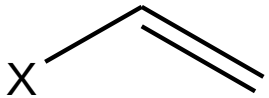


Non-reactive

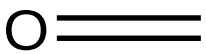
Reaction Mechanistic Domains

- Michael acceptors
- Schiff Base formers
- S_N2 electrophiles
- S_NAr electrophiles
- Acylating agents
- Non-reactive

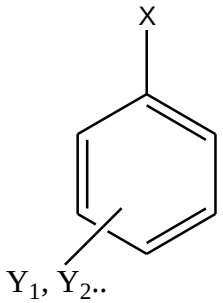
Structural Features



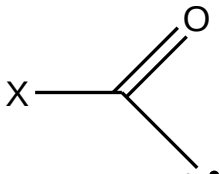
X = e.g. -CHO, COR, CN



X = e.g. F, Cl, Br, I



Y = e.g. $-NO_2$, CN, CHO



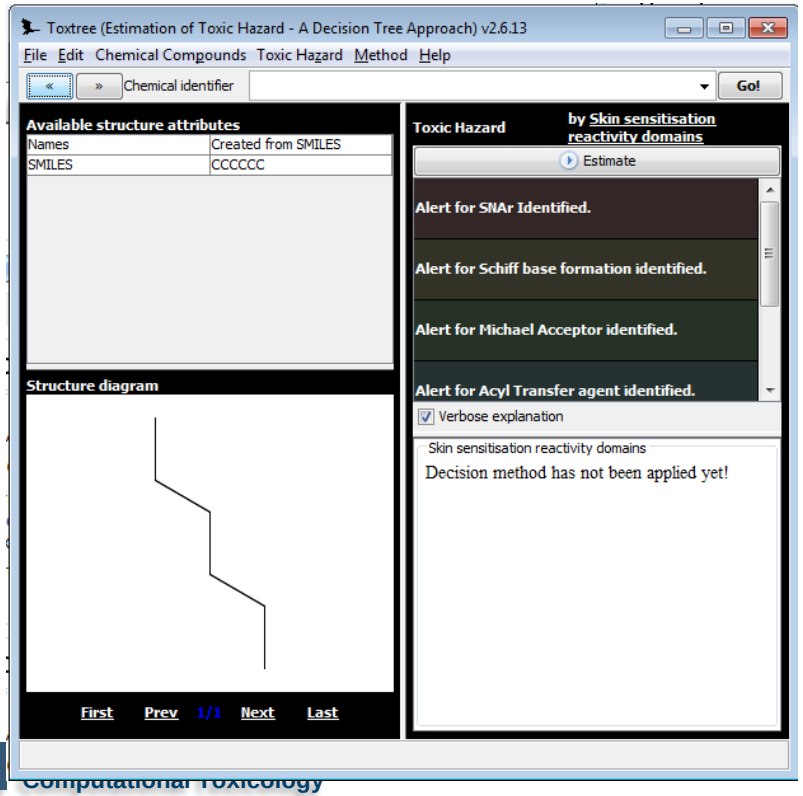
X = e.g. F, Cl, Br, I, $-OC_6H_5$

no reactive groups

Roberts & Aptula, 2006

Identifying reaction mechanistic domains

- By chemical inspection
- Protein Binding Profilers within the OECD Toolbox
- http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm



- Reactivity domains implemented within Toxtree http://toxtree.sourceforge.net/download.html

Skin sensitisation AOP (OECD, 2012)

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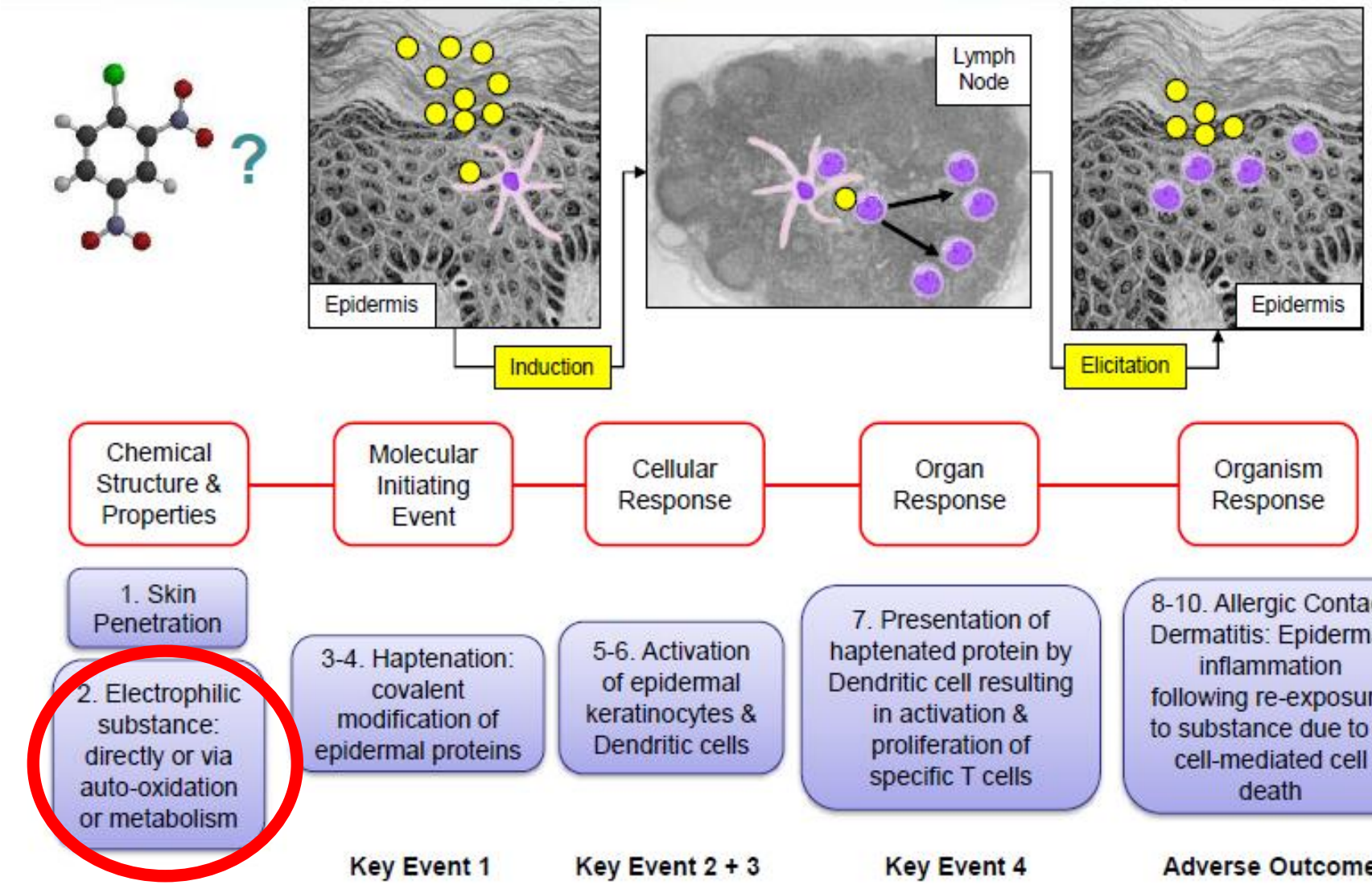
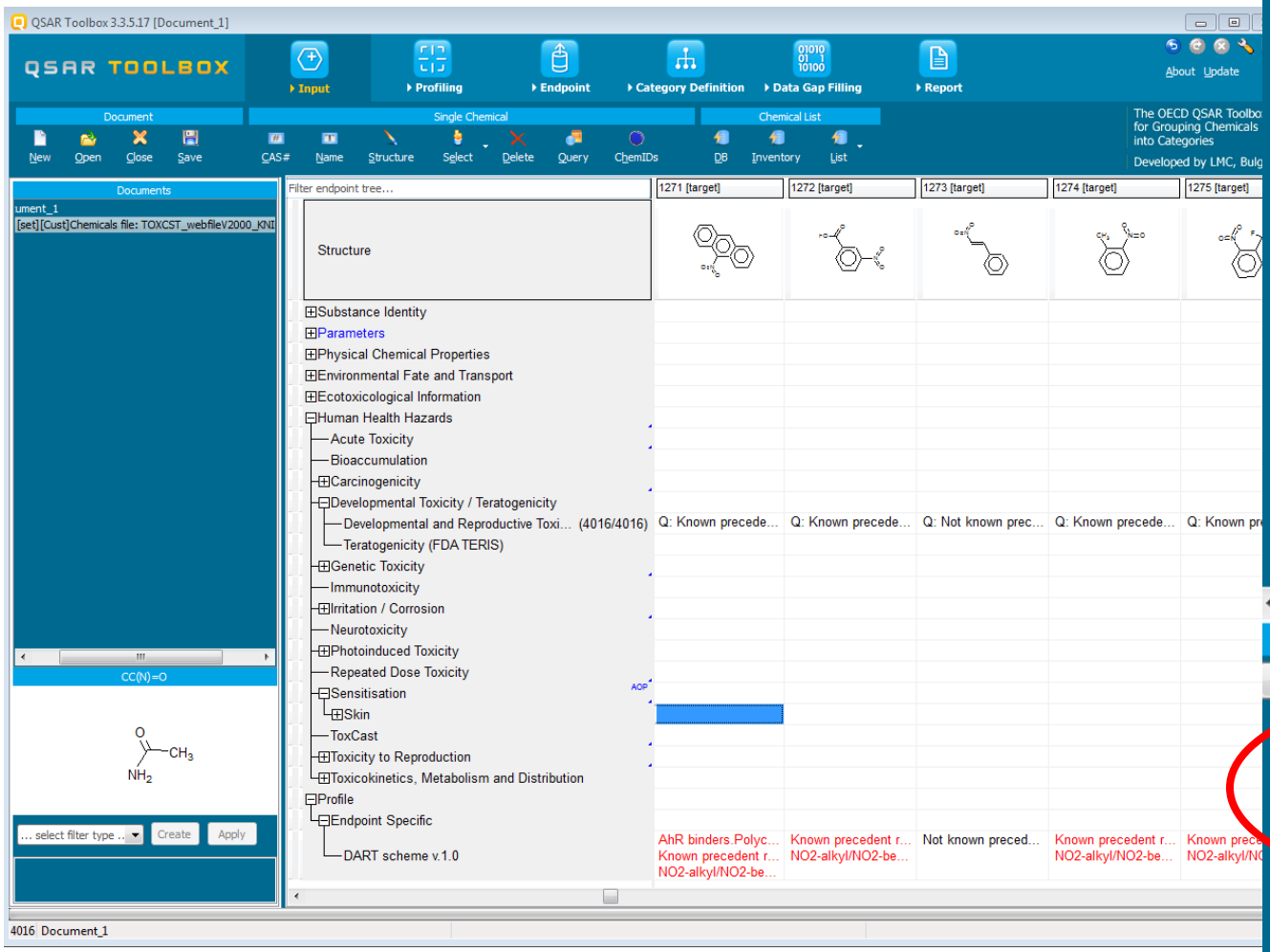
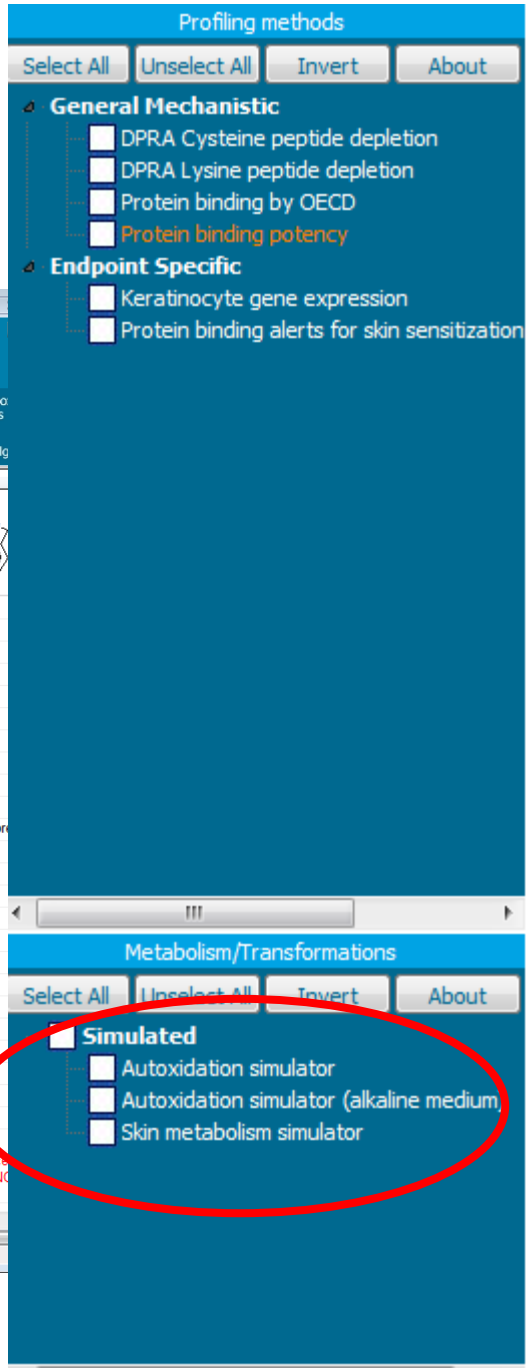


Identifying potential pre- and pro-haptens

- By expert judgement
- Literature searching
- Simulating metabolites using tools notably the simulators within the OECD Toolbox and the additional capabilities that are available within the TIMES-SS platform (Refer to Saby's presentation)

Identifying potential pre- and pro-haptens





QSAR models – Quantitative Mechanistic Models (QMMs)

Predictive Mechanistic Models

- **Michael Acceptors**: Roberts & Natsch (2009)

$$pEC3 = 0.24 \log k + 2.11$$

$$n = 10,\ R^2 = 0.836,\ s = 0.11,\ \text{and}\ F = 40.8$$

k – reactivity (rate constant for reaction with a nucleophile)

- **Schiff Bases**: Roberts et al (2006)

$$pEC3 = 1.12(\pm 0.07)Ss^* + 0.42(\pm 0.04)\log P - 0.62(\pm 0.13)$$

$$n = 16,\ R^2 = 0.952,\ s = 0.12,\ \text{and}\ F = 129.6$$

- logP : partitioning (octanol-water partition coefficient)
- Ss* : reactivity (sum of Taft *s** values)
- **S_NAr**: Roberts & Aptula (2014)

$$pEC3 = 2.81\ (\pm 0.12)RP - 5.44(\pm 0.36)$$

$$n = 10,\ R^2 = 0.987,\ s = 0.13,\ \text{and}\ F = 594$$

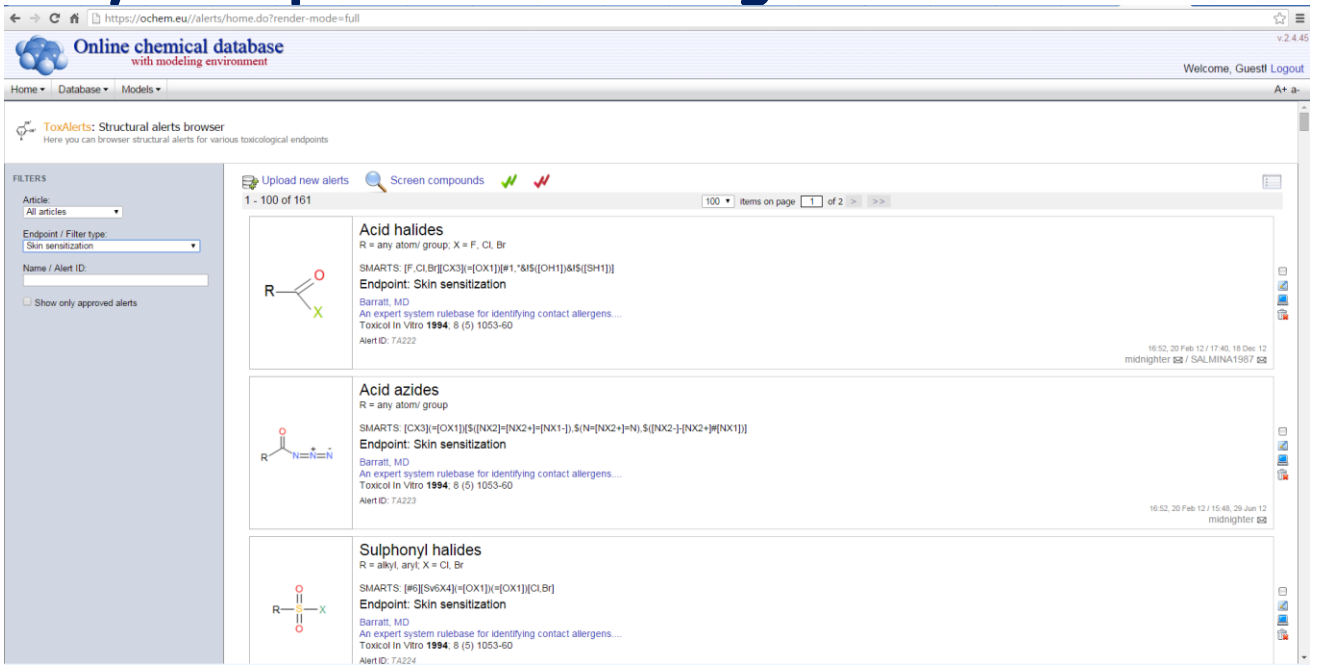
- RP - reactivity parameter, which is based on a combination of σ* and σ– substituent constants

Predictive Mechanistic Models

- No models available yet for
  - S_N2 domain chemicals
  - Acylating agents
- For non-reactive chemicals
  - Possibility of using a TTC type value - Dermal Sensitisation Threshold (DST) approach (Safford et al, 2011)
  - NB Has since been extended to incorporate chemicals categorised as reactive and to exclude "High Potency" chemicals (see Safford et al, 2015 & Roberts et al, 2015)

Read-across approaches

- Identify analogues and evaluate them on the basis of reaction domains, structural alerts to perform a "mechanistically based read-across"
- Tools such as the OECD Toolbox*, Toxtree, Ochem's Toxalerts, Derek Nexus are helpful to evaluate "similarity" of potential analogues



Expert systems

- Knowledge based – e.g. Derek Nexus
- Statistical based – e.g. TOPKAT, MCASE
- Hybrid – TIMES-SS

Derek Nexus

- Comprises alerts, reasoning rules and examples
- Alerts are substantiated by evidence and associated references.
- The reasoning rules describe the relationships between factors such as physicochemical properties, species etc that allows a confidence level to be associated with a given prediction.
- Calculator for LogKow to make skin permeability predictions (Kp) is used to refine the confidence levels for skin sensitization predictions.
- Some alerts do have information captured for metabolites (HQ – precursor to benzoquinone)

TOPKAT

- Static model based on GPMT data
- Gives a yes/no outcome, a potency score (semi quantitative) and information on the applicability domain
- No accounting for metabolism

TIMES-SS

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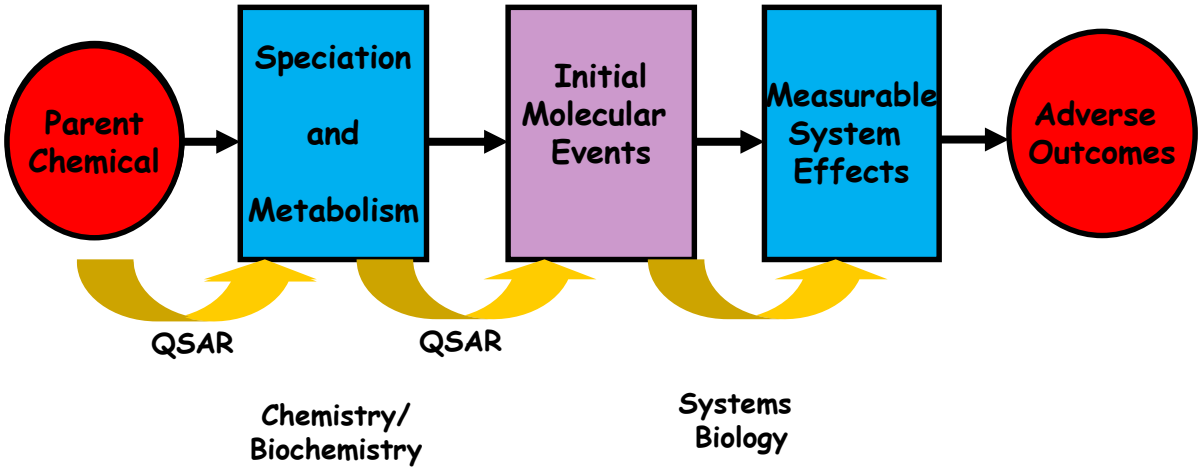
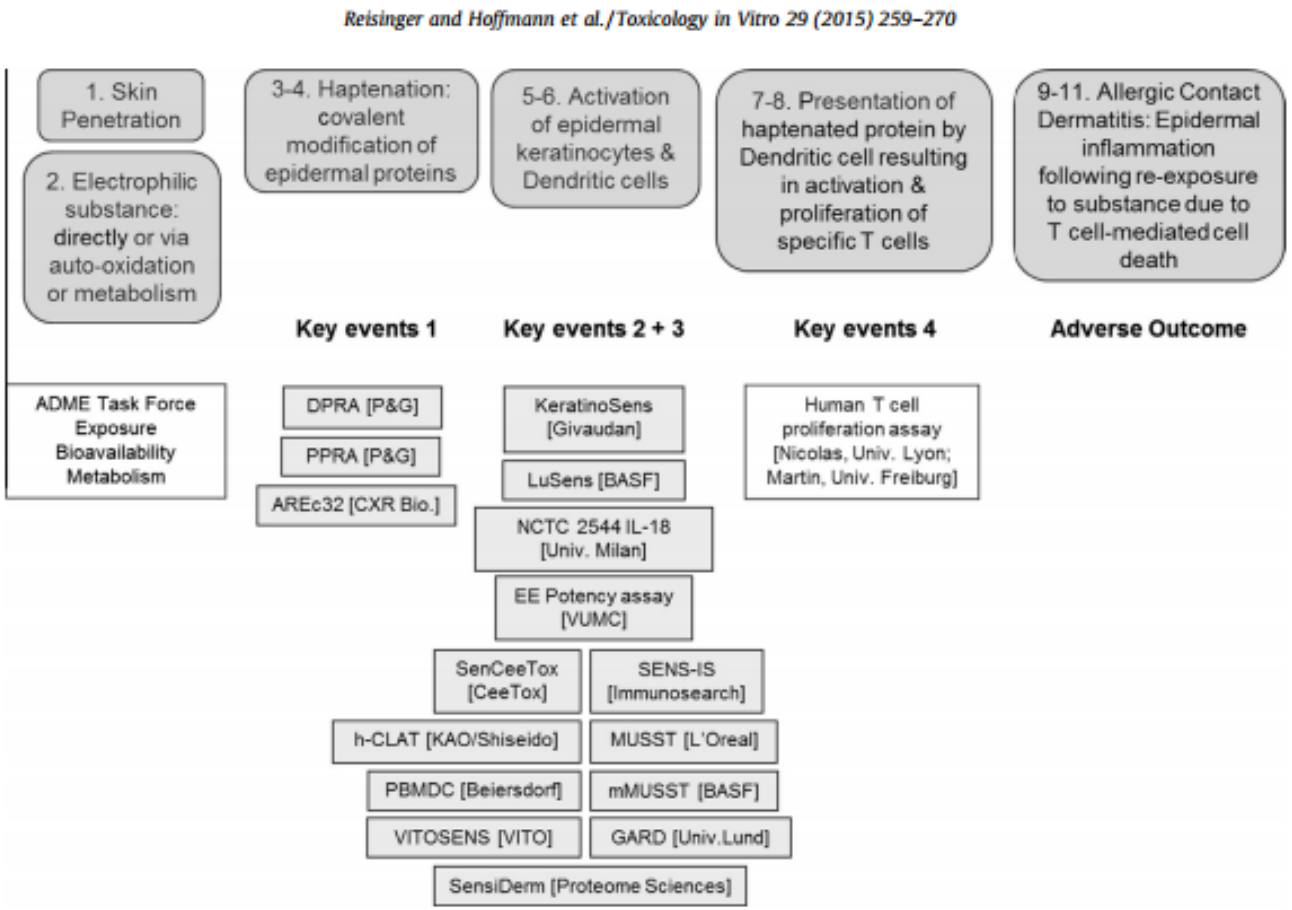
- Hybrid expert system
- Based on dataset of 875 chemicals tested by LLNA, GPMT and chemicals from the BfR list
- Structure-activity and structure metabolism rules
- Incorporates an autoxidation simulator
- Mechanistically transparent
- Predicts skin sensitisation effect in three classes: strong, weak and non-sensitisers
- Reliability of skin sensitisation prediction is assessed based on applicability domain, alert performance and mechanistic justification of the protein binding mechanism.

Moving towards IATA pipleline approaches

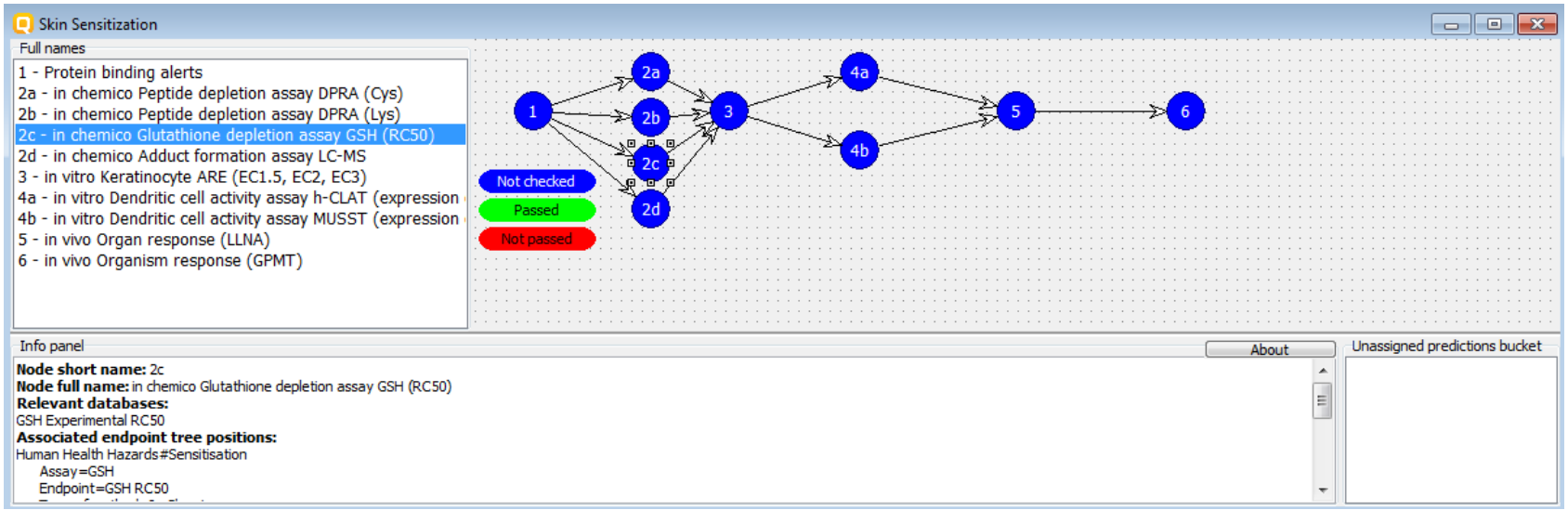


1. Identify plausible MIEs
2. Explore Linkages in Pathways to Downstream Effects
3. Develop QSARs to predict MIEs from Structure or characterise other KEs as SARs

AOP for skin sensitisation (SS) and assays mapped to KEs



AOP as implemented in the OECD Toolbox



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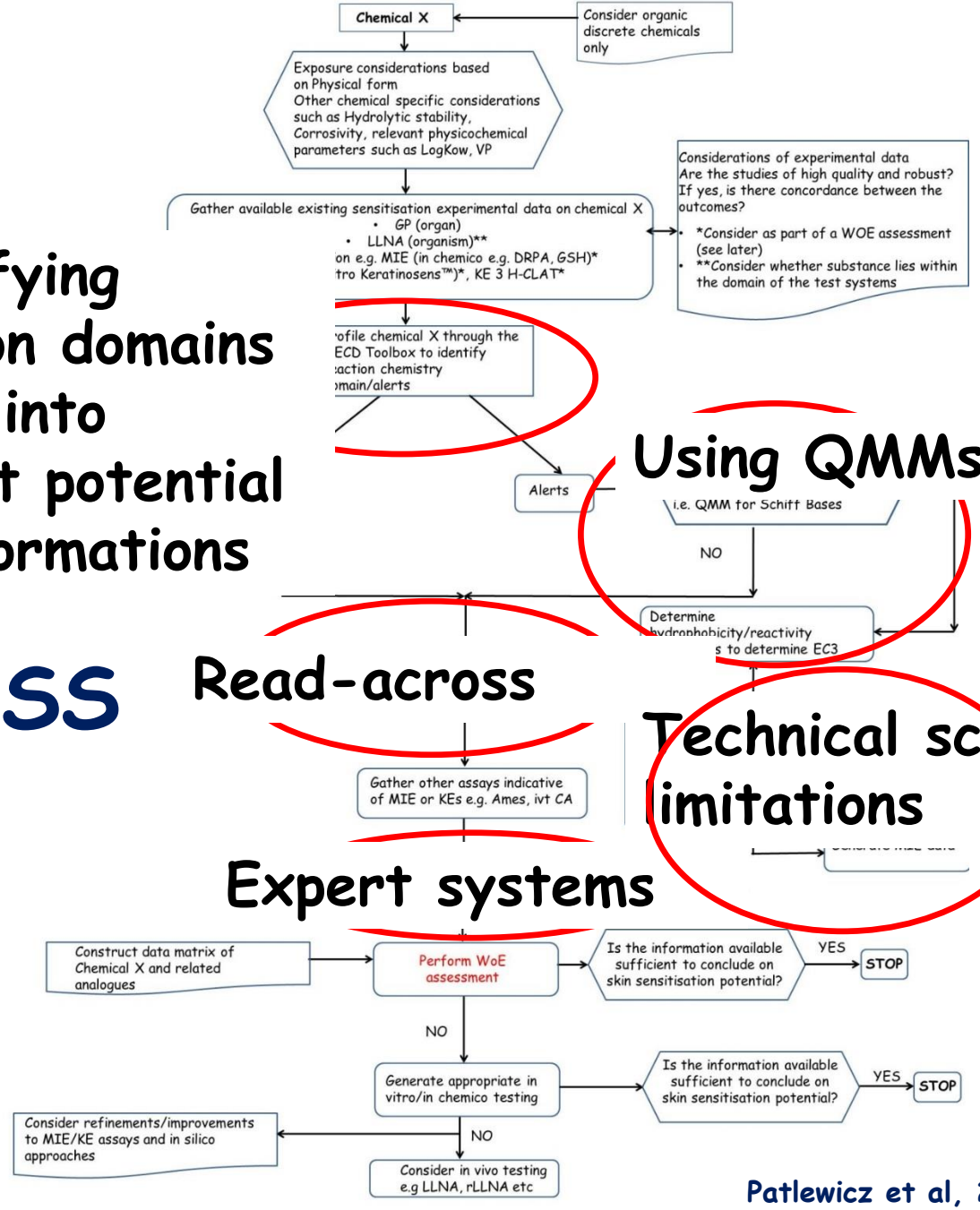
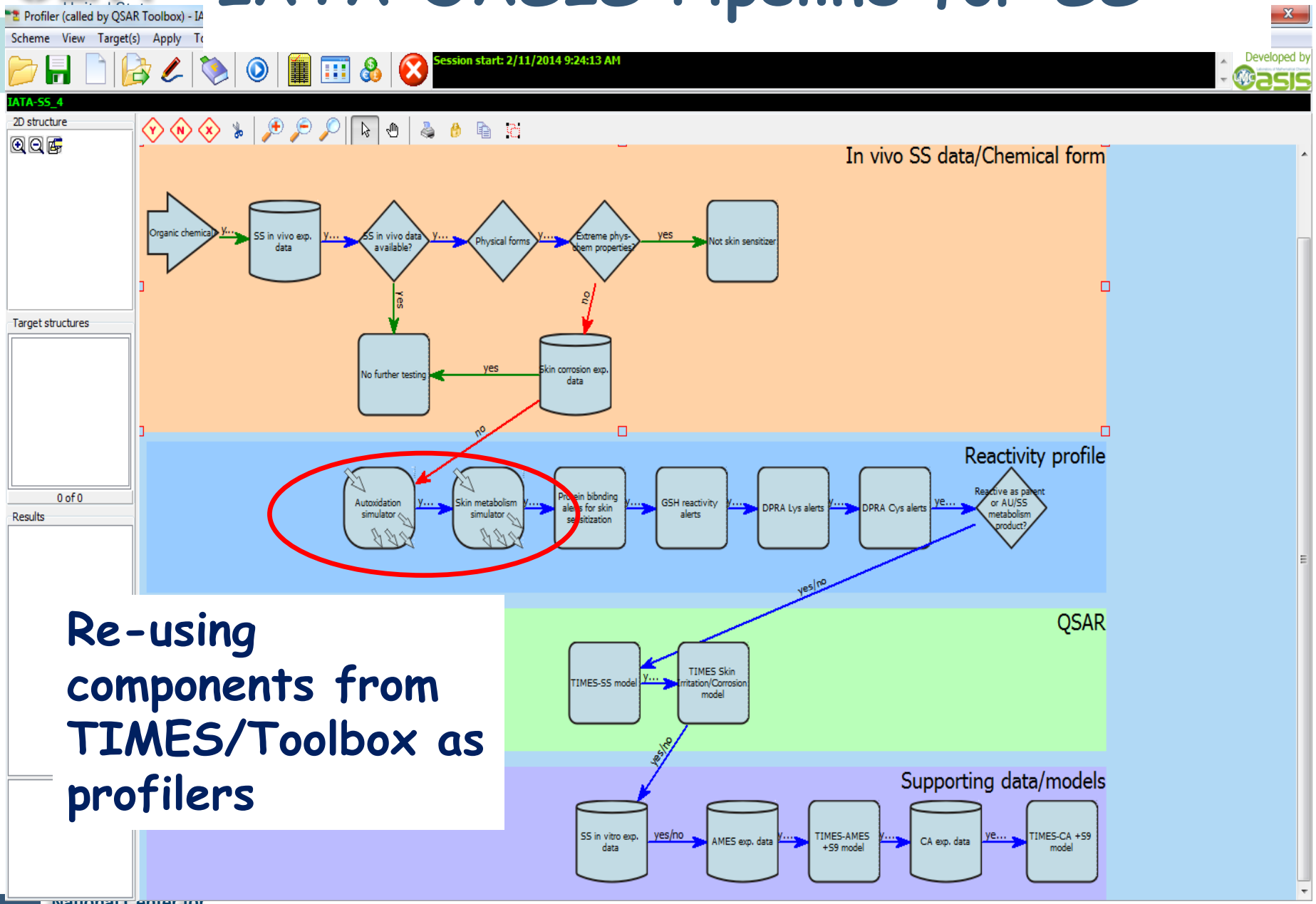
IATA for SS

Identifying reaction domains taking into account potential transformations



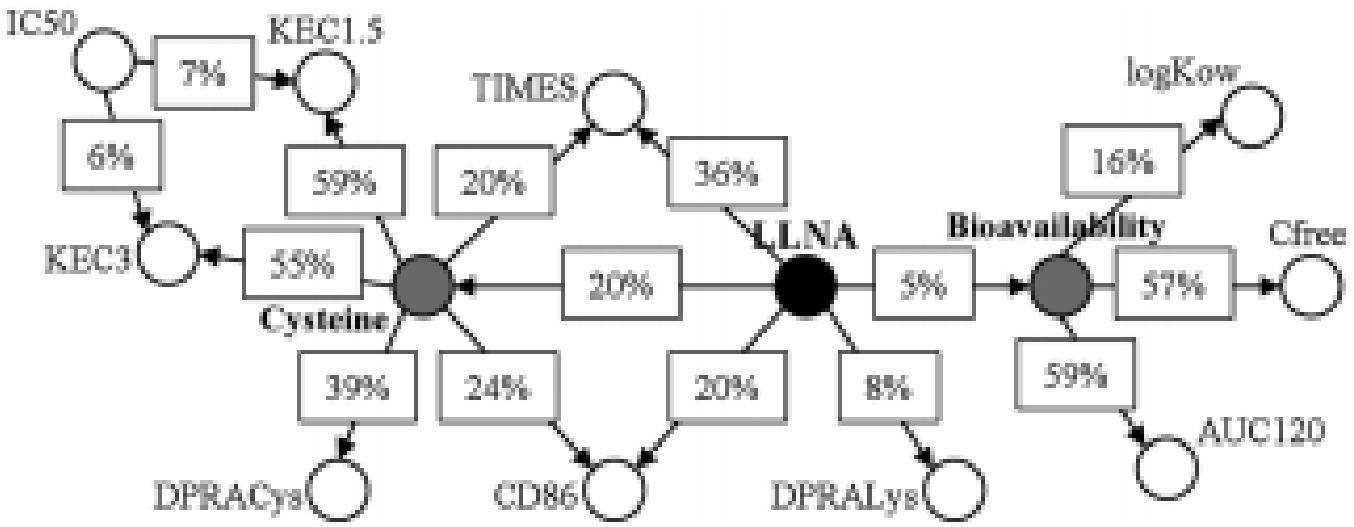
Patlewicz et al, 2014

IATA OASIS Pipeline for SS



Re-using components from TIMES/Toolbox as profilers

ITS-2 Integrated in AOP information using a Bayesian network



Jaworska et al, 2013

Take home messages

- A number of in silico approaches are available – profiling, read-across, QSAR, expert systems
  - Limited by the availability of measured reactivity data
- Shifting towards AOP informed IATA
  - Critical to understand the scope/technical limitations of the IATA elements e.g. analytical validity of individual assays
- Limited in our ability to systematically predict air oxidation products and metabolites by in silico tools
  - in silico approaches and even IATA developed to date do not typically account for pre-or pro-haptens