

Overview of the status of predictive computer models



Expert Meeting: identification of pre- and pro-haptens

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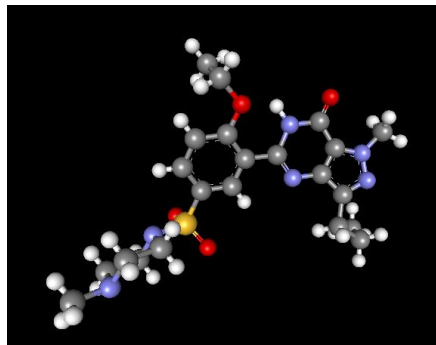
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Overview

- 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

Activity = Function



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

Chemical grouping

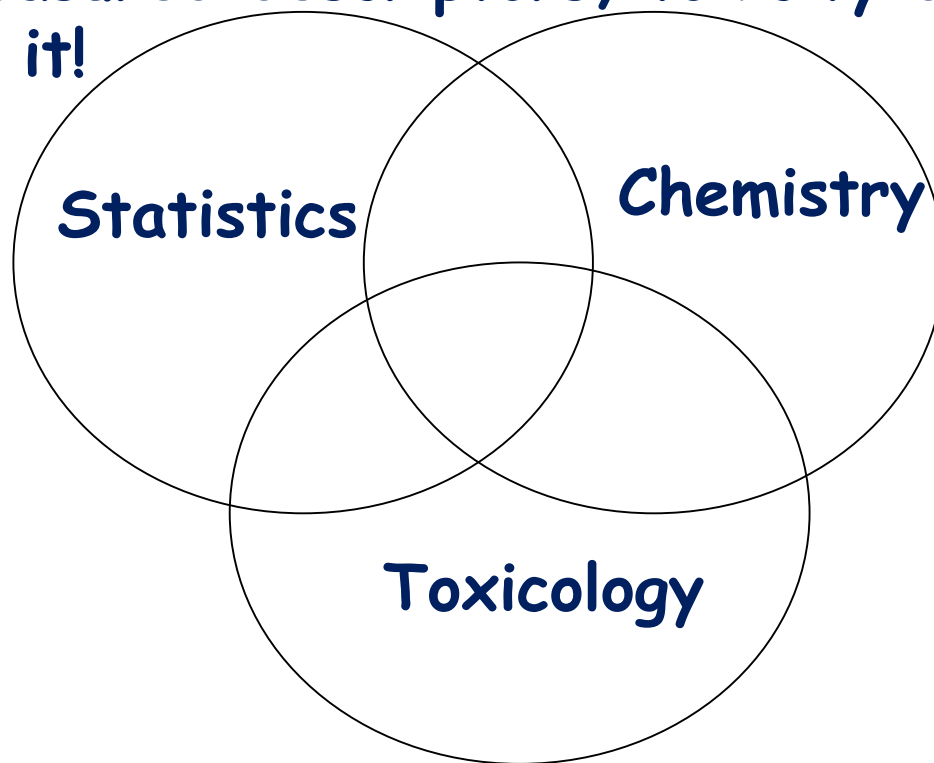
(Q)SARs

Less Formalised
in structure

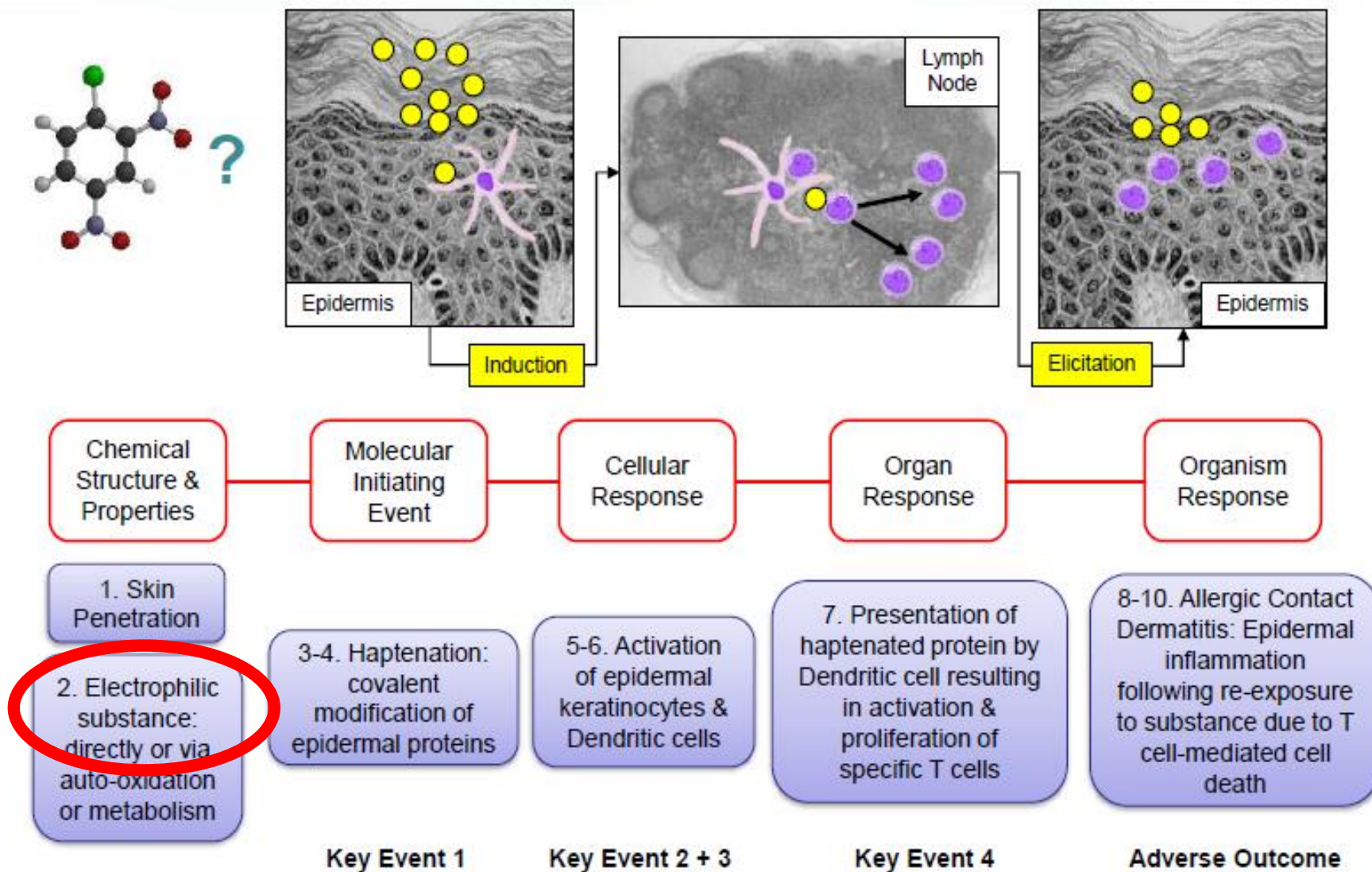
More Formalised
in structure

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!**

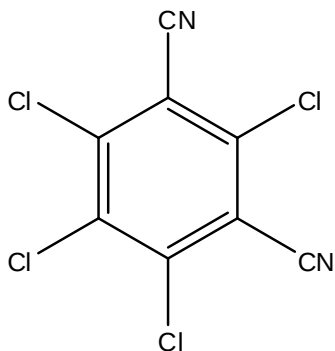


Skin sensitisation AOP (OECD, 2012)

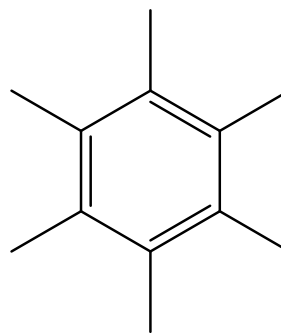


Physico-chemical Basis of Skin Sensitisation

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



Reactive

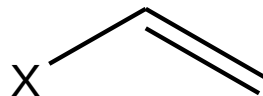


Non-reactive

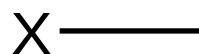
Reaction Mechanistic Domains

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

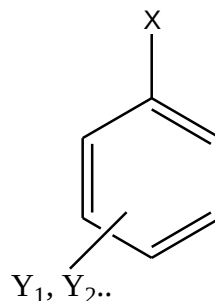
Structural Features



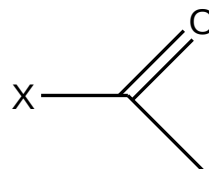
X = e.g. -CHO, COR, CN



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



Y = e.g. -NO₂, CN, CHO

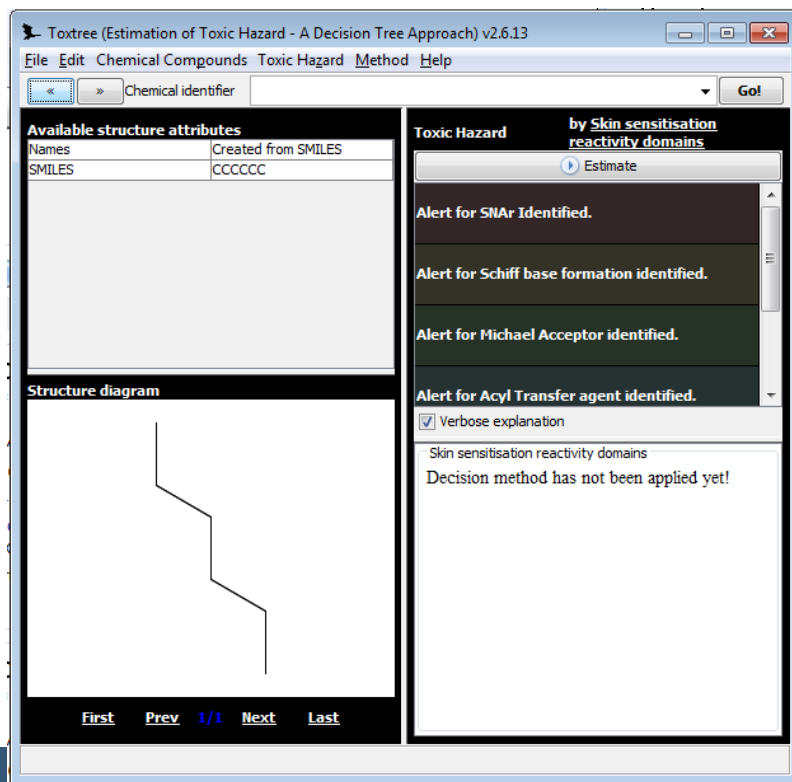


X = e.g. F, Cl, Br, I, -OC₆H₅

no reactive groups

Identifying reaction mechanistic domains

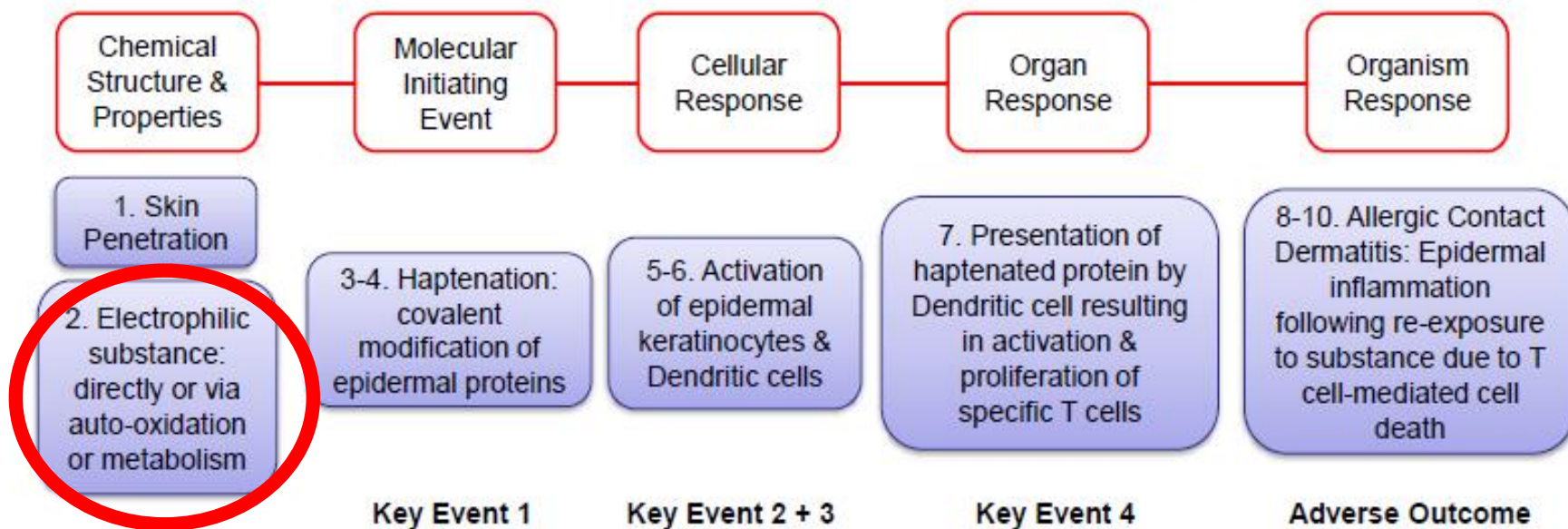
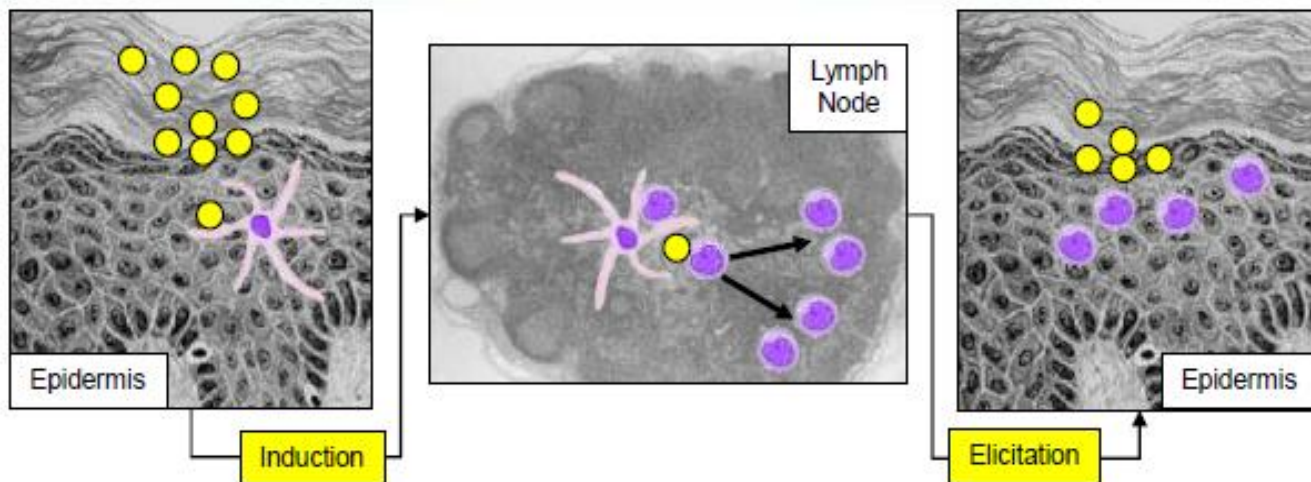
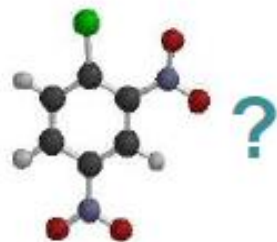
- By chemical inspection
- Protein Binding Profilers within the OECD Toolbox
- <http://www.oecd.org/chemicalsafety/risk-assessment/theoecdqsartoolbox.htm>



• Reactivity domains implemented within Toxtree

<http://toxtree.sourceforge.net/download.html>

Skin sensitisation AOP (OECD, 2012)



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)



United States
Environmental Protection
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Identifying potential pre- and pro-haptens

QSAR Toolbox 3.3.5.17 [Document_1]

QSAR TOOLBOX

Input Profiling Endpoint Category Definition Data Gap Filling Report

Document: New Open Close Save CAS# Name Structure Select Delete Query ChemIDs DB Inventory List

Documents: Document_1 [set][Cust][Chemicals file: TOXCST_webfileV2000_JNI]

Filter endpoint tree...

- Structure
- Substance Identity
- Parameters
- Physical Chemical Properties
- Environmental Fate and Transport
- Ecotoxicological Information
- Human Health Hazards
 - Acute Toxicity
 - Bioaccumulation
 - Carcinogenicity
 - Developmental Toxicity / Teratogenicity
 - Developmental and Reproductive Toxi... (4016/4016)
 - Teratogenicity (FDA TERIS)
 - Genetic Toxicity
 - Immunotoxicity
 - Irritation / Corrosion
 - Neurotoxicity
 - Photoinduced Toxicity
 - Repeated Dose Toxicity
 - Sensitisation
 - Skin
 - ToxCast
 - Toxicity to Reproduction
 - Toxicokinetics, Metabolism and Distribution
- Profile
 - Endpoint Specific
 - DART scheme v.1.0

CC(N)=O

... select filter type ... Create Apply

4016 Document_1

1271 [target]	1272 [target]	1273 [target]	1274 [target]	1275 [target]
Q: Known precede...	Q: Known precede...	Q: Not known prec...	Q: Known precede...	Q: Known precede...
AhR binders.Polyc...	Known precedent r...	Not known preced...	Known precedent r...	Known precedent r...
Known precedent r...	NO2-alkyl/NO2-be...		NO2-alkyl/NO2-be...	NO2-alkyl/NO2-be...
NO2-alkyl/NO2-be...				

Profiling methods

Select All Unselect All Invert About

- General Mechanistic
 - ☐ DPRA Cysteine peptide depletion
 - ☐ DPRA Lysine peptide depletion
 - ☐ Protein binding by OECD
 - ☒ Protein binding potency
- Endpoint Specific
 - ☐ Keratinocyte gene expression
 - ☐ Protein binding alerts for skin sensitization

Metabolism/Transformations

Select All Unselect All Invert About

- ☒ Simulated
 - ☐ Autoxidation simulator
 - ☐ Autoxidation simulator (alkaline medium)
 - ☐ Skin metabolism simulator

QSAR models - Quantitative Mechanistic Models (QMMs)

Predictive Mechanistic Models

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

$$\text{pEC3} = 0.24 \log k + 2.11$$

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

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

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

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

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

- $\log P$: partitioning (octanol-water partition coefficient)

- Ss^* : reactivity (sum of Taft s^* values)

- **S_NAr** : Roberts & Aptula (2014)

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

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

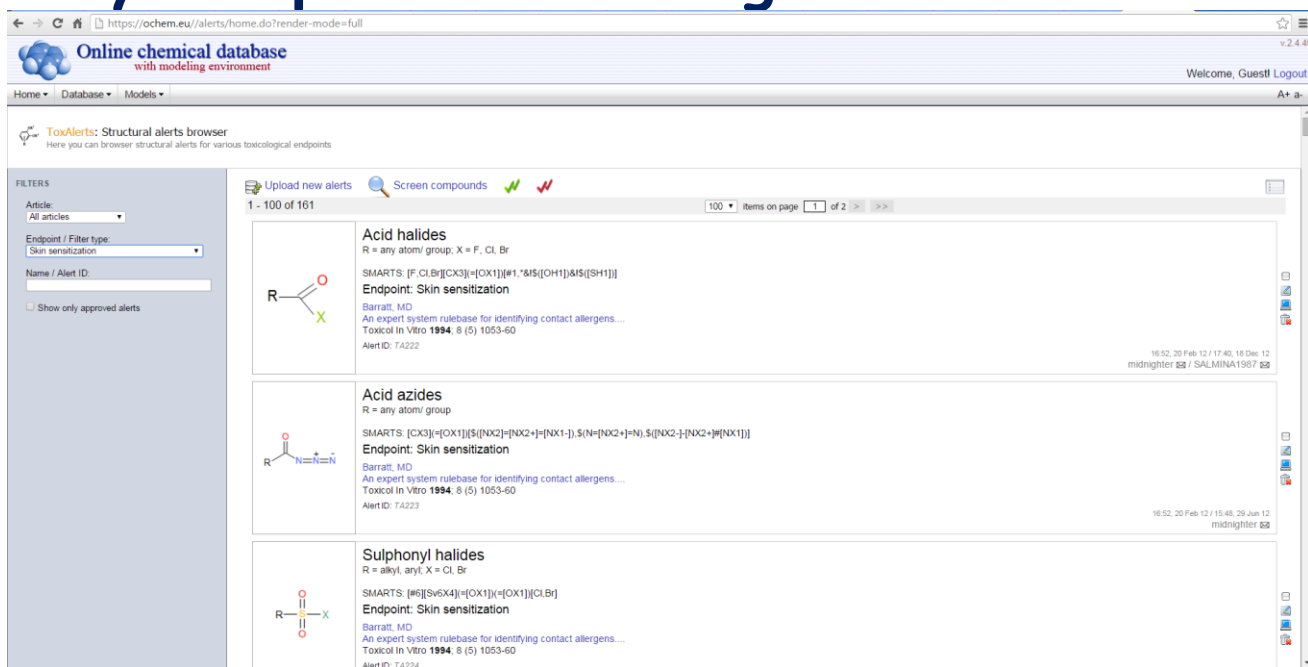
- RP – reactivity parameter, which is based on a combination of σ^* and σ^- substituent constants

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



The screenshot displays the 'Online chemical database with modeling environment' interface. The main section is titled 'ToxAlerts: Structural alerts browser' and lists three types of structural alerts for skin sensitization:

- Acid halides**: R = any atom/ group, X = F, Cl, Br. SMILES: [F,Cl,Br][CX3]=[OX1][*1.*8.[OH1]&[SH1]]. Endpoint: Skin sensitization. Barratt, MD. An expert system rulebase for identifying contact allergens... Toxicol In Vitro 1994; 8 (5) 1053-60. Alert ID: 7A222.
- Acid azides**: R = any atom/ group. SMILES: [CX3]=[OX1][*1.[NX2]=[NX1-].\$.[N]=[NX2-].[N].\$.[NX2-].[NX2-].[NX1]]. Endpoint: Skin sensitization. Barratt, MD. An expert system rulebase for identifying contact allergens... Toxicol In Vitro 1994; 8 (5) 1053-60. Alert ID: 7A223.
- Sulphonyl halides**: R = alkyl, aryl, X = Cl, Br. SMILES: [*6][S(=O)(=O)[OX1]=[OX1][Cl,Br]. Endpoint: Skin sensitization. Barratt, MD. An expert system rulebase for identifying contact allergens... Toxicol In Vitro 1994; 8 (5) 1053-60. Alert ID: 7A224.

The interface includes a left sidebar with filters (Article, Endpoint / Filter type, Name / Alert ID) and a top navigation bar with links to Home, Database, and Models.

Expert systems

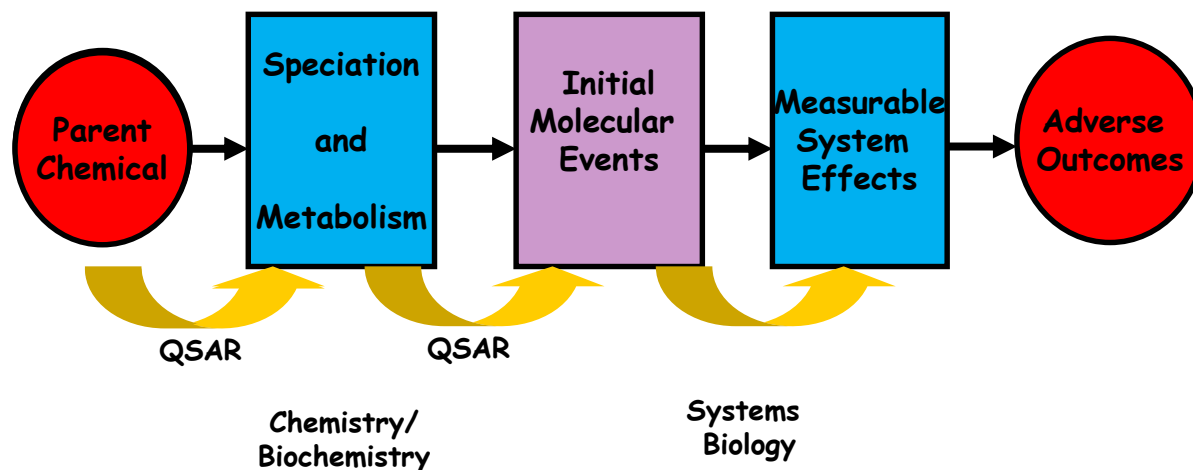
- Knowledge based - e.g. Derek Nexus
- Statistical based - e.g. TOPKAT, MCASE
- Hybrid - TIMES-SS

- 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 (K_p) is used to refine the confidence levels for skin sensitization predictions.
- Some alerts do have information captured for metabolites (HQ - precursor to benzoquinone)

- 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

- 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.

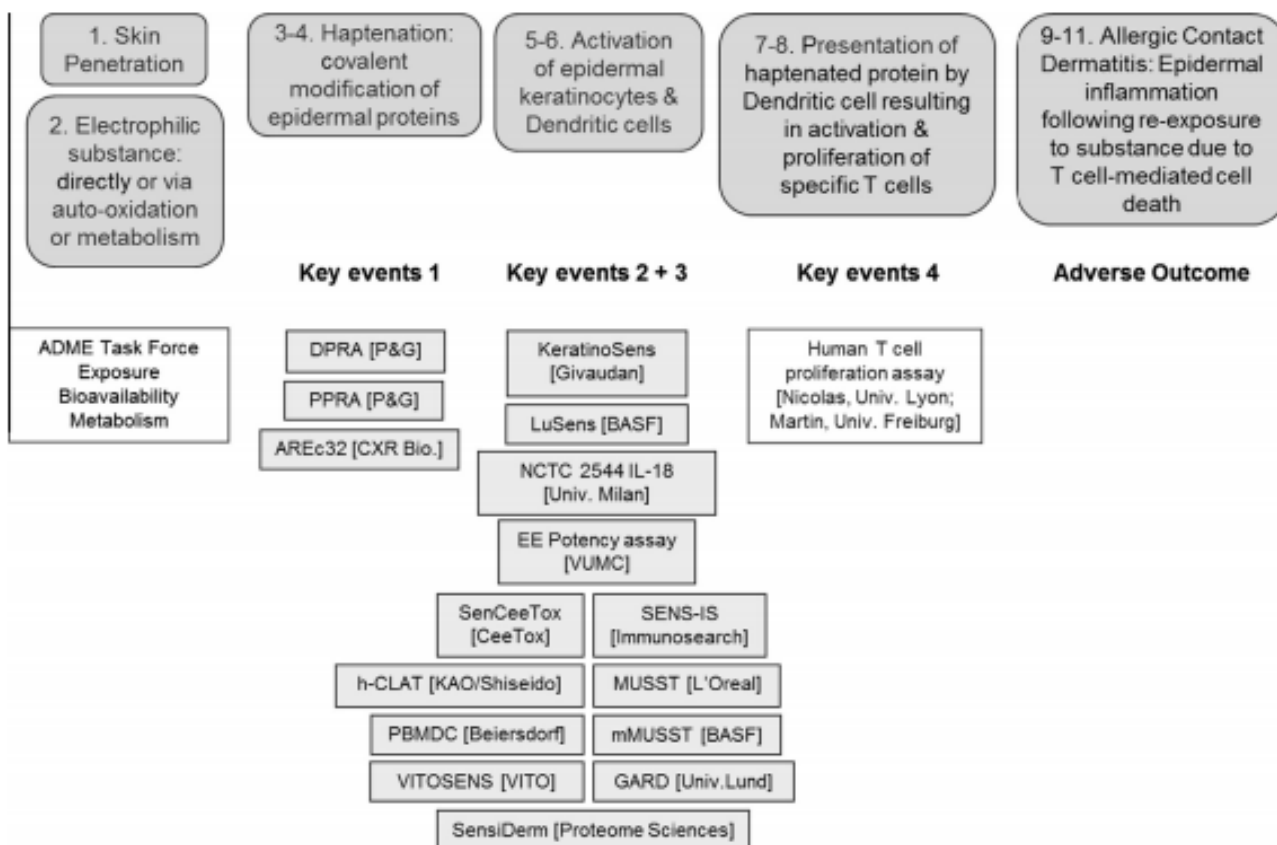
Moving towards IATA pipeline approaches



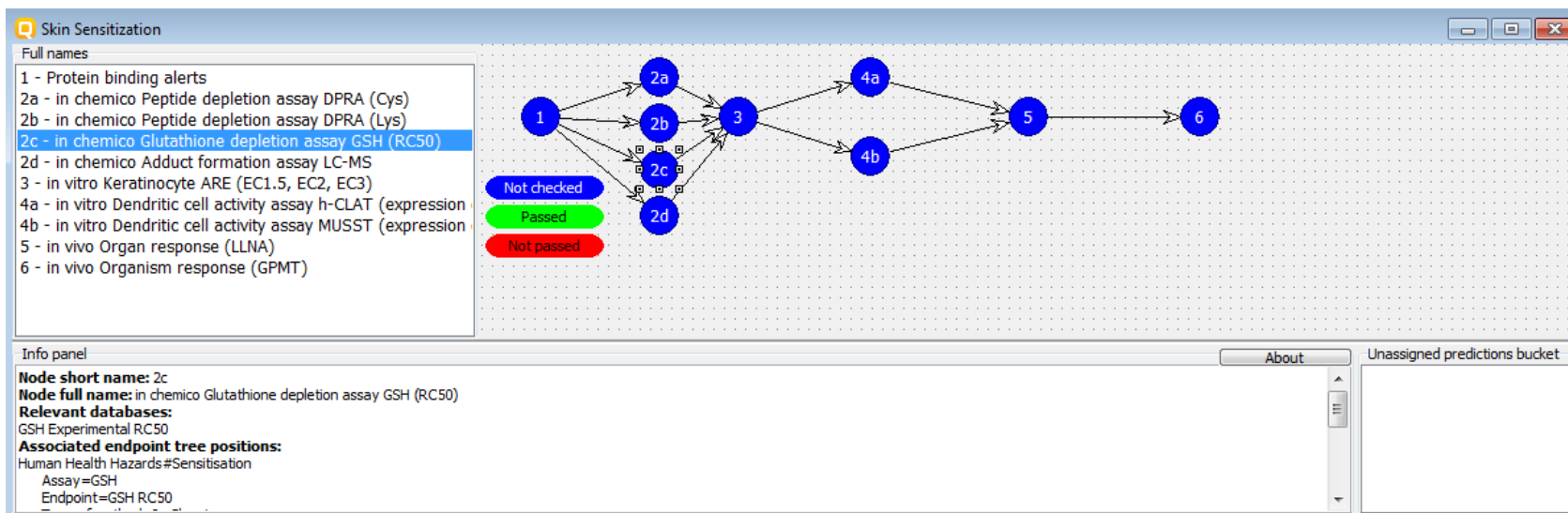
1. Identify plausible MIEs
2. Explore Linkages in Pathways to Downstream Effects
3. Develop QSARs to predict MIEs from Structure or characterise other KEs as SARs

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

Reisinger and Hoffmann et al./Toxicology in Vitro 29 (2015) 259–270

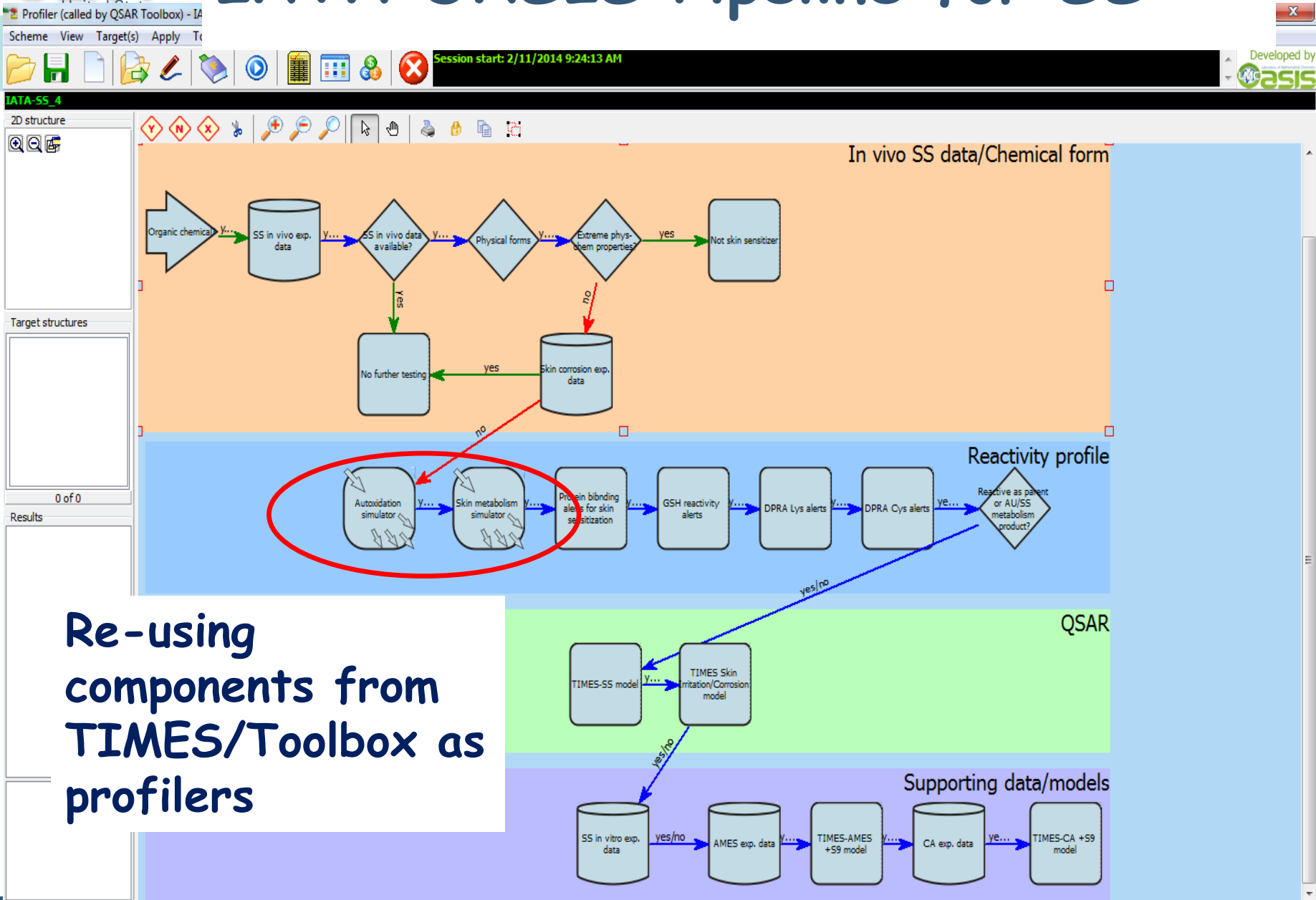


AOP as implemented in the OECD Toolbox

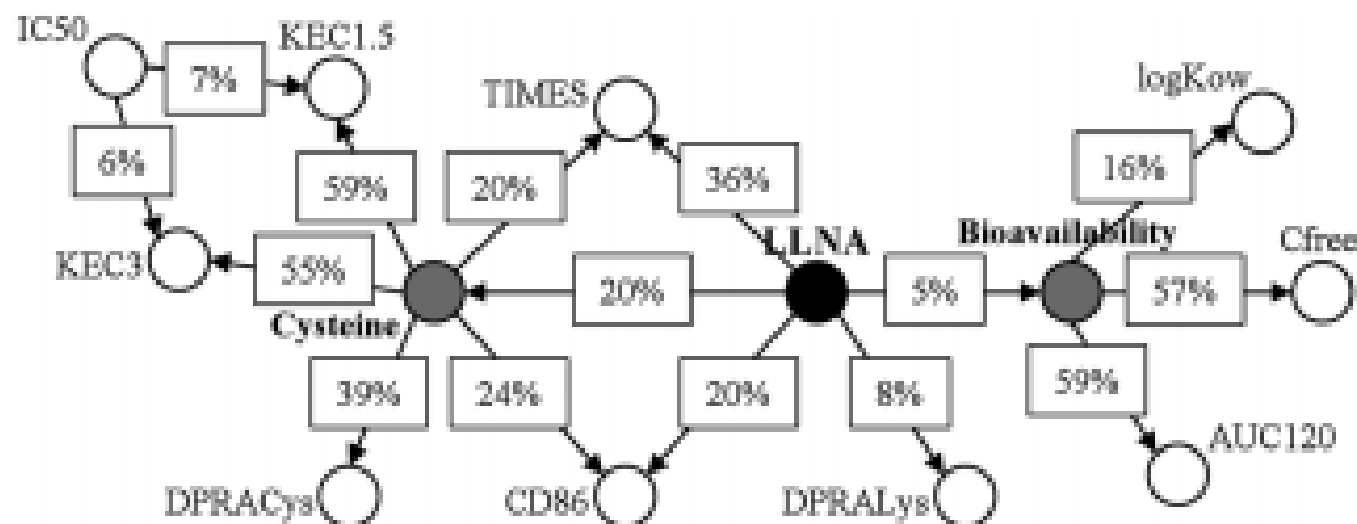




IATA OASIS Pipeline for SS



ITS-2 Integrated in AOP information using a Bayesian network



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