In Silico Models in the OSIRIS Web-Tool: Skin Sensitisation

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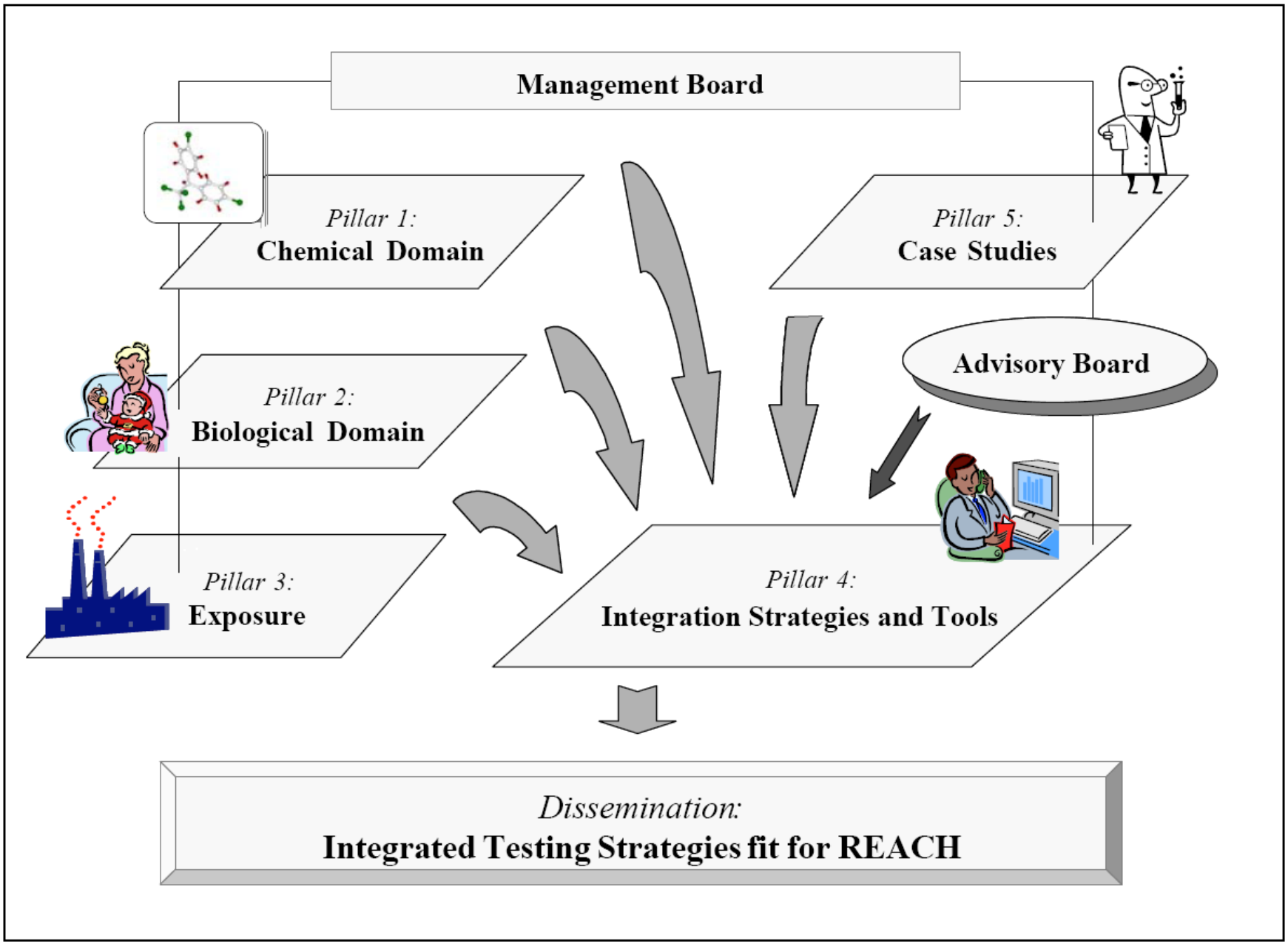
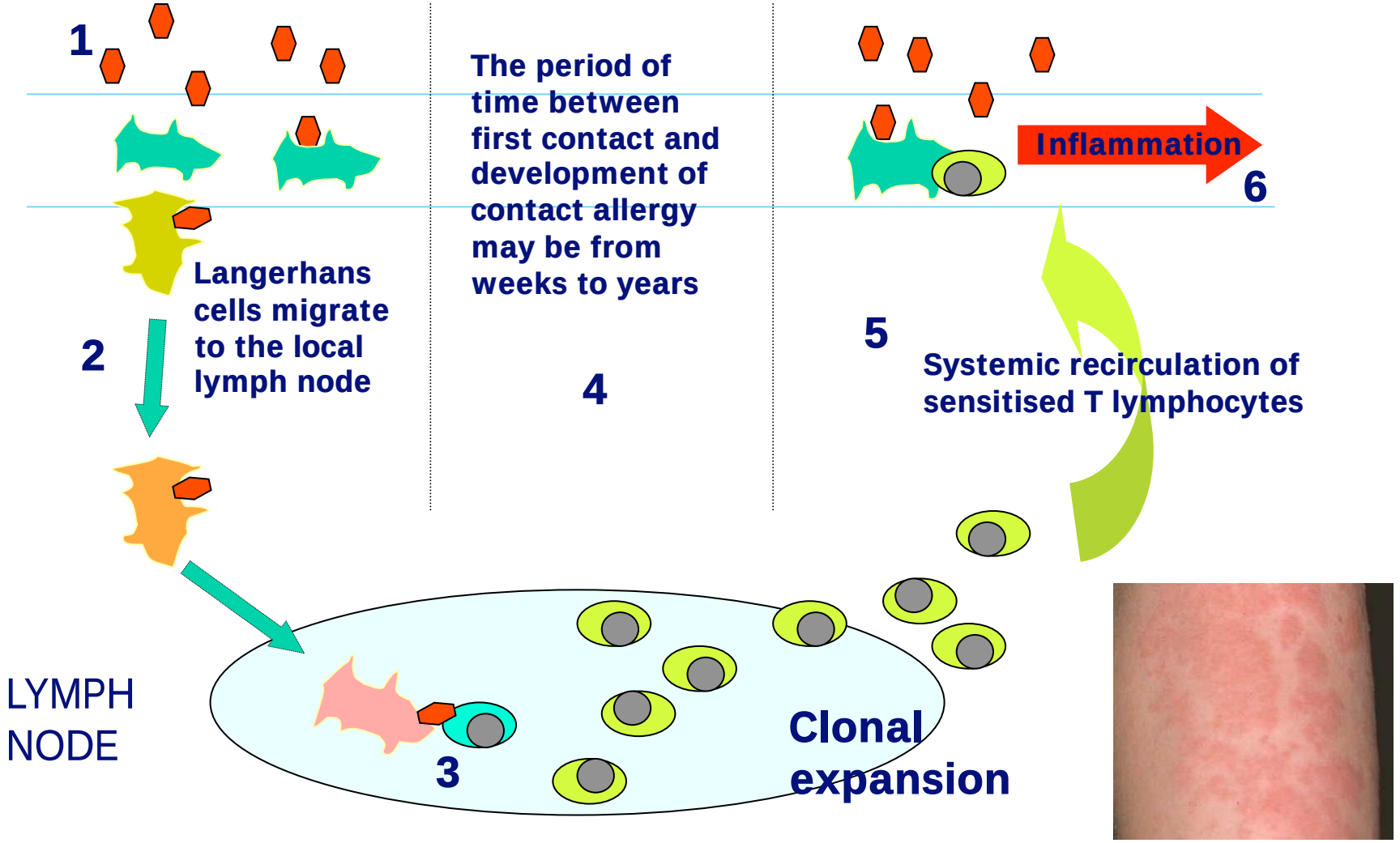

Management Board
Pillar 1:
Chemical Domain
Pillar 5:
Case Studies
Advisory Board
Pillar 2:
Biological Domain
Pillar 3:
Exposure
Pillar 4:
Integration Strategies and Tools
Dissemination:
Integrated Testing Strategies fit for REACH

Skin Sensitisation: Current Knowledge



In Silico Approaches for Predicting Skin Sensitisation

- SMARTS Strings
- DEREK
- TIMES
- TOPKAT
- M-CASE

} In the Web-Tool

- CAESAR
- OECD (Q)SAR Application Toolbox

In Silico Approaches for Predicting Skin Sensitisation

- SMARTS Strings – Fragments (organic chemistry)
- DEREK - Structural alerts
- TIMES - Hybrid – QSAR and metabolism
- TOPKAT - QSAR
- M-CASE - QSAR

- CAESAR – QSAR
- OECD (Q)SAR Application Toolbox - Categories

In Silico Approaches for Predicting Skin Sensitisation

- SMARTS Strings – Mechanistic (chemistry)
- DEREK - Mechanistic (chemistry / biology)
- TIMES - Mechanistic (chemistry / biology)
- TOPKAT – Non-mechanistic
- M-CASE - Non-mechanistic

- CAESAR – Non-mechanistic
- OECD (Q)SAR Toolbox – Mechanistic (chemistry)

In Silico Approaches for Predicting Skin Sensitisation

- SMARTS Strings – Freely available (via e-mail)
- DEREK - Commercial (not for profit)
- TIMES - Commercial
- TOPKAT - Commercial
- M-CASE - Commercial

- CAESAR – Freely available via internet server
- OECD (Q)SAR Toolbox – Freely downloadable

SMARTS Strings Described Reaction Chemistry Mechanistic Applicability Domains

Michael acceptor

S_NAr

S_N2

Schiff base

Acyl transfer

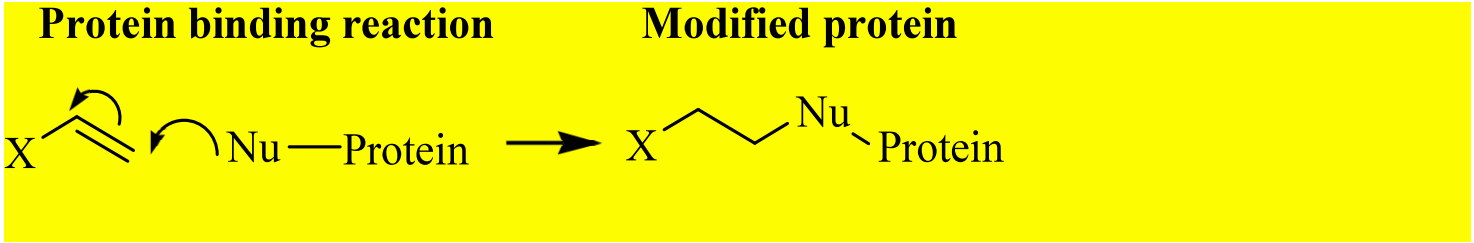
S_N1

Non-reactive, non-proreactive

Enoch SJ *et al* (2008) *Chem. Res. Toxicol. 2*1:513-520

Rules for Mechanistic Domain Assignment

Michael Acceptor Domain



Identification characteristics:

Double or triple bond with substituent X

-CHO, -COR, -CO_2R, -CN, -SO_2R, -NO_2, also

2- or 4- pyridino

p-, o-quinones

Enoch SJ *et al* (2008) *Chem. Res. Toxicol. 2*1:513-520

SMARTS Strings – Identify Chemistry

Mechanism	*SMARTS pattern*
S_NAr	c1([F, Cl, Br, I, $(N(=O)~O)])c([F, Cl, Br, I, $(N(=O)~O), $(C#N), $(C=O), $(C(F)(F)F), $(S=O)])cc[F, Cl, Br, I, $(N(=O)~O), $(C#N), $(C=O), ($(C(F)(F)F), $(S=O)])cc1 c1([F, Cl, Br, I, $(N(=O)~O)])c([F, Cl, Br, I, $(N(=O)~O), $(C#N), $(C=O), ($(C(F)(F)F), $(S=O)])ccccc1([F, Cl, Br, I, $(N(=O)~O), $(C#N), $(C=O), $(C(F)(F)F), $(S=O)]) c1([F, Cl, Br, I, $(N(=O)~O)])ncc([F, Cl, Br, I, $(N(=O)~O), $(C#N), $(C=O), $(C(F)(F)F), $(S=O)])cc1 c1([F, Cl, Br, I, $(N(=O)~O)])nccccc1([F, Cl, Br, I, $(N(=O)~O), $(C#N), $(C=O), $(C(F)(F)F), $(S=O)]) c1([F, Cl, Br, I, $(N(=O)~O)])ncccn1 c1([F, Cl, Br, I, $(N(=O)~O)])ncncc1 c1([F, Cl, Br, I, $(N(=O)~O)])ncc([F, Cl, Br, I, $(N(=O)~O), $(C#N), $(C=O), $(C(F)(F)F), $(S=O)])nc1 c1nc([F, Cl, Br, I, $(N(=O)~O)])ncn1

A simple tool is freely available to use the SMARTS strings

Enoch SJ *et al* (2008) *SAR QSAR Environ. Res.* 19:555-578

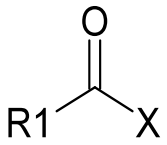
Derek for Windows / Derek Nexus

- Knowledge based expert system
- www.lhasalimited.org
- Searches molecule for structural alerts (fragments) of a molecule associated with skin sensitisation
- Fragments developed by expert toxicologists
- If no fragments are found, then DfW states "*nothing to report*" – not necessarily a negative prediction

Derek for Windows / Derek Nexus

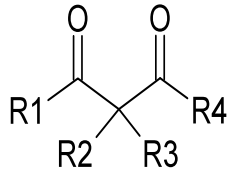
- Derek (ver 11) contains 65 alerts for skin sensitsation

Alert 401 - Carboxylic acid halide



R1 = Any
X = F, Cl, Br

Alert 420 - 1,3-Diketone



R1, R4 = C
R2, R3 = Any

- It does not have a “skin sensitisation database”
  - Alerts are supported by data
  - Some approaches to applicability domain exist

TIMES

- A hybrid system
  - QSARs for reactive chemistry
  - Prediction of skin metabolism
- www. oasis-lmc.org
- Identifies reactive chemistry associated with protein binding (47 alerting groups)
- Skin metabolism simulator predicts plausible metabolites (from 236 transformations)
- Approximately 800 compounds (LLNA, GPMT, BfR)
- Assessment of applicability domain

TOPKAT

- A (statistical) QSAR system based on QSARs developed from discriminant analysis of 2-D structural descriptors
  - Molecular connectivities, e-state indices
- Approximately 300 compounds (GPMT)
- Predicts non/ weak / moderate / strong sensitisers
- Optimum prediction space (OPS) for applicability domain
- http://accelrys.com/products/discovery-studio/predictive-toxicology.html

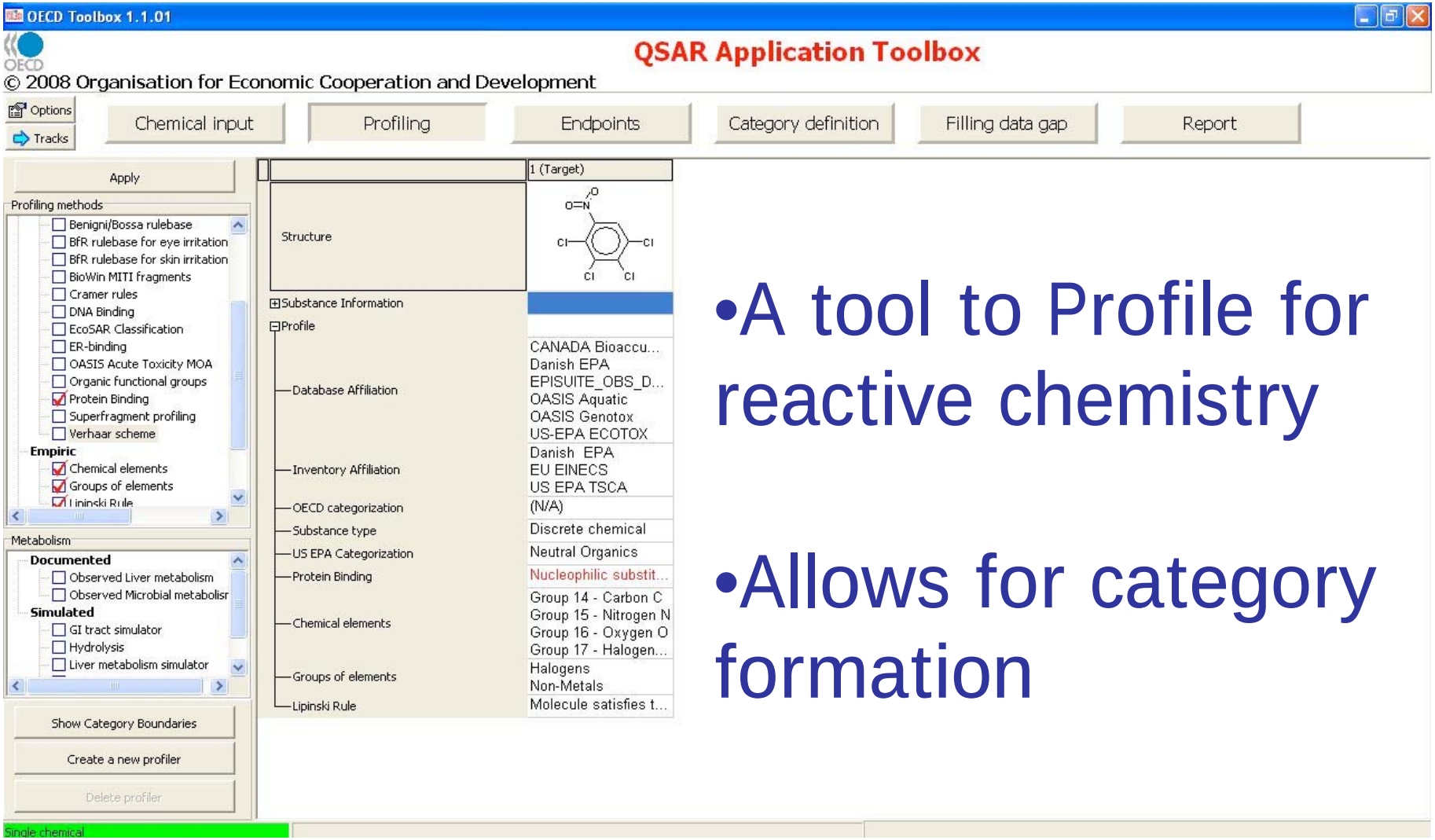
M-CASE

- A (statistical) QSAR system based on molecular fragments
- Molecules are divided up into fragments from two to *n* atoms
- Fragments related statistically to any biological activity
  - Fragments are related to sensitisation (biophores) or non-sensitisation (biophobes)
- Fragments could be used as structural alerts or more commonly in a regression approach

M-CASE

- It is possible to put a mechanistic interpretation on fragments
- Over 1000 compounds (Human data)
- Identifies fragments in a molecule not found in the training set i.e. a form of applicability domain
- www.multicase.com

OECD Toolbox – Not in Webtool



- A tool to Profile for reactive chemistry
- Allows for category formation

www.oecd.org

CAESAR Model – Not in Webtool

- QSAR approach based on nearest neighbours as defined by 2-D descriptors
- 211 compounds (LLNA)
- www.caesar-project.eu

Conclusions

- Webtool contain five QSAR approaches
- QSAR approaches will overlap, but differ significantly
  - Mechanistic vs non-mechanistic
  - Modelling approaches
  - QSAR vs protein binding
  - Number of compounds
  - LLNA vs GPMT vs Human
- This is not an exercise to find the “best” QSAR
- Different approaches may provide complementary information
- We need a method to integrate the predictions ……

Acknowledgements

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