Computational Tools and Guidance developed by the JRC

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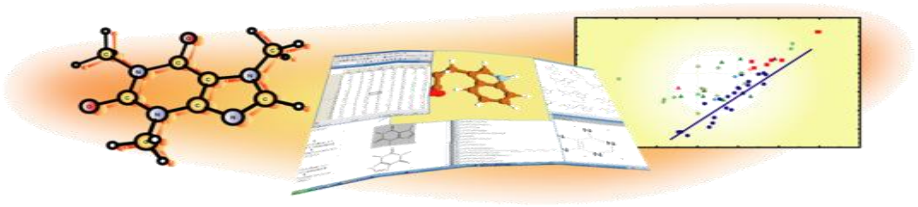
http://ecb.jrc.ec.europa.eu/qsar/



Overview

1. Computational toxicology at the JRC
2. Role of computational methods in risk assessment
3. Filling data gaps: read-across and (Q)SARs
4. Documenting the results of read-across and (Q)SARs
5. Non-testing strategy – a stepwise approach
6. Conclusions

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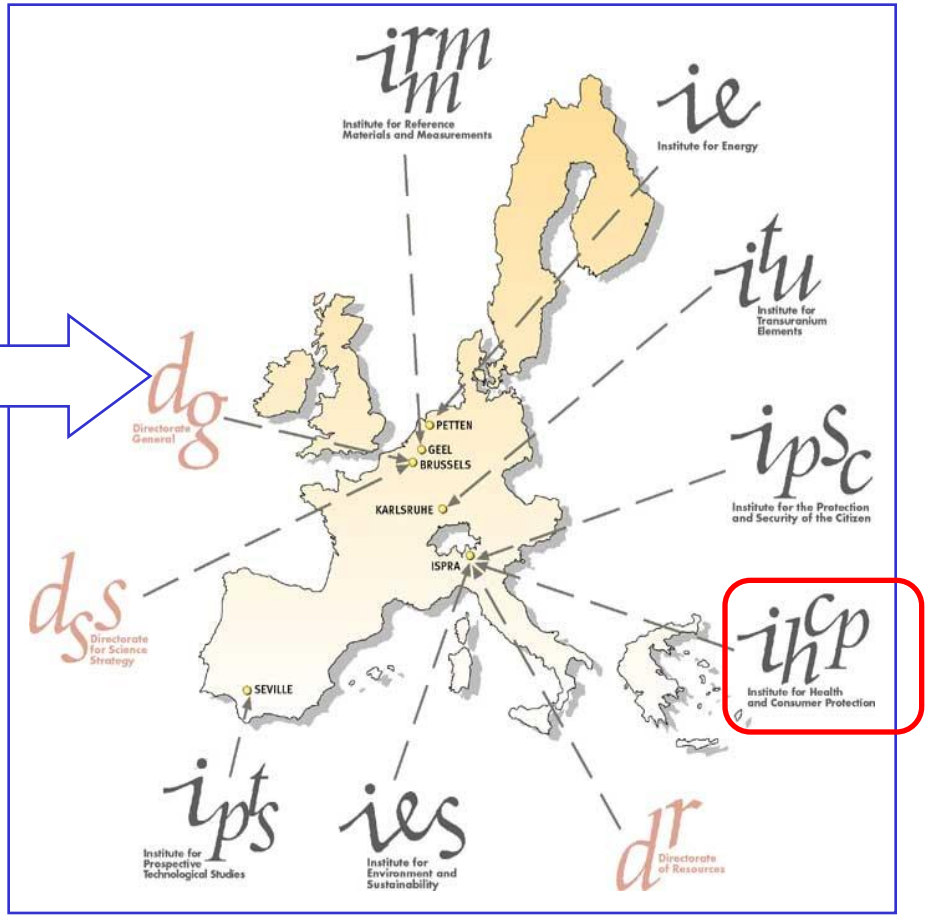

Molecular Biology
In Vitro Methods
Nanobiosciences
Chemical Assessment & Testing
Systems Toxicology

Genetically Modified Organisms
Alternative Methods & ECVAM
Nanotechnology
Health and Environment
Consumer Products & Nutrition

Policy Areas

Computational Toxicology at the JRC

Overall aim: to promote the development, assessment, acceptance and implementation of computer-based methods potentially suitable for the regulatory assessment of chemicals

Applications: REACH, Water Framework Directive, Cosmetics Directive, Biocides Directive, Plant Protection Products Directive

Main approaches: SAR, QSAR, molecular modelling, ranking

Computational methods provide information for use in hazard and risk assessment → "non-testing" or alternative methods

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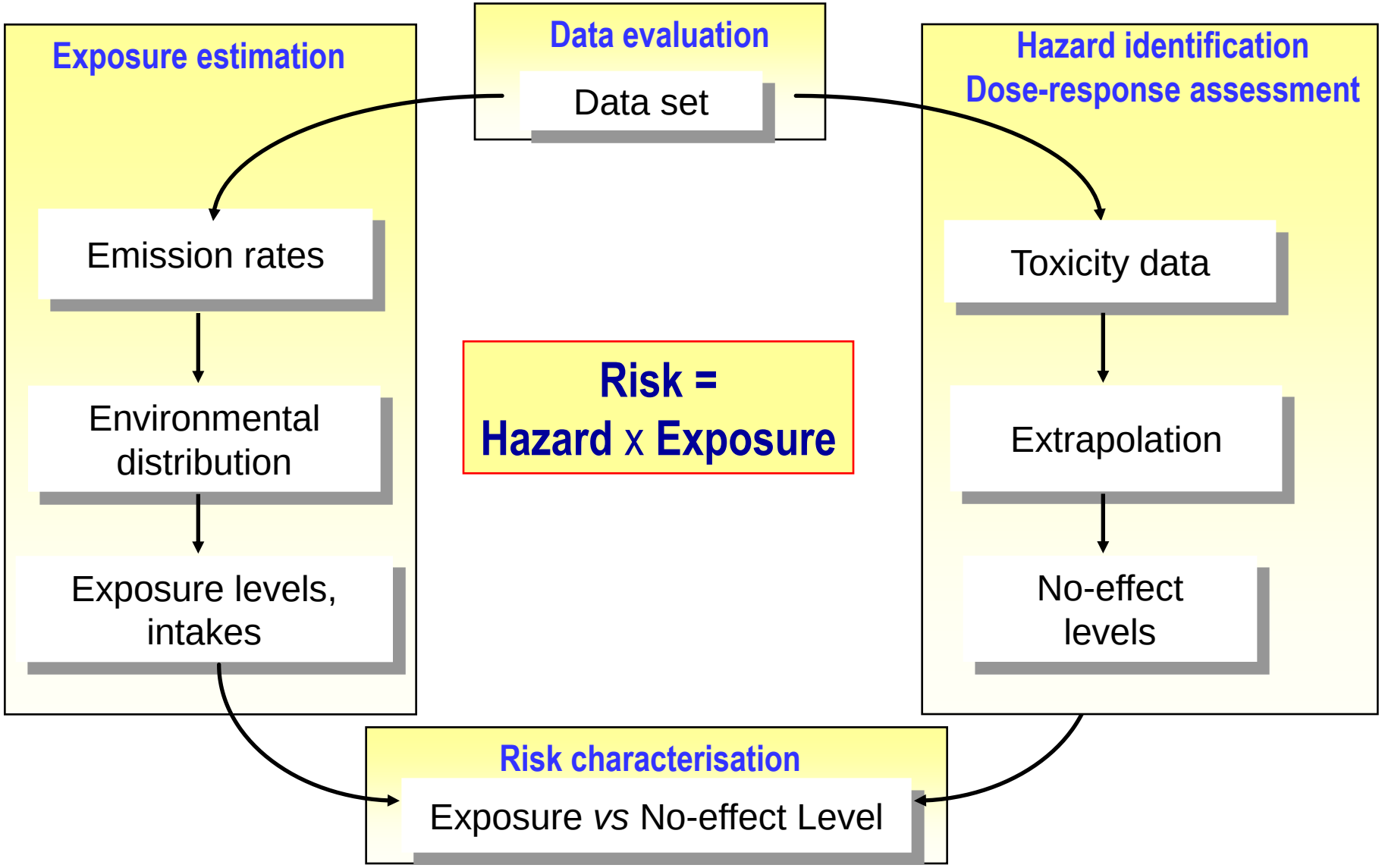
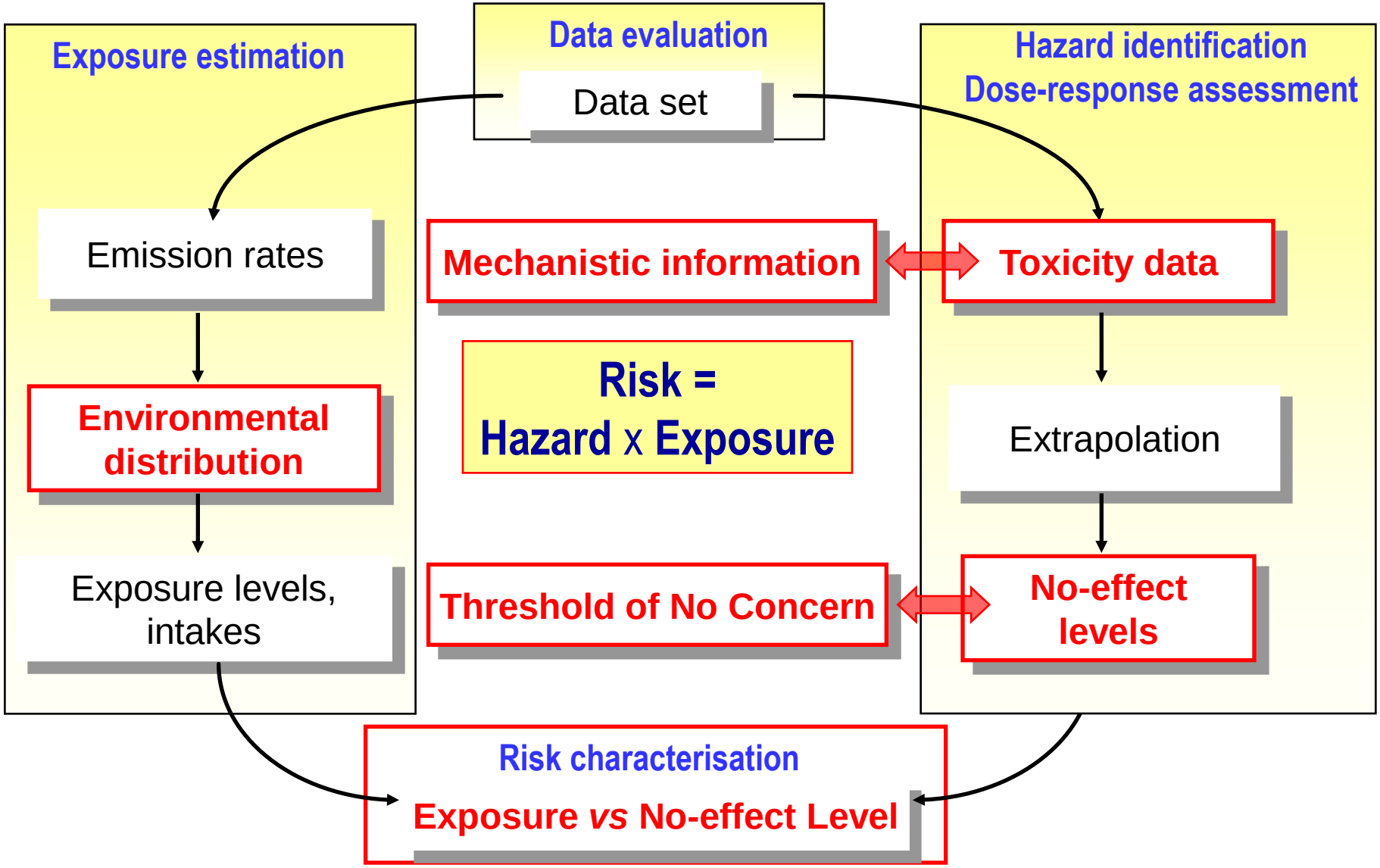
Risk assessment process



Role of computational methods



Information requirements under REACH

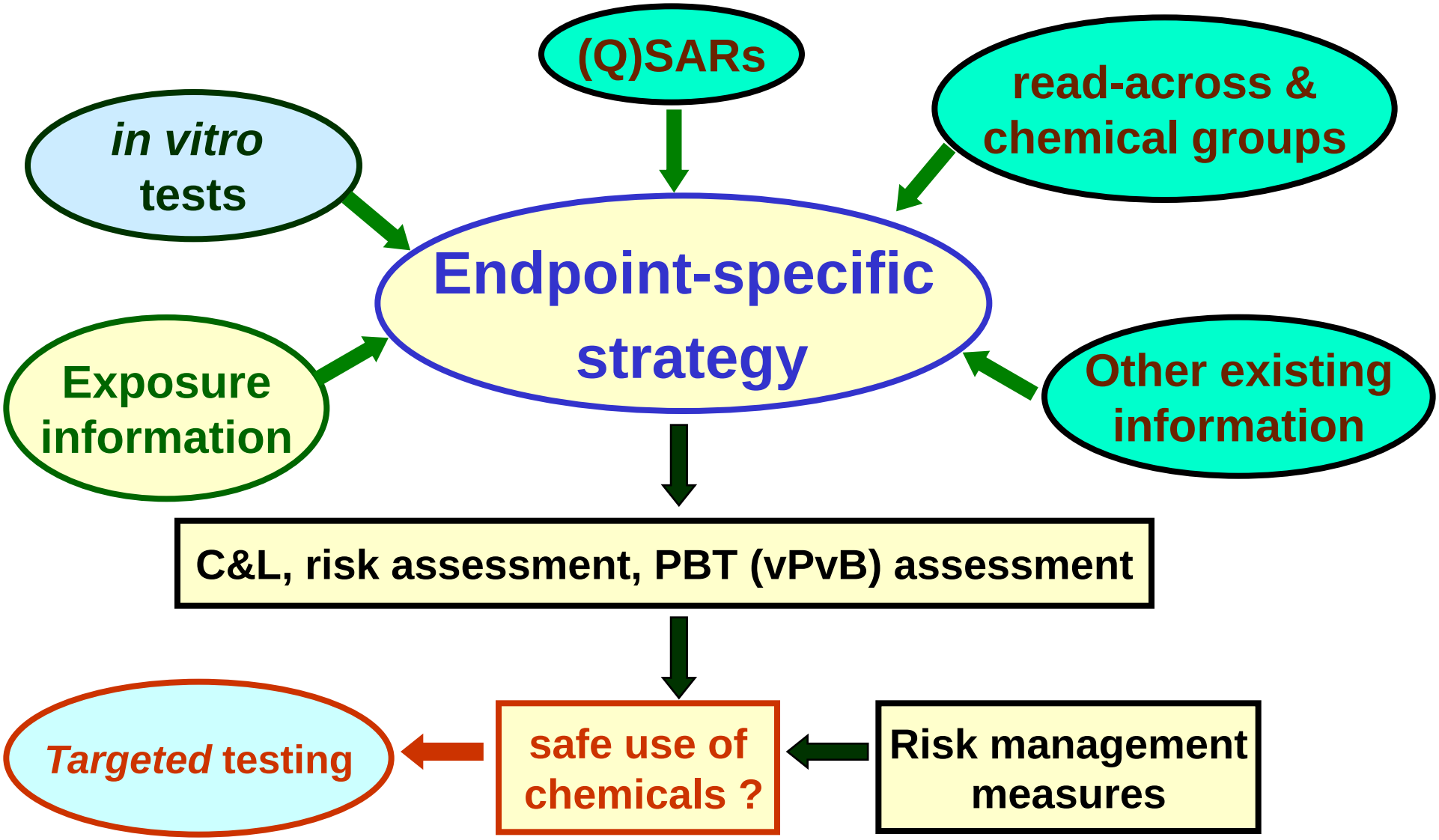
Information requirements are largely tonnage dependent, however …

"Information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met" (Article 13)

(Animal) testing can be reduced or avoided by "replacing traditional test data with predictions or equivalent data"

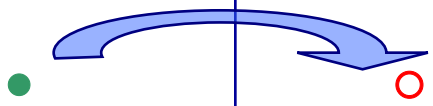
… however a number of conditions apply

Integrated Testing Strategies (ITS)

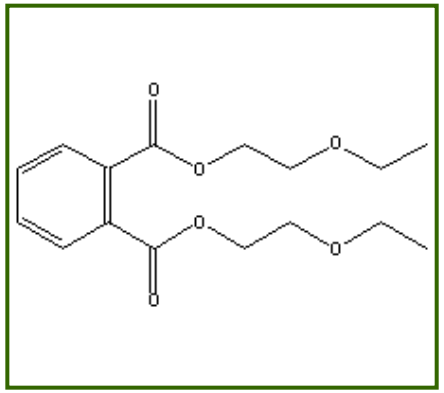


Filling data gaps by read-across

Known information on the property of a substance (source chemical) is used to make a prediction of the same property for another substance (target chemical) that is considered "similar"

	Source chemical	Target chemical
Property		

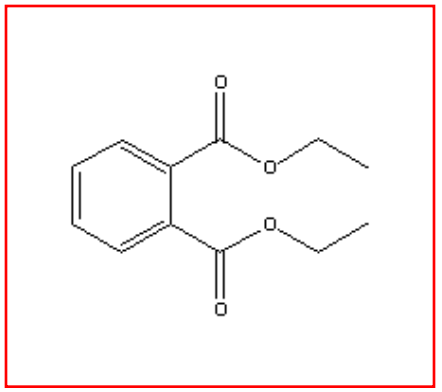
1,2-Benzenedicarboxylic acid, bis(2-ethoxyethyl) ester



Known to be harmful: 1 < log LC50 < 2

Acute fish toxicity?

diethyl phthalate

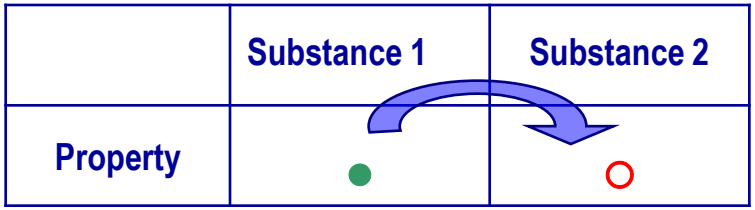


Predicted to be harmful

Read-across in the analogue approach

The analogue approach refers to the grouping of chemicals and application of read-across for a single endpoint based on a relatively small number of analogues

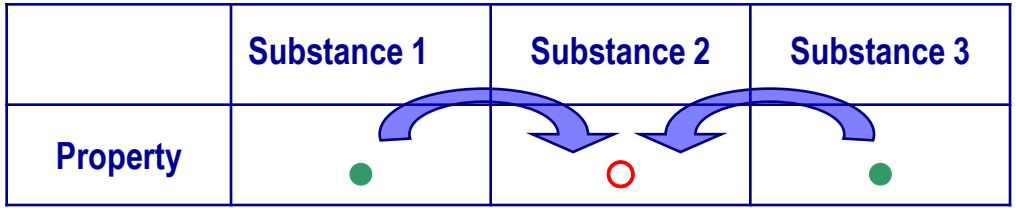
one-to-one



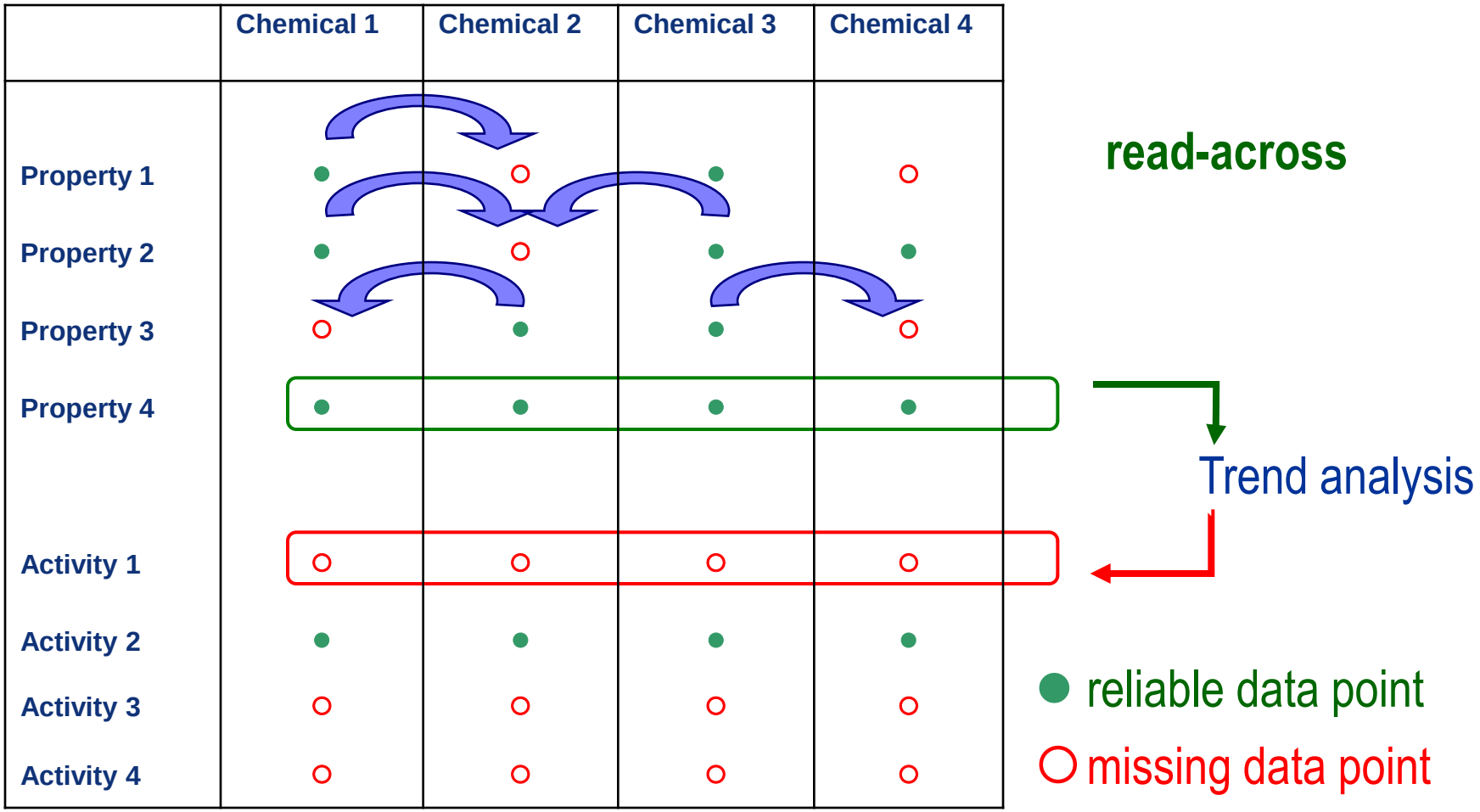
● reliable data point

○ missing data point

many-to-one



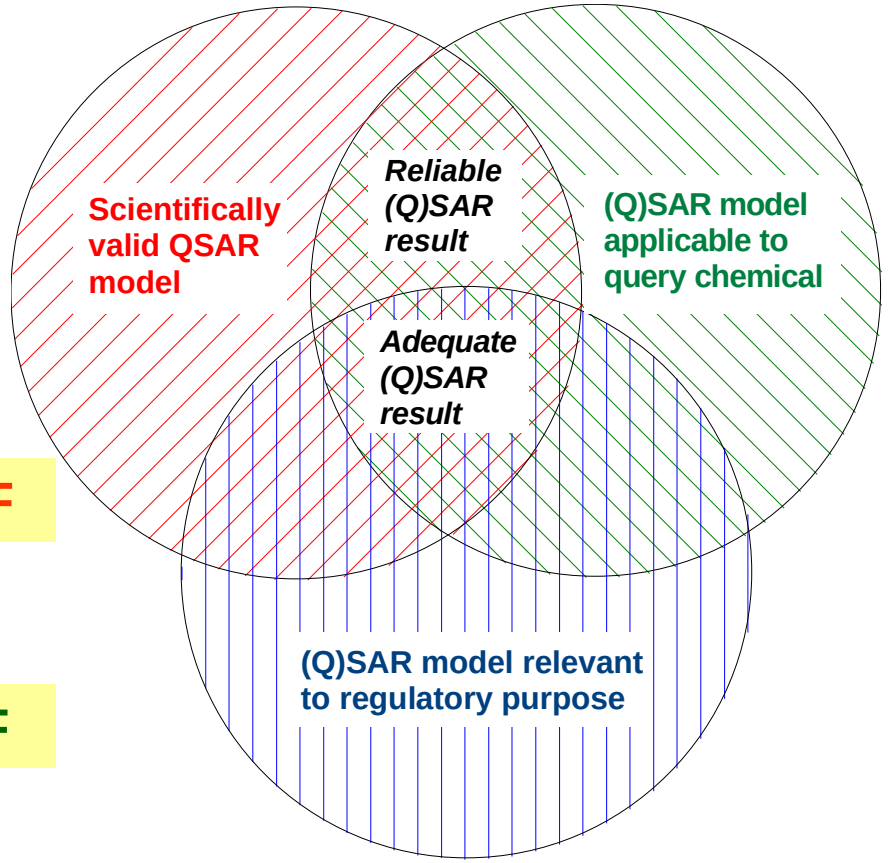
Read-across in the category approach



The category approach refers to a wider approach, based on more analogues, multiple endpoints, and in which trends are also apparent

Adequacy of (Q)SAR prediction

In order for a (Q)SAR result to be adequate for a given regulatory purpose, the following conditions must be fulfilled:



- the estimate should be generated by a valid (reliable) model → **QMRF**
- the model should be applicable to the chemical of interest with the necessary level of reliability → **QPRF**
- the model endpoint should be relevant for the regulatory purpose → **QPRF**

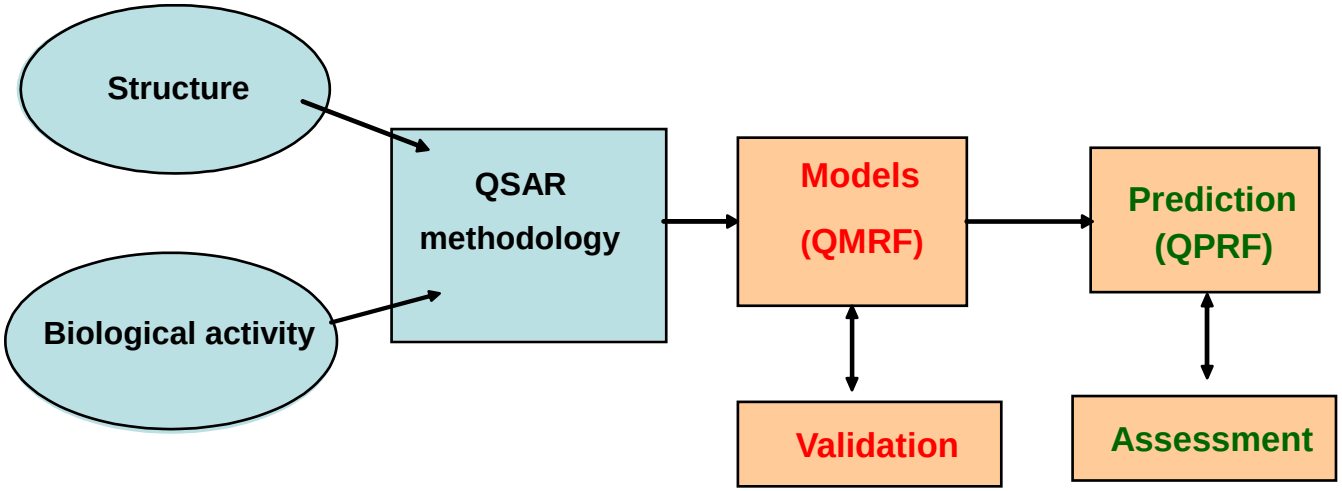
http://ecb.jrc.ec.europa.eu/qsar/qsar-tools/

Standardised (Q)SAR Reporting Formats

The need for "adequate and reliable" documentation is met by using standardised reporting formats:

A (Q)SAR Model Reporting Format (QMRF) is a robust summary of a (Q)SAR model, which reports key information on the model according to the OECD validation principles

A (Q)SAR Prediction Reporting Format (QPRF) is a description and assessment of the prediction made by given model for a given chemical



(Q)SAR Reporting Formats: QMRF

QMRF captures information on fulfilment of OECD validation principles, but no judgement or "validity statement" is included

A (Q)SAR should be associated with the following information:

1. a defined endpoint
2. an unambiguous algorithm
3. a defined applicability domain
4. appropriate measures of goodness-of-fit, robustness and predictivity
5. a mechanistic interpretation, if possible

- **Principles adopted by 37th Joint Meeting of Chemicals Committee and Working Party on Chemicals, Pesticides & Biotechnology; 17-19 Nov 2004**
- **ECB preliminary Guidance Document published in Nov 2005**
- **OECD Guidance Document published in Feb 2007**
- **OECD Guidance summarised in REACH guidance (IR and CSA)**

(Q)SAR Reporting Formats: QPRF

QPRF captures information on the substance and its prediction, and is intended to facilitate considerations of the adequacy of a prediction

1. Substance information
2. General (administrative) information on QPRF
3. Information on prediction (endpoint, algorithm, applicability domain, uncertainty, mechanism)
4. Adequacy (optional, legislation-specific, and includes judgement and indicates whether additional information is needed for WoE assessment)

- Assessment of adequacy depends on reliability and relevance of prediction, but also on the availability of other information, and the consequence of being wrong
- Not just a scientific consideration, but also a policy decision

Outline of a non-testing strategy

1. Existing information
2. Preliminary assessment of reactivity & fate
3. Classification schemes & structural alerts
4. Preliminary assessment of reactivity, fate & toxicity
5. Chemical grouping & read-across
6. QSARs

Working Matrix

	A	B	C
Chemical			
Metabolite 1			
Metabolite 2			

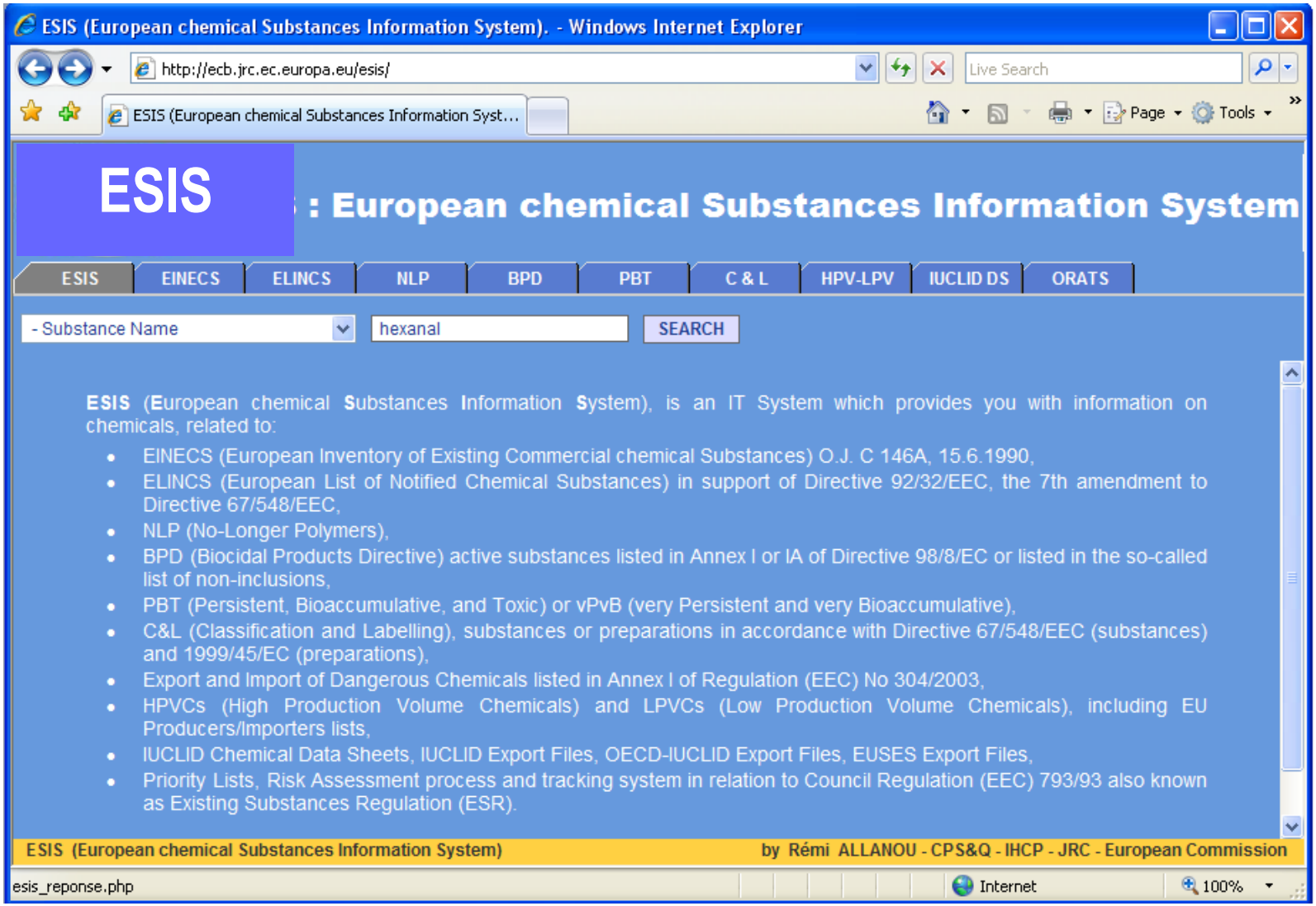
Assess adequacy

Conclusion or targeted testing

Step 1: Information collection

- Chemical composition (components, purity/impurity profile)
- Structure generation and verification
- Key chemical features (functional groups, protonation states, isomers)
- Experimental data: physicochemical properties, (eco)toxicity, fate
  - Freely-accessible web resources (ESIS, ChemSpider, PubChem, AMBIT2)
  - Databases in freely-available software tools (OECD Toolbox)
  - Commercial databases (Vitic, …)
- Estimated data: pre-generated QSAR or read-across estimates
  - Freely-accessible web resources (ChemSpider, Danish QSAR database)
  - Chemical category databases (OECD Toolbox)

European chemical Substances Information System



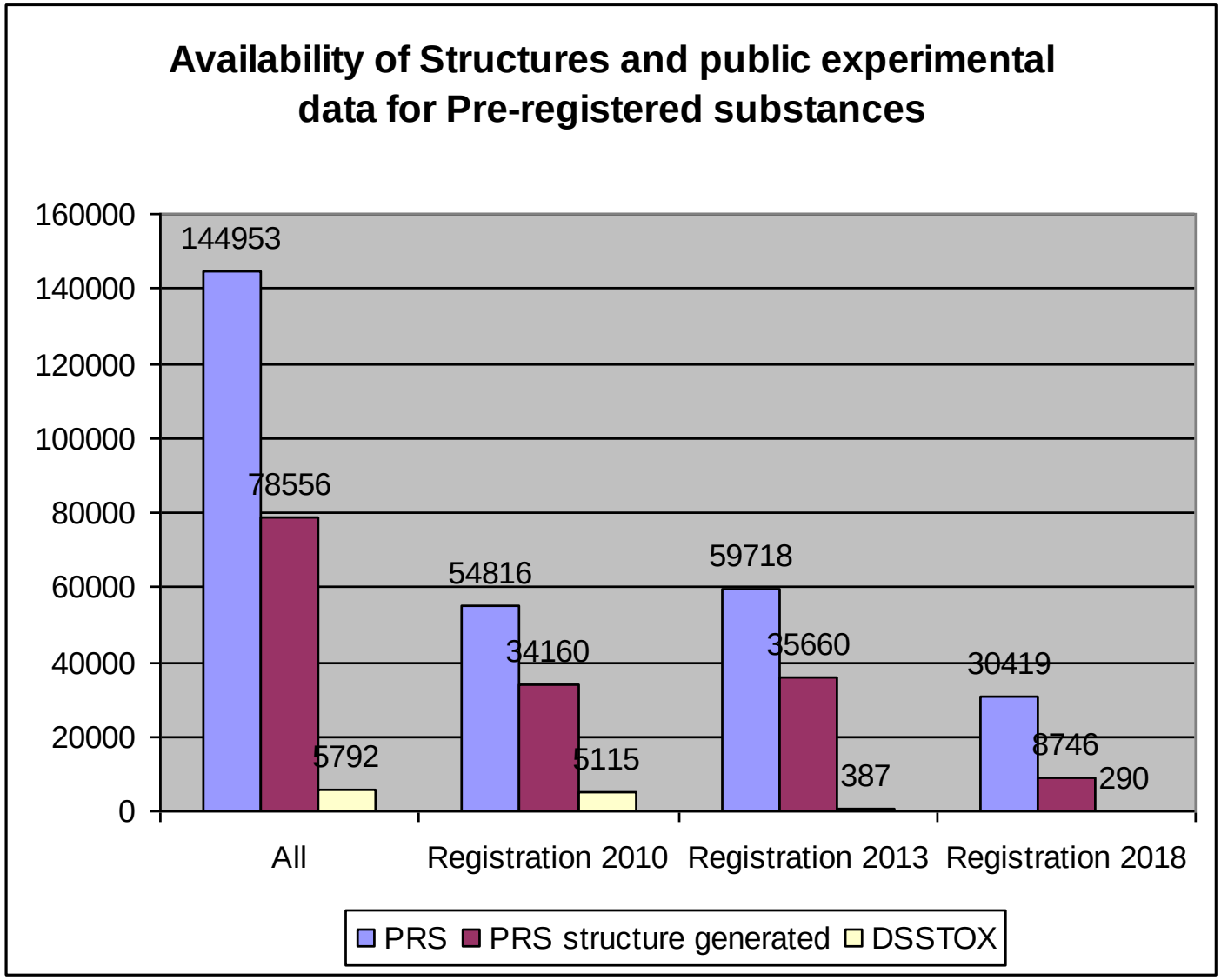
http://ecb.jrc.ec.europa.eu/esis/

PRS – Inventory Production

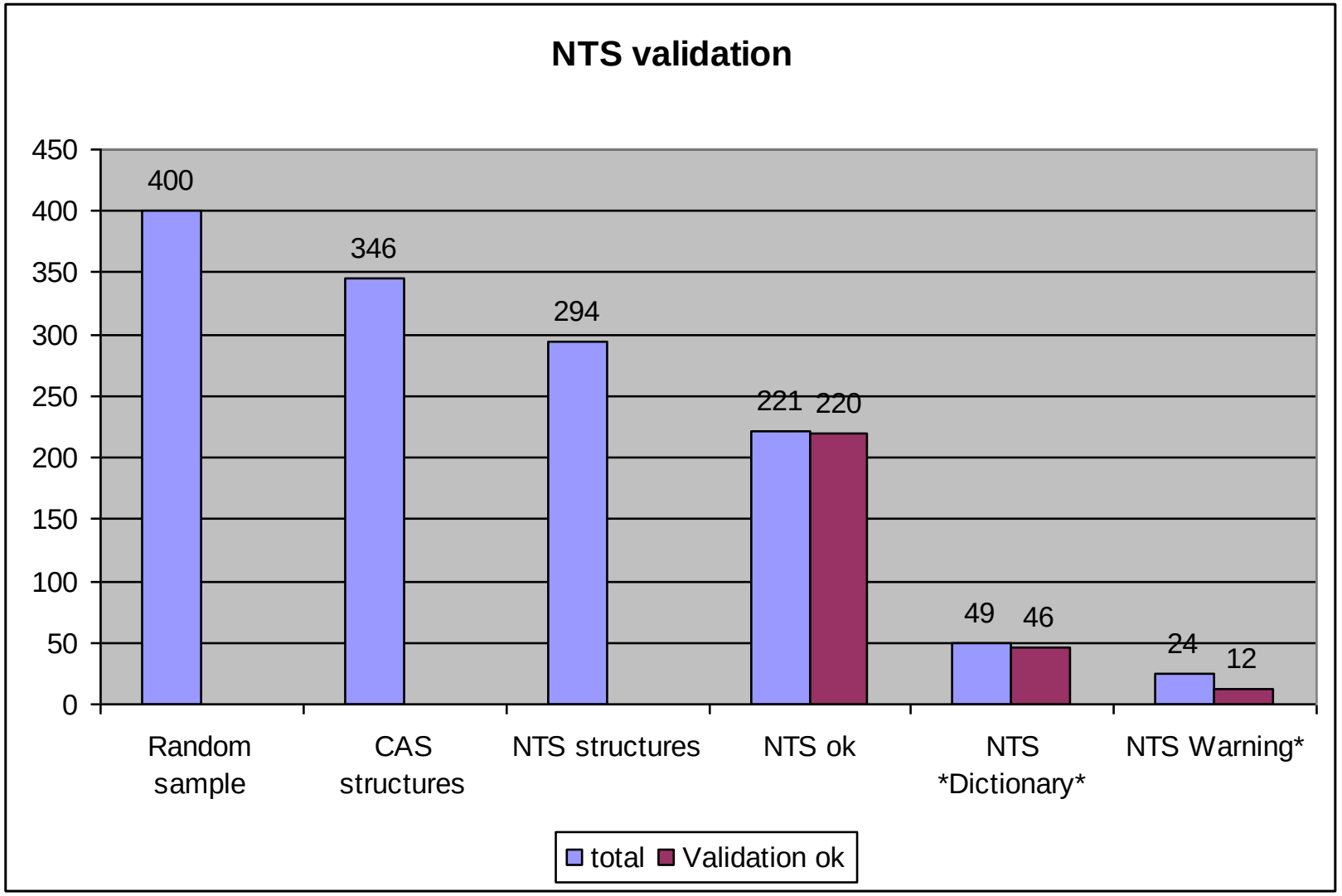
1. Structure Generation from Name – ACD Labs Name
2. Validation of structures by CAS-Registry random sample
3. Manually refinements, data mining e.g. DSSTOX
4. Merge, filter, standardisation of structure representation for organic substances
5. Descriptors: substance identification and estimated physical-chemical data (ACDLabs, Pipeline Pilot, ADMET Predictor)

http://ecb.jrc.ec.europa.eu/qsar/information-sources/ec_inventory/

PRS-Inventory: Availability of structures

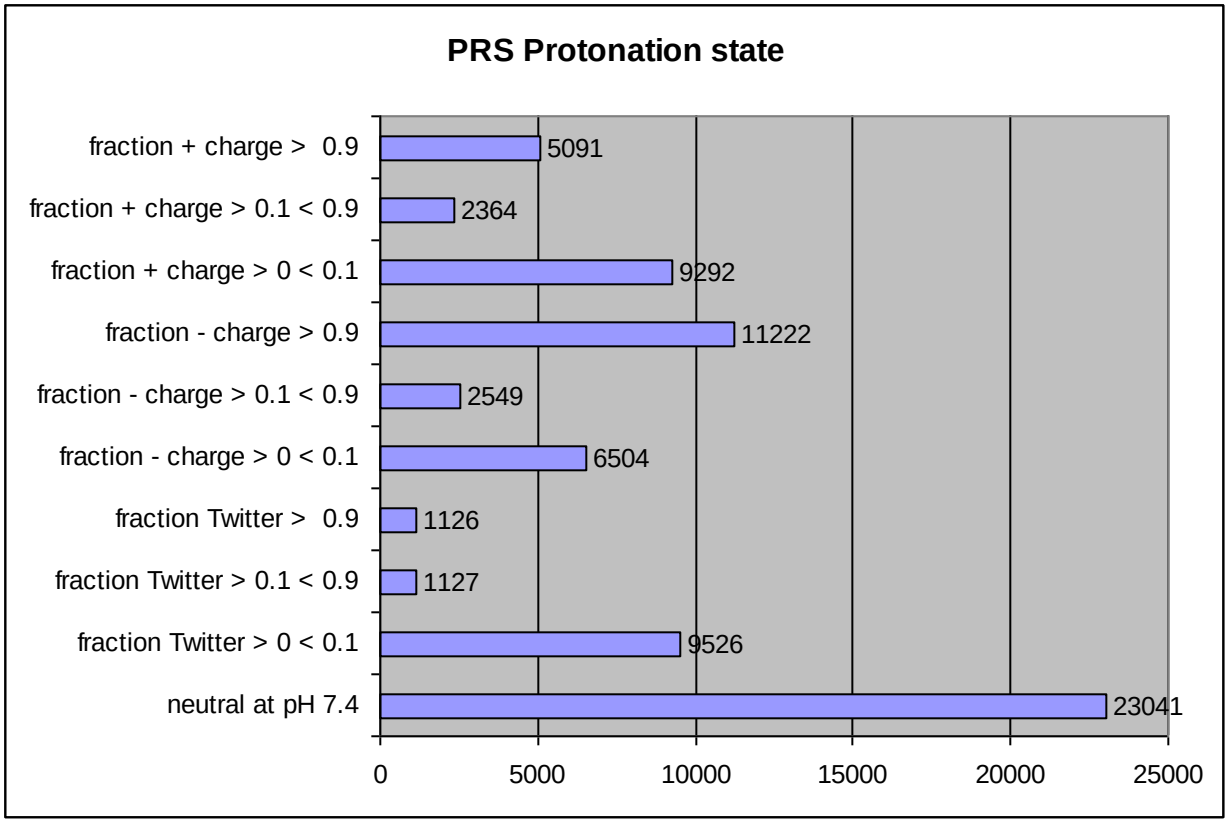


Validation of generated structures



PRS-Inventory: Phys-chem descriptors

logP, pKa, logD, Water Solubility by ADMET Predictor, see benchmarking: Calculation of molecular lipophilicity: State-of-the-art and comparison of logP methods on more than 96,000 compounds, Mannhold, R.; Poda, G.I.; Ostermann, C.; Tetko, I.V. *Journal of Pharmaceutical Sciences* **2009**, 98(3), 861-893.



ENDDA – Endocrine Active Chemicals Database

European Commission
Joint Research Centre
Institute for Health and Consumer Protection

European Commission JRC IHCP CPSQ ENDDA New Search

Home Search External Resources Qsar Models

Search

name:

cas:

smiles:

Search by Structure

File Edit View Insert Tools Help

H C N O F React Select Erase Paste Undo Redo Zoom

- + P S Cl More Br I

Type of Search: Substructure

Chemical Group

-all-
(organo) metals
Alkylbenzenes and styrenes
Alkylphenols and derivatives
Benzamidazoles
Biphenyls
Bisphenols
Carbamates
Chlorinated cyclodienes and camphenes
Chlorinated paraffins (CPs)
Chlorophenols and benzenes
Chlorophenoxy compounds
DDT, derivatives and metabolites
Dicarboximides
Diesel exhaust particle (DEP)
Dinitroanilid
Dioxins
Diphenylpro
Dithiocarba
Furans
Hexachloro
Hydroxyben
Linuron, diur
Methoxychlo
Musk Fragra

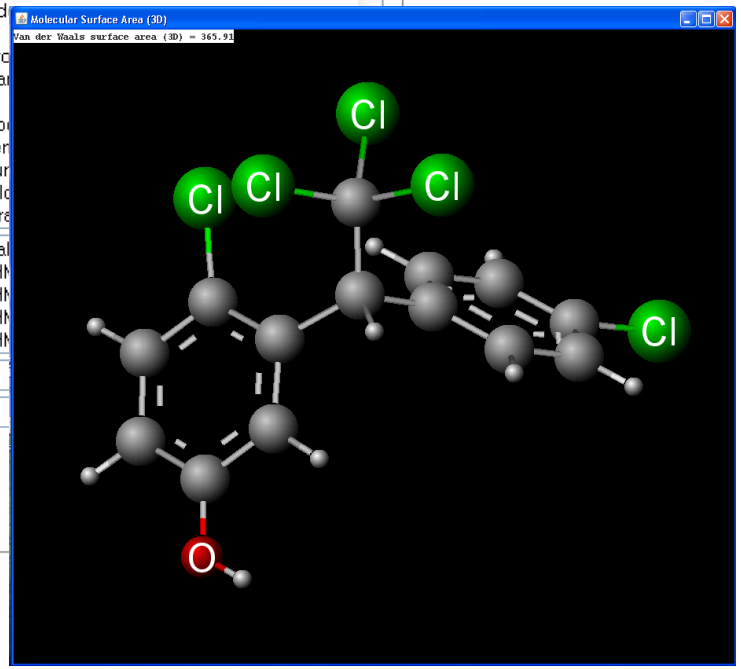
Moa

-all-
(+)e
(+)th
+e
+pi

mol. w. between

logP between

Send Reset

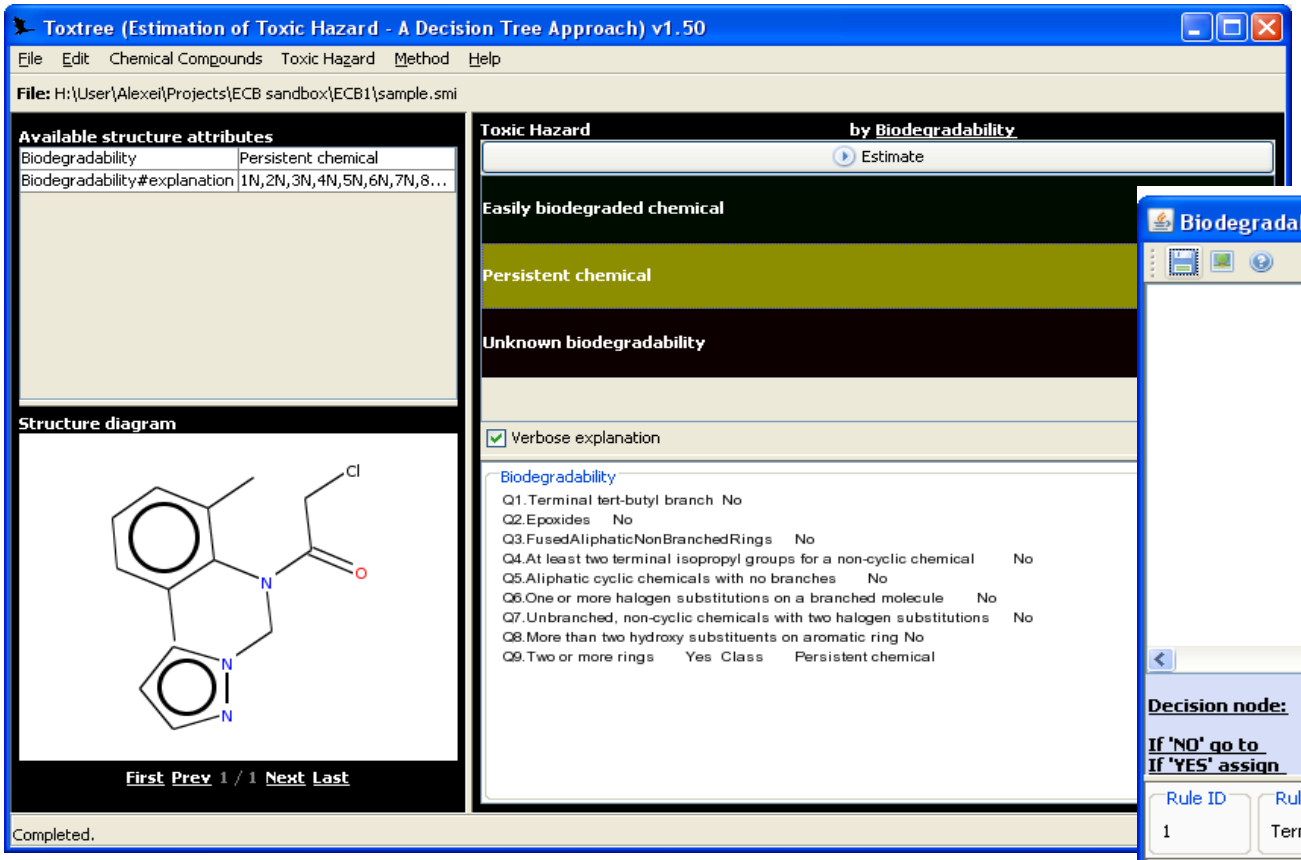


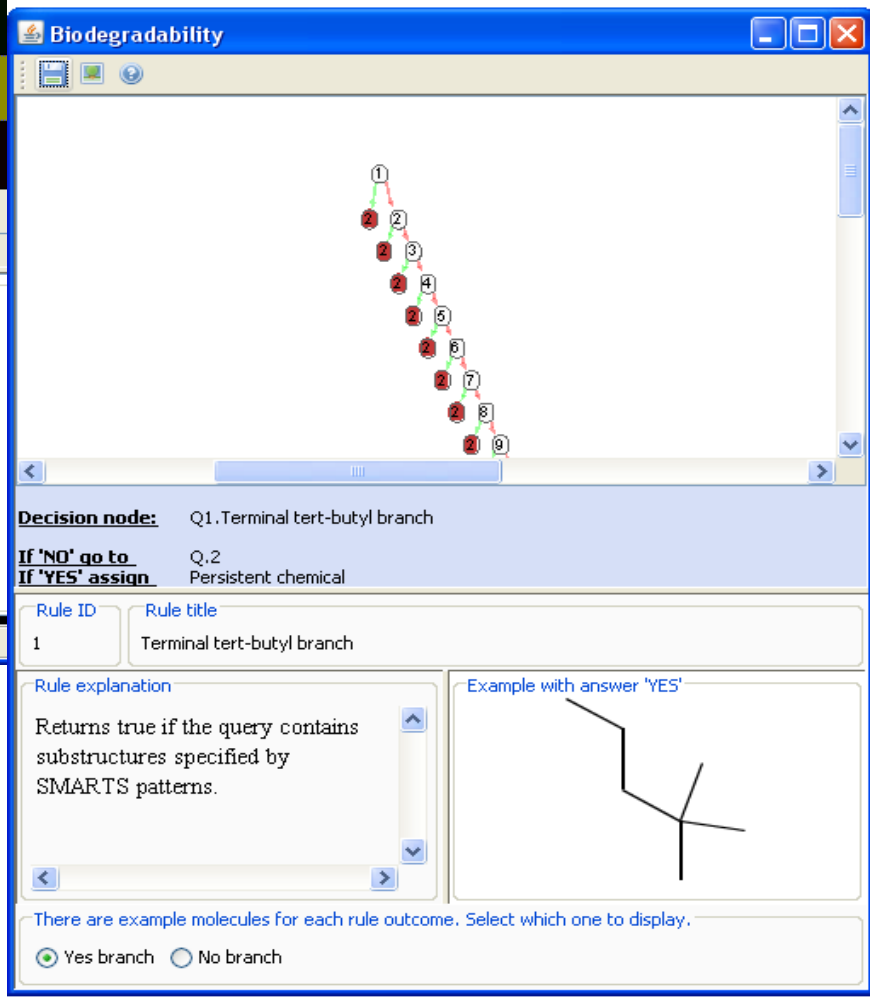
web-accessible database under development

Step 2: Preliminary assessment of reactivity & fate

- Prediction of abiotic / biotic reactivity to identify reactive potential and possible transformation products / metabolites
- Freely-available software
  - CRAFT (Chemical Reactivity & Fate Tool)
  - START (Structural Alerts in Toxtree)
  - OECD Toolbox
- Commercial software and databases
  - CATABOL, TIMES, Meteor, Mexalert, MetabolExpert …
  - MetaPath, SciFinder, MDL Reaction Database …

START - STructural Alerts for Reactivity in Toxtree

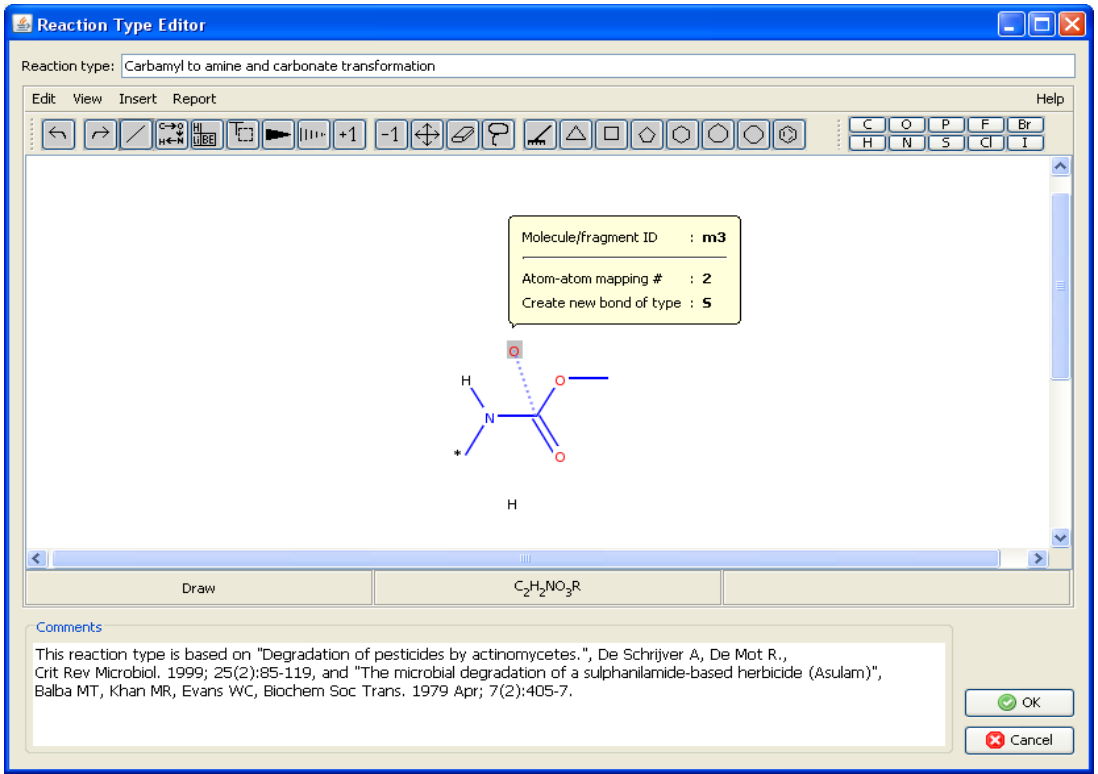


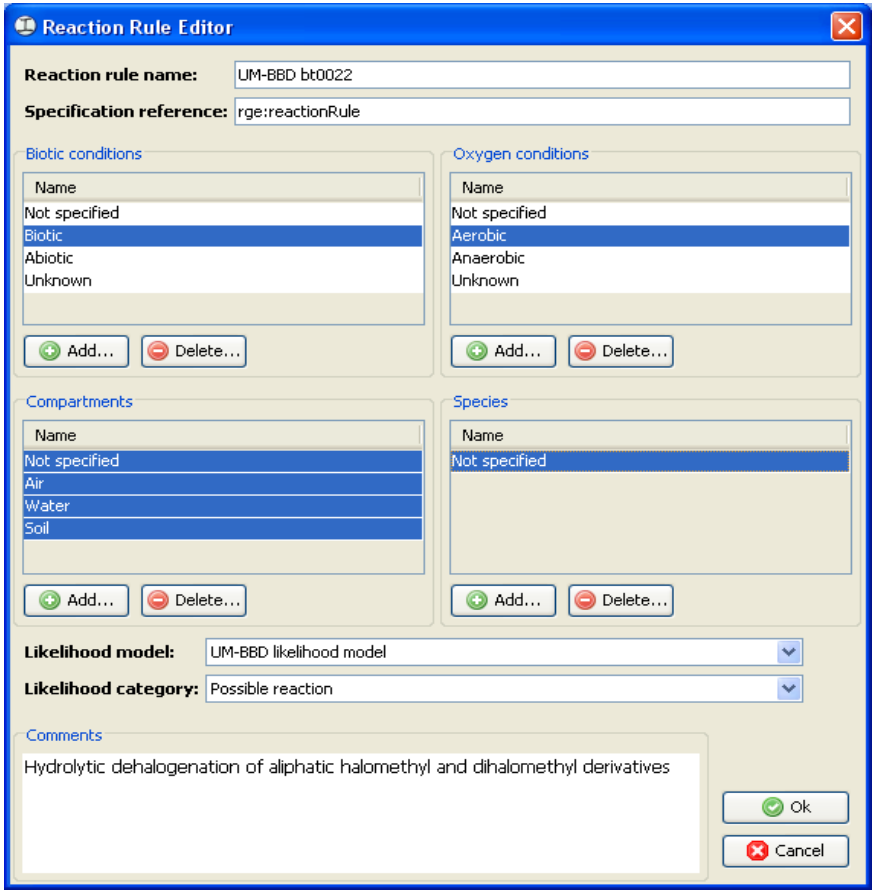


- Collaboration with Molecular Networks (Germany)
- Toxtree plug-in
- Estimates biodegradation potential

CRAFT - Chemical Reactivity And Fate Tool

- Collaboration with Molecular Networks (Germany)
- Generates & visualises reactions, ranks transformation products
- Initial emphasis on abiotic processes & microbial biodegradation
- Data model based on AMBIT technology
- User can modify knowledge base and rulebase





Steps 3 & 6: SARs, QSARs and expert systems

- Models and rulebases for mode-of-action classification, hazard identification, hazard classification and potency prediction
- Freely-available software
  - Episuite, Toxtree, AMBIT2, OECD Toolbox …
  - OpenTox framework (http://www.opentox.org)
- Commercial software
  - DEREK, MultiCASE, HazardExpert, ToxAlert, ToxBoxes …
  - *Insilico*first consortium (Multicase Inc, Lhasa Ltd, Molecular Networks GmbH, Leadscope Inc)
- QSAR Model Databases (QMDBs)
  - JRC QSAR Model Database
  - OECD Toolbox

Toxicity Estimation Tool: Toxtree

Toxtree is a flexible, user-friendly, open source application, which is able to classify chemicals into modes of action and estimate toxic hazard by applying decision tree approaches

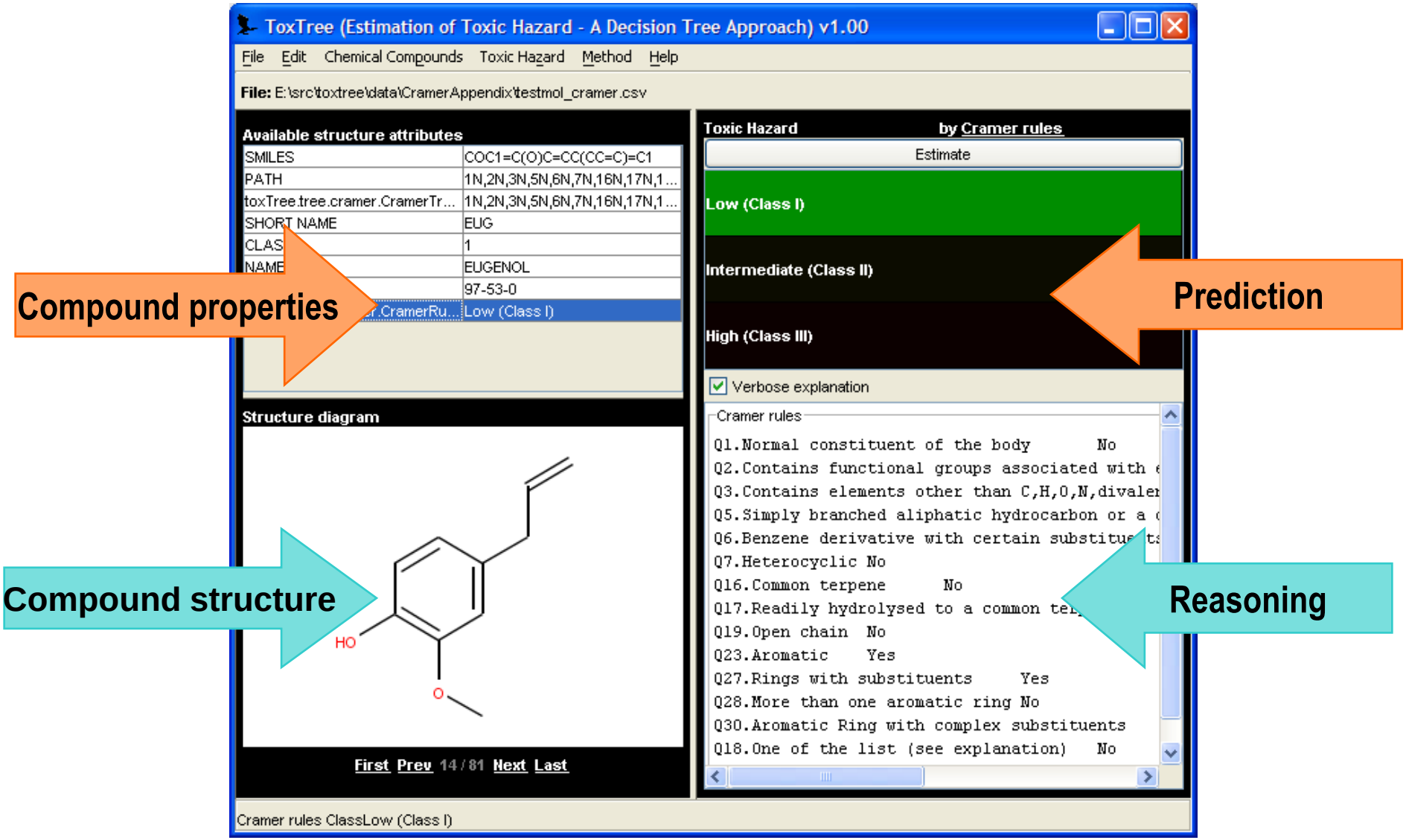
Collaboration with Ideaconsult (BG)

Rulebases in version 1.51 (June 2008):

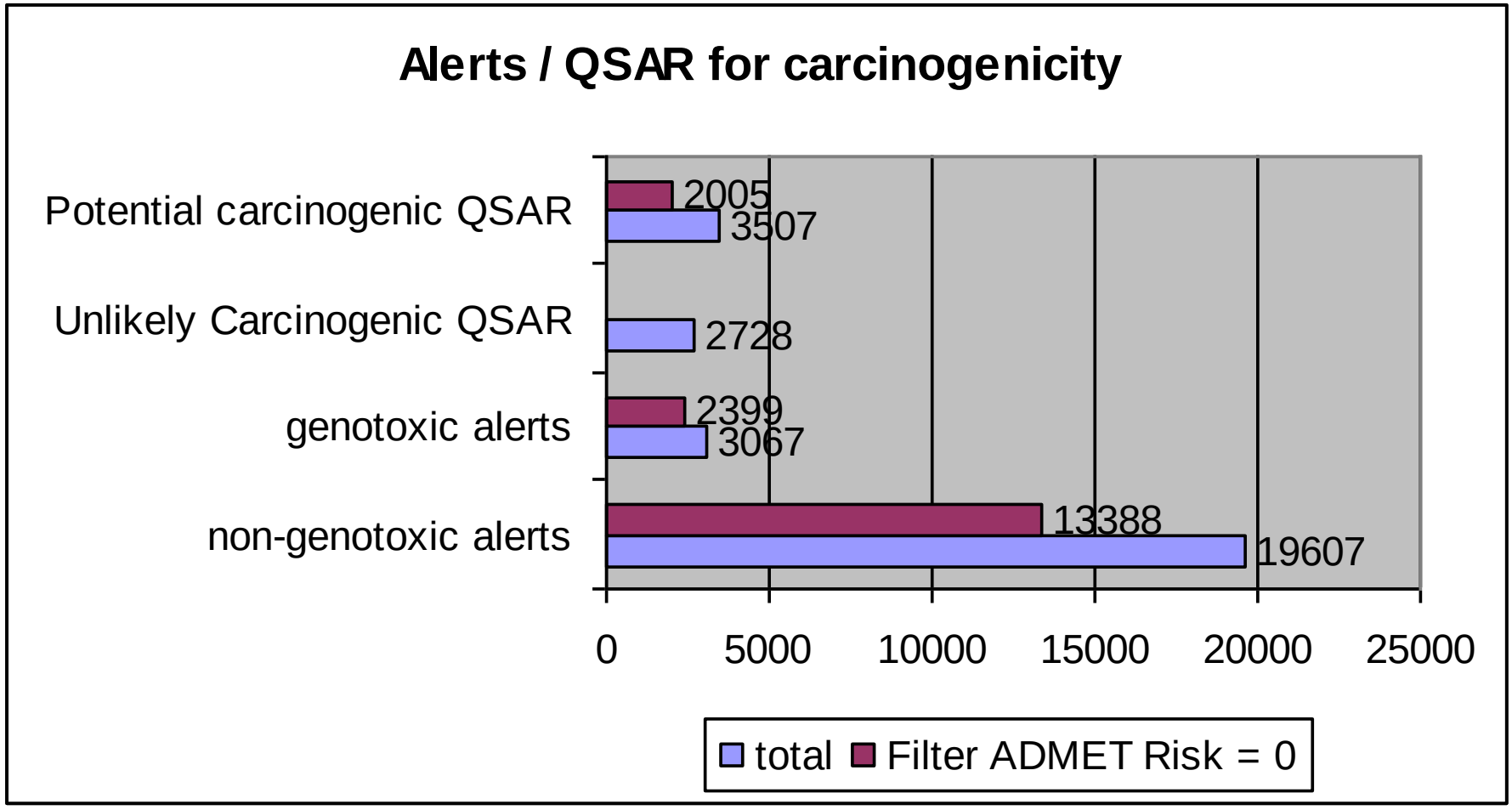
- Acute Fish Toxicity (Verhaar scheme)
- Oral systemic toxicity (Cramer scheme)
- Skin irritation & corrosion potential (BfR rulebase)
- Eye irritation & corrosion potential (BfR rulebase)
- Mutagenicity & carcinogenicity (Benigni-Bossa rulebase)

http://ecb.jrc.ec.europa.eu/qsar/qsar-tools/

Main screen in Toxtree



Toxtree Predictions for Carcinogenicity



ADMET Risk estimates from ADMET Predictor

Evaluation of Toxtree implementation

The implementation of the Cramer classification scheme in the Toxtree software was evaluated to evaluate its concordance and highlight potential software modifications

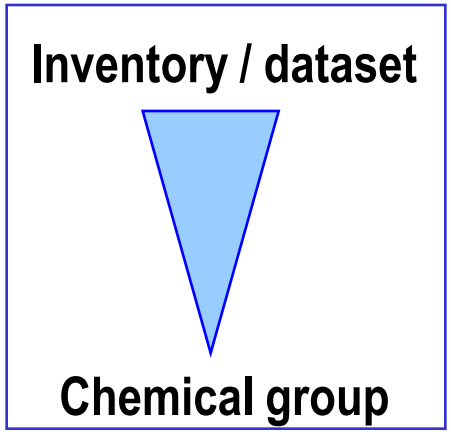
The results were promising with an overall good concordance between the reported classifications and those generated by Toxtree

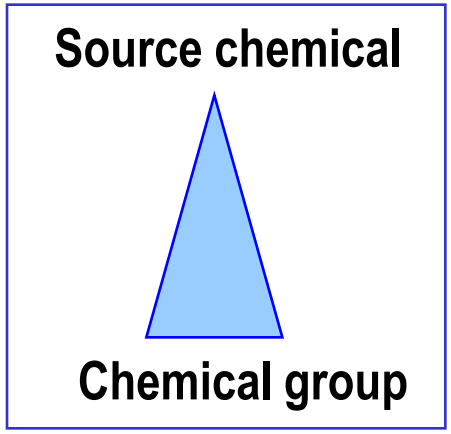
Improvements for Toxtree were proposed. Notable of these is a necessity to update the lists of common food components and normal body constituents as these accounted for the majority of false classifications observed.

Patlewicz G, Jeliazkova N, Safford RJ, Worth AP & Aleksiev B (2008). An evaluation of the implementation of the Cramer classification scheme in the Toxtree software. *SAR and QSAR in Environmental Research* 19, 495-524.

Step 5: Chemical grouping and read-across

- Chemical read-across within analogue and category approaches
- Biological read-across (between endpoints or species)
- Chemical grouping by a top-down approach
  - Supervised and unsupervised statistical methods
  - Ranking methods (DART)
- Chemical grouping by a bottom-up approach
  - Freely available tools with analogue-searching capability (Toxmatch, AMBIT2, AIM, PubChem, OECD Toolbox)

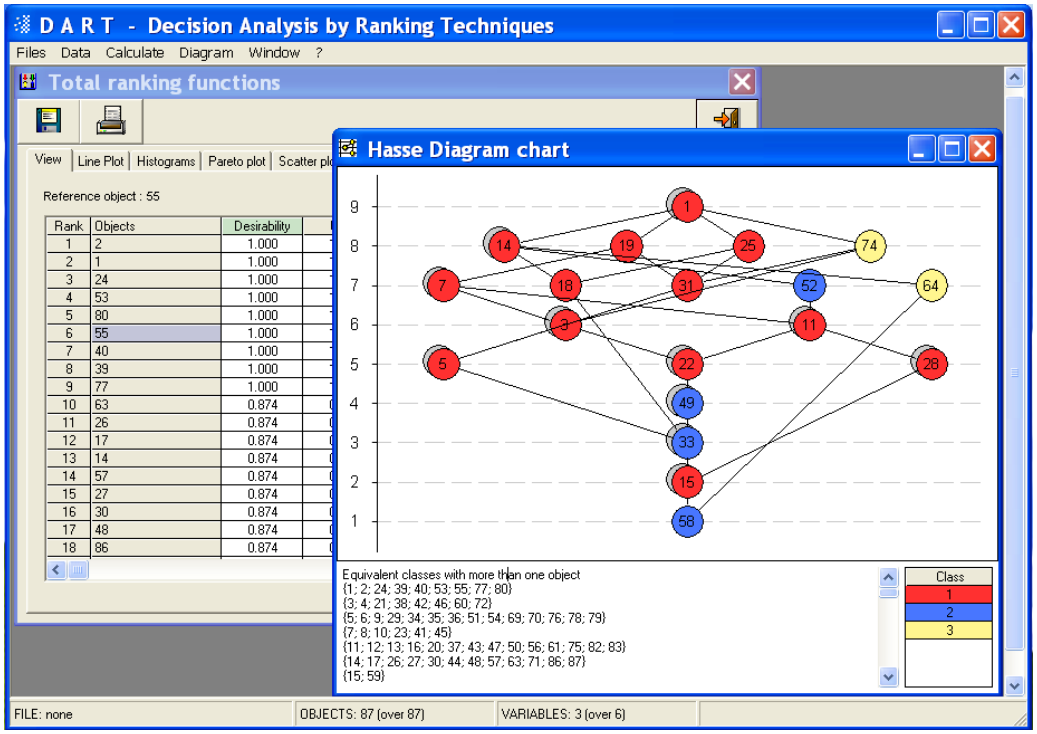


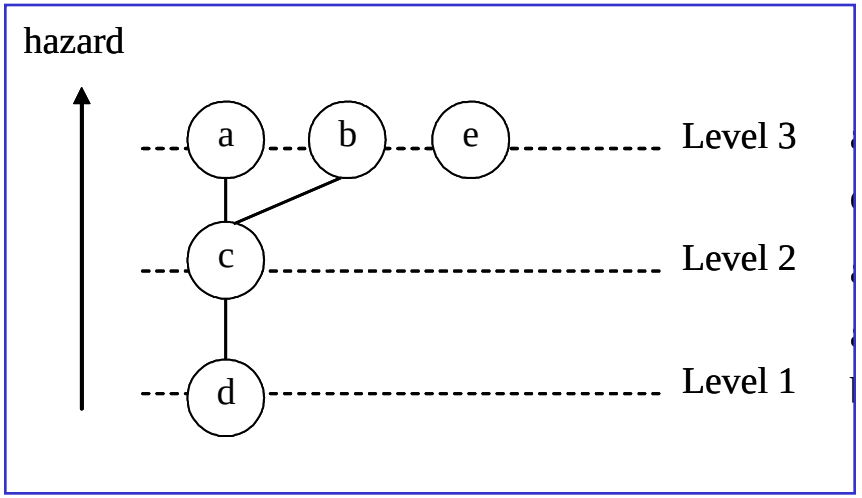


Worth A et al (2007). The Use of Computational Methods in the Grouping and Assessment of Chemicals - Preliminary Investigations. EUR 22941 EN

Ranking tool: DART

DART (Decision Analysis by Ranking Techniques) is a flexible, user-friendly, open source application, which is able to rank and group chemicals according to properties of concern

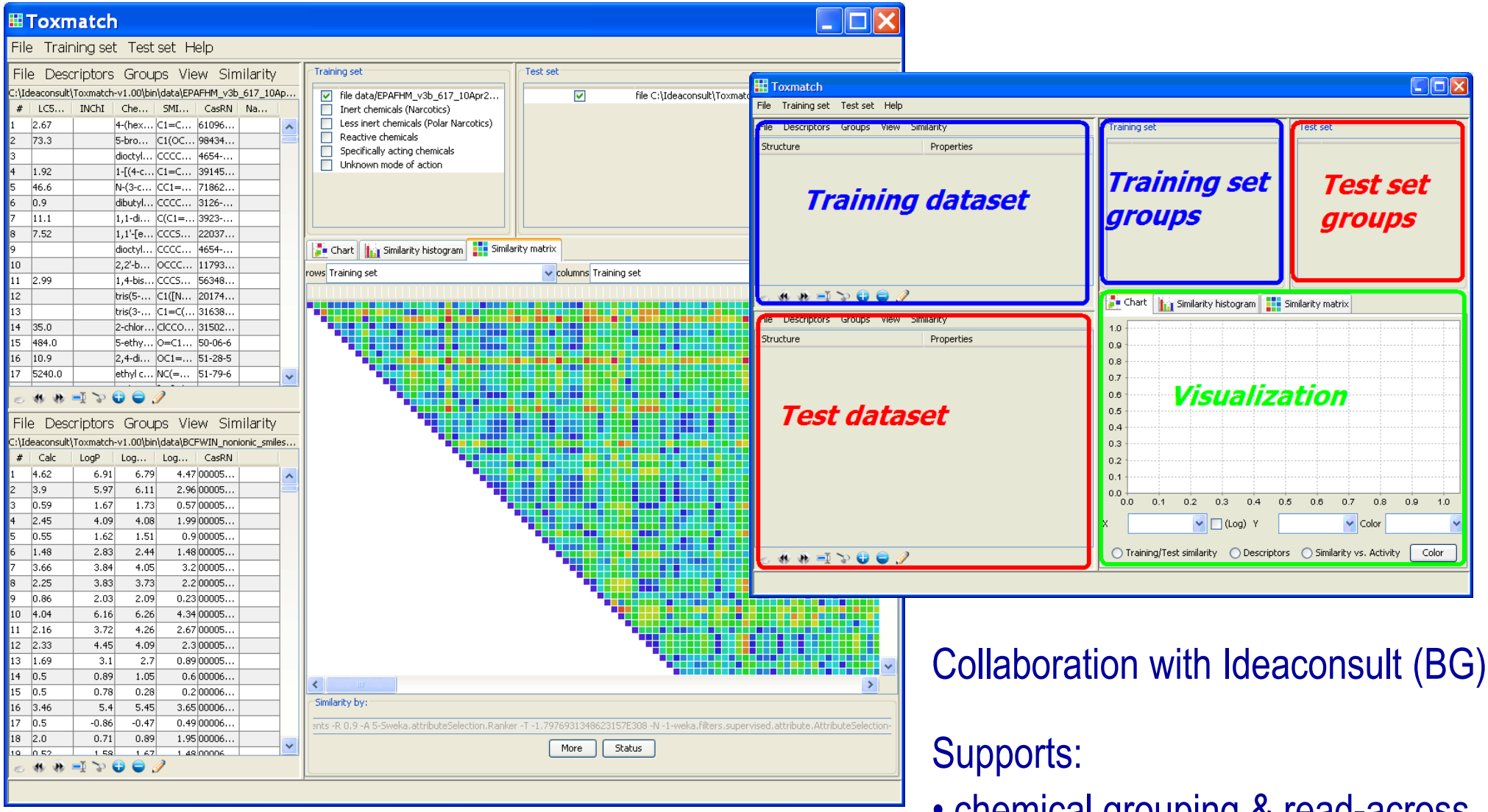




- collaboration with Talete srl (Italy)
- supports priority setting of chemicals

Pavan M & Worth AP (2008). A set of case studies to illustrate the applicability of DART (Decision Analysis by Ranking Techniques) in the ranking of chemicals. EUR 23481 EN.

Toxmatch: chemical similarity tool



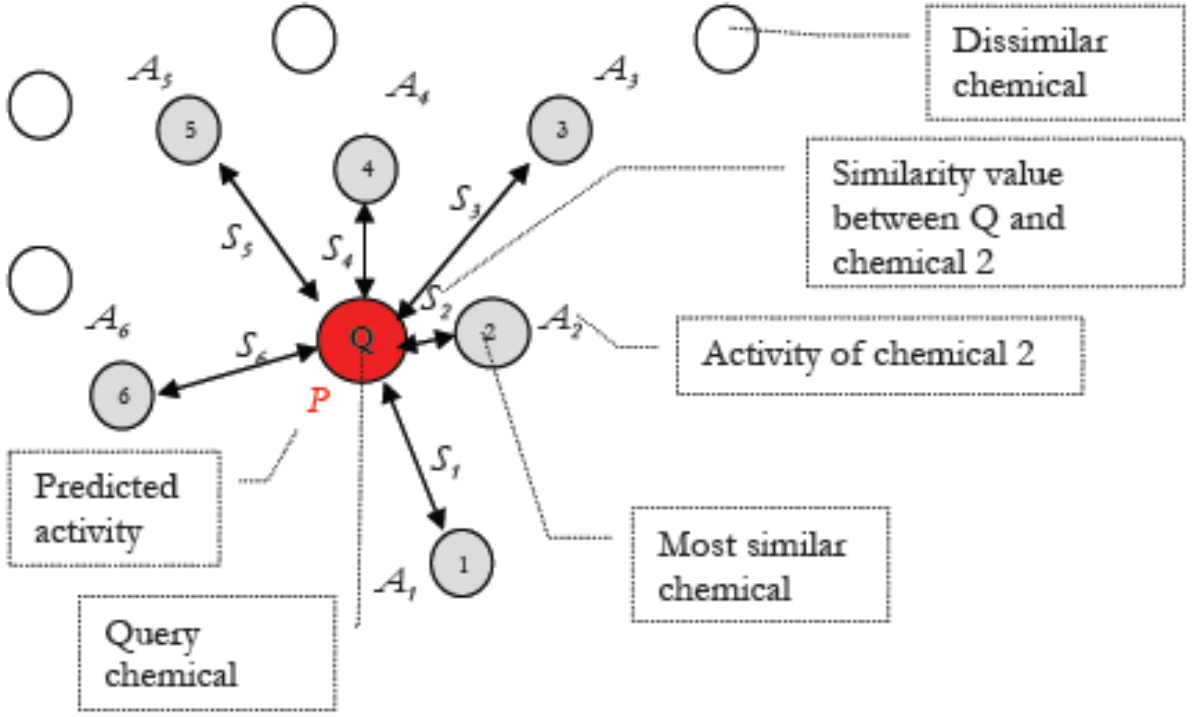
Collaboration with Ideaconsult (BG)

Supports:

- chemical grouping & read-across
- comparison of training & test sets

http://ecb.jrc.ec.europa.eu/qsar/qsar-tools/

Many-to-one read-across of a quantitative property (*k* Nearest Neighbours)

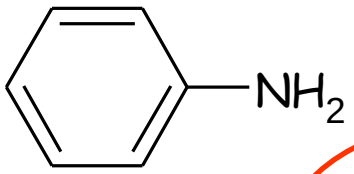


Patlewicz G, Jeliazkova N, Gallegos Saliner A & Worth AP (2008). Toxmatch – A new software tool to aid in the development and evaluation of chemically similar groups. *SAR and QSAR in Environmental Research* 19, 397-412.

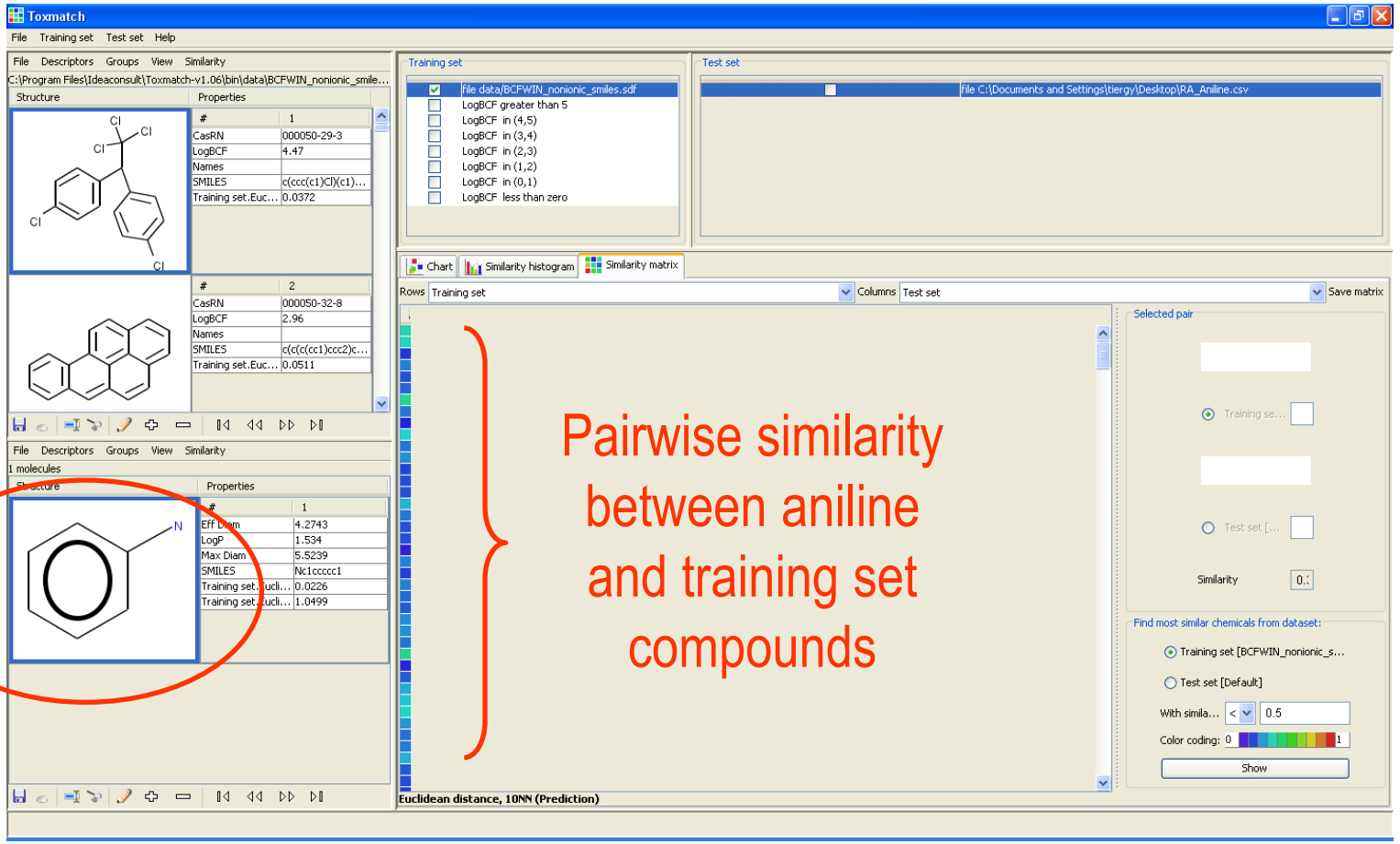
Example of read-across in Toxmatch

- BCF of aniline predicted on basis of effective diameter, maximum diameter and LogP
- Predicted LogBCF = 1.05
- Experimental LogBCF = 0.78 (Hazardous Substances Databank)

Training set of 610 chemicals



Aniline - test chemical

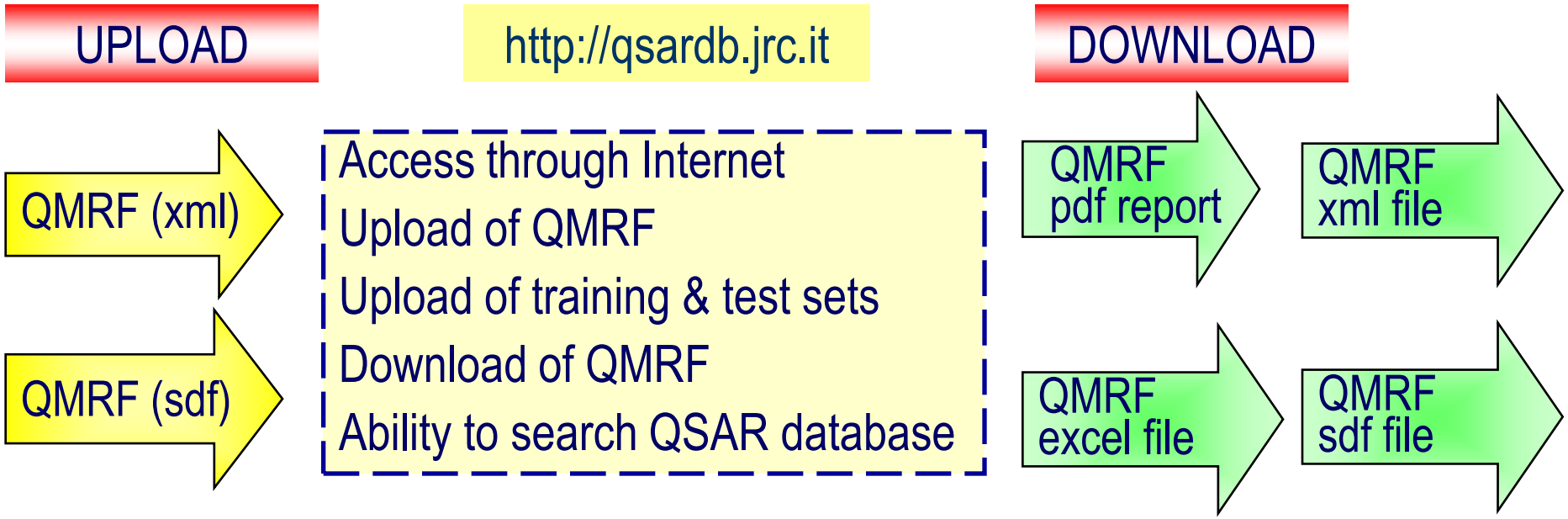


Step 6: JRC QSAR Model Database

Need to identify and use relevant, reliable and well documented (Q)SARs

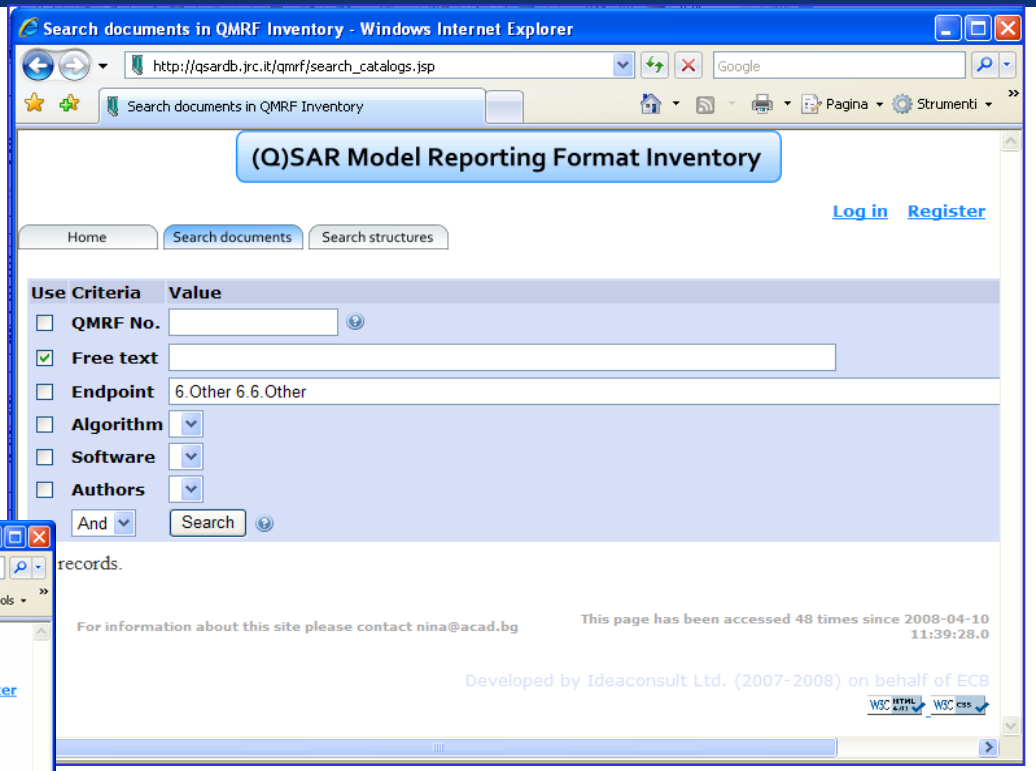
The JRC QSAR Model Database is a searchable inventory of peer-reviewed information on (Q)SAR models

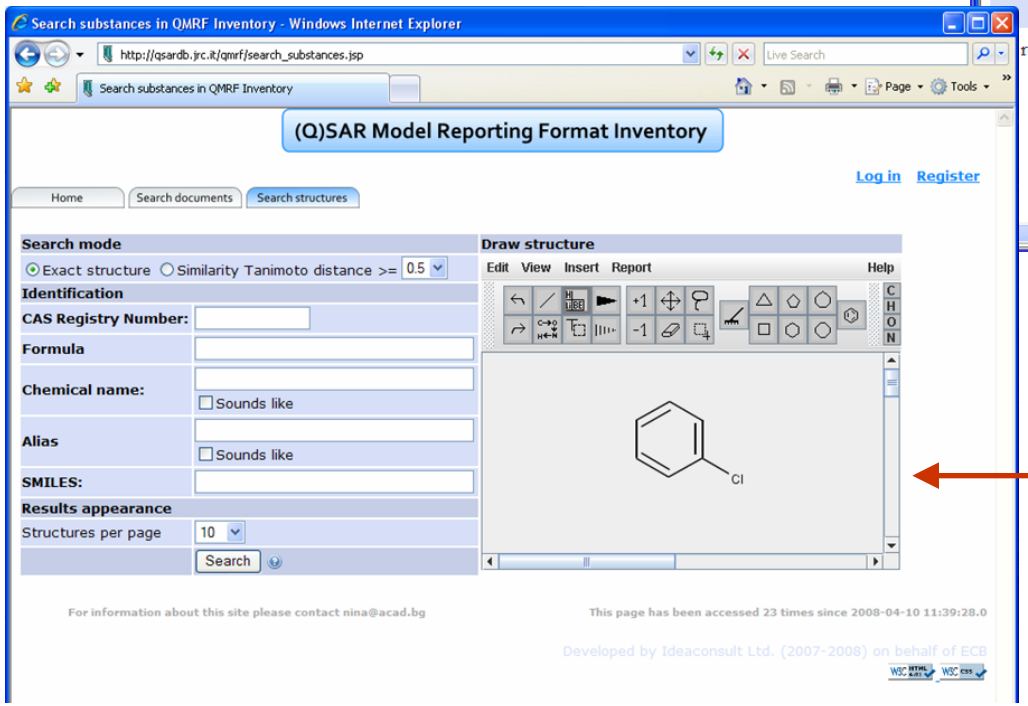
Developers and users of (Q)SAR models can submit information on (Q)SARs by using the (Q)SAR Model Reporting Format (QMRF)



Searching the QSAR database

- QMRF No.
- Free text
- Endpoint
- Algorithm
- Software
- Authors





- CAS No.
- Formula
- Chemical name
- Alias
- SMILES

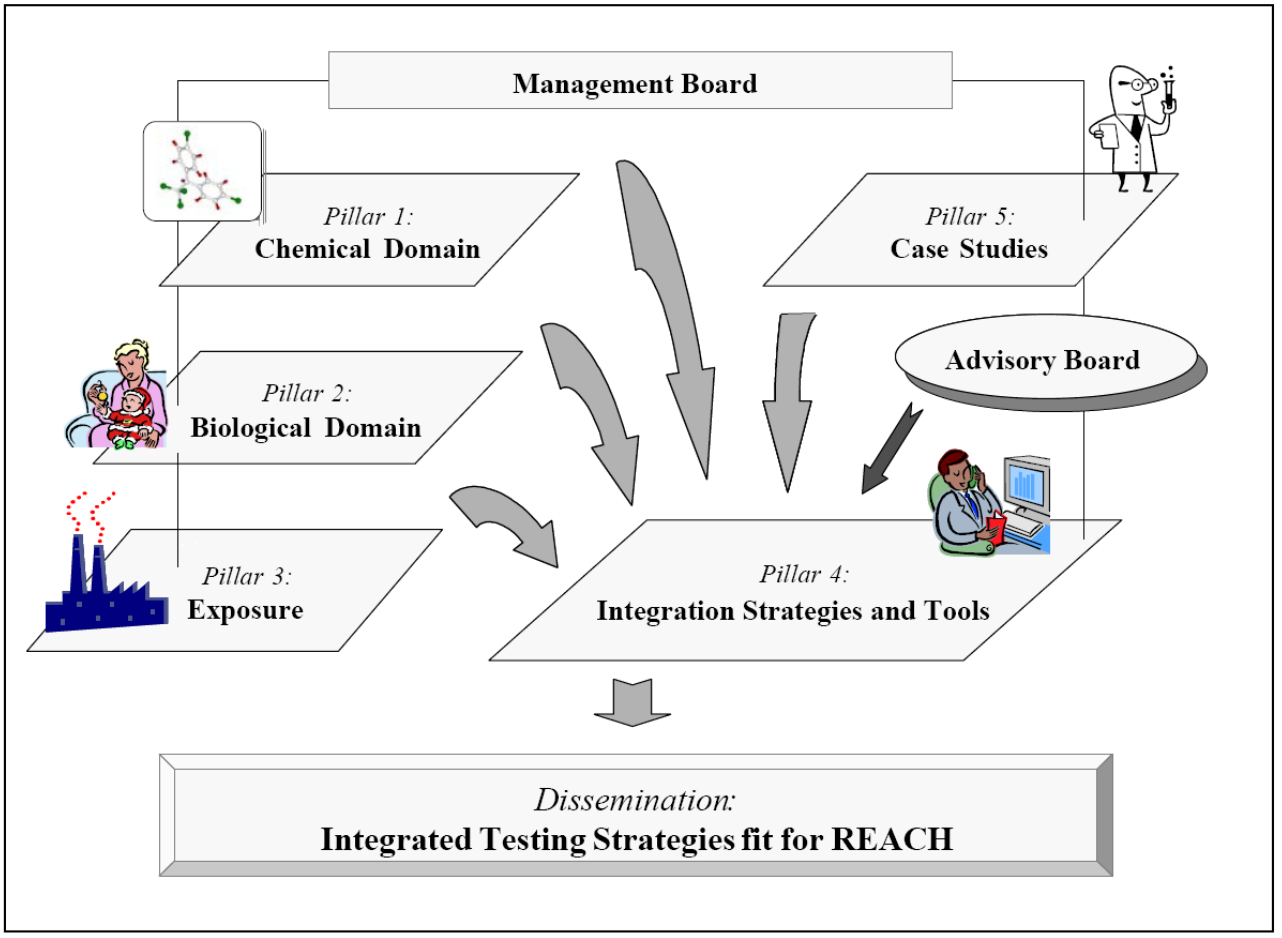
http://qsardb.jrc.it

JRC-EFSA project on pesticide modelling

- Need to assess the toxicological significance of pesticide active metabolites and degradation products (not tested under *Directive 91/414/EEC*)
- Three projects funded by EFSA (2009-2010)
  - Applicability of QSAR analysis in assessing metabolite toxicity
  - Applicability of the TTC concept in assessing metabolite toxicity
  - Impact of metabolism on toxicological properties
- Next steps by EFSA
  - Opinion of the PPR panel (2010-2011)
  - Guidance document on pesticide residue definition for dietary risk assessment (2011-2012)

OSIRIS – an EU Project on Integrated Testing

Optimized Strategies for Risk Assessment of Industrial Chemicals through Integration of Non-Test and Test Information (OSIRIS)



http://www.osiris-reach.eu/

Concluding remarks

- To optimise the use of non-testing data, a conceptual framework is provided in the REACH guidance documentation
- There is a need to incorporate mechanistic knowledge in the models (e.g. based on chemical reactivity and “omic” data)
- An increasing number of models are being implemented in a range of software tools
- There is a need to facilitate the use of multiple tools by developing automated workflows
- Further guidance is needed on how to assess the adequacy of non-testing and alternative test data by weight-of-evidence approaches