

# APPLICATION OF STRUCTURE ACTIVITY-RELATIONSHIPS IN THE CHEMICAL HAZARD ASSESSMENT

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## INTRODUCTION

In the **regulatory framework** there is a growing need for *in silico* methods that can be used to gain information about **environmental fate and ecological and health effects of chemicals**. The different techniques that are used to derive non-testing information include: **(quantitative) structure-activity relationship models, expert systems, and read-across/category** approaches. National and international agencies have a number of reasons to encourage the use of *in silico* methods. First of all, computational methods are faster and cheaper compared to empirical testing methods, and their use results in considerable savings of time and money during the assessment of chemical hazard.

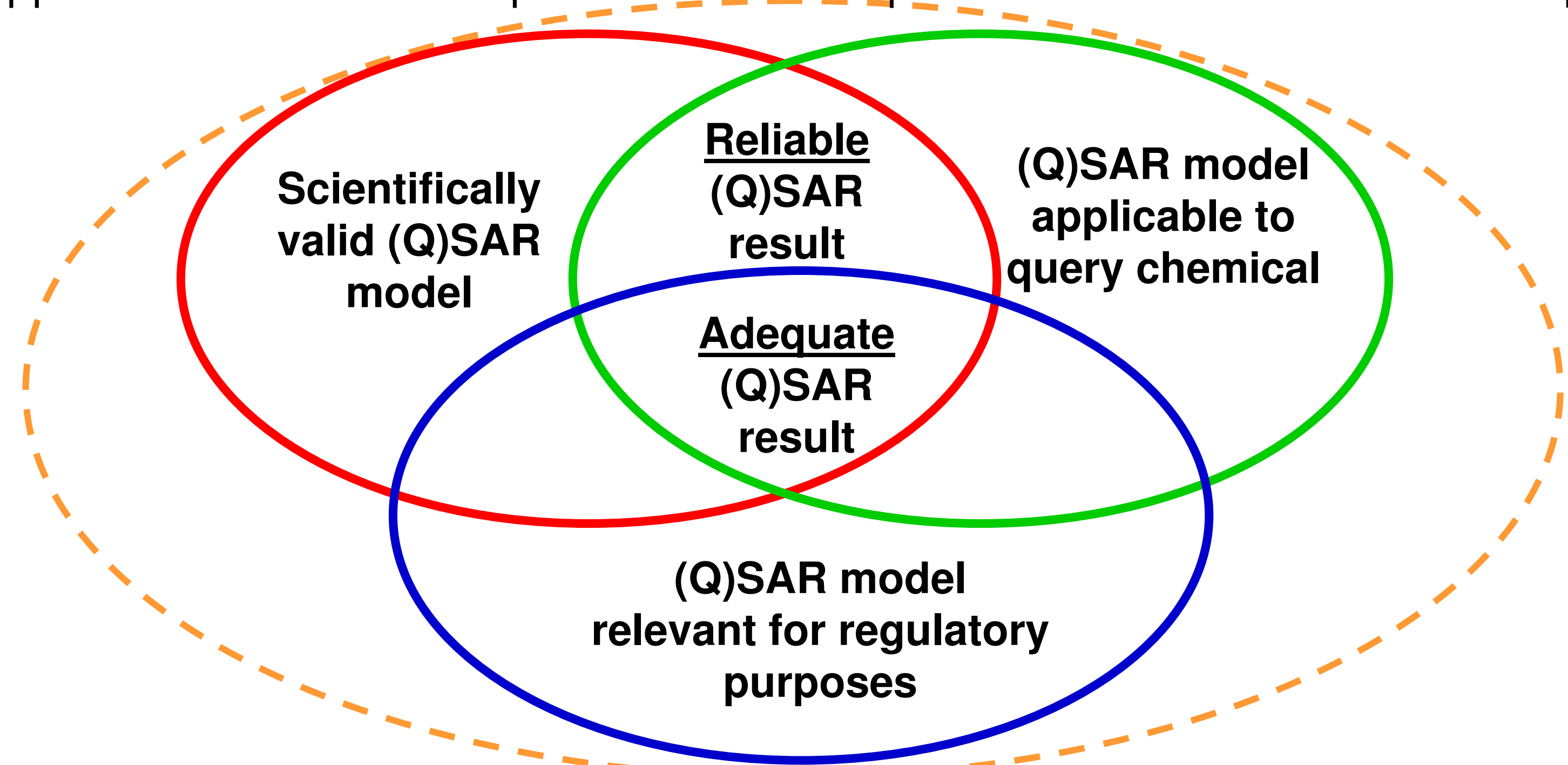
**REACH (Registration, Evaluation and Authorisation of CHemicals)** is the new EU regulatory framework aiming at improving the protection of human health and the environment through a better and earlier identification of the intrinsic properties of chemical substances.

To limit the cost and the number of animals used for testing, REACH explicitly encourages the use of computer-aided methods such as (Q)SAR methods and category/read-across approaches for filling in the enormous knowledge gap of chemical information.

**S-IN provides services to generate non-testing data in the chemicals regulatory framework.**

## Valid, reliable and adequate predictions

In order to be used in place of experimental data, REACH requires that the *in silico* methods meet certain conditions. For example, in the case of (Q)SARs, these requirements include: 1) the model has to be valid; 2) the substance has to fall within the applicability domain; 3) the prediction has to be adequate for the regulatory purpose; 4) the applied method has to be provided with adequate and reliable documentation [1].

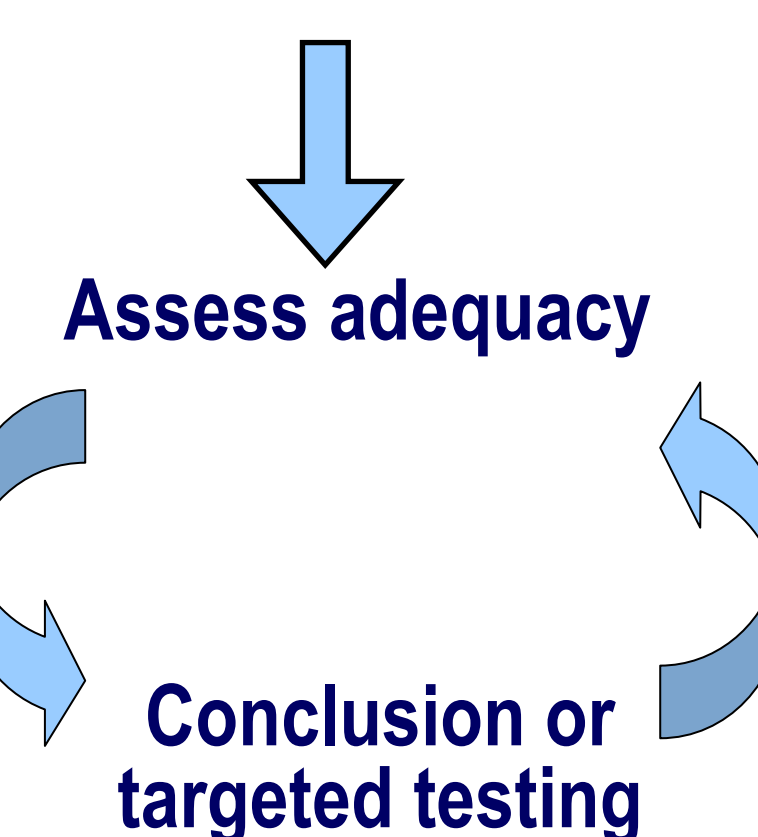


## Outline of non-testing strategy [1,2,3]

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

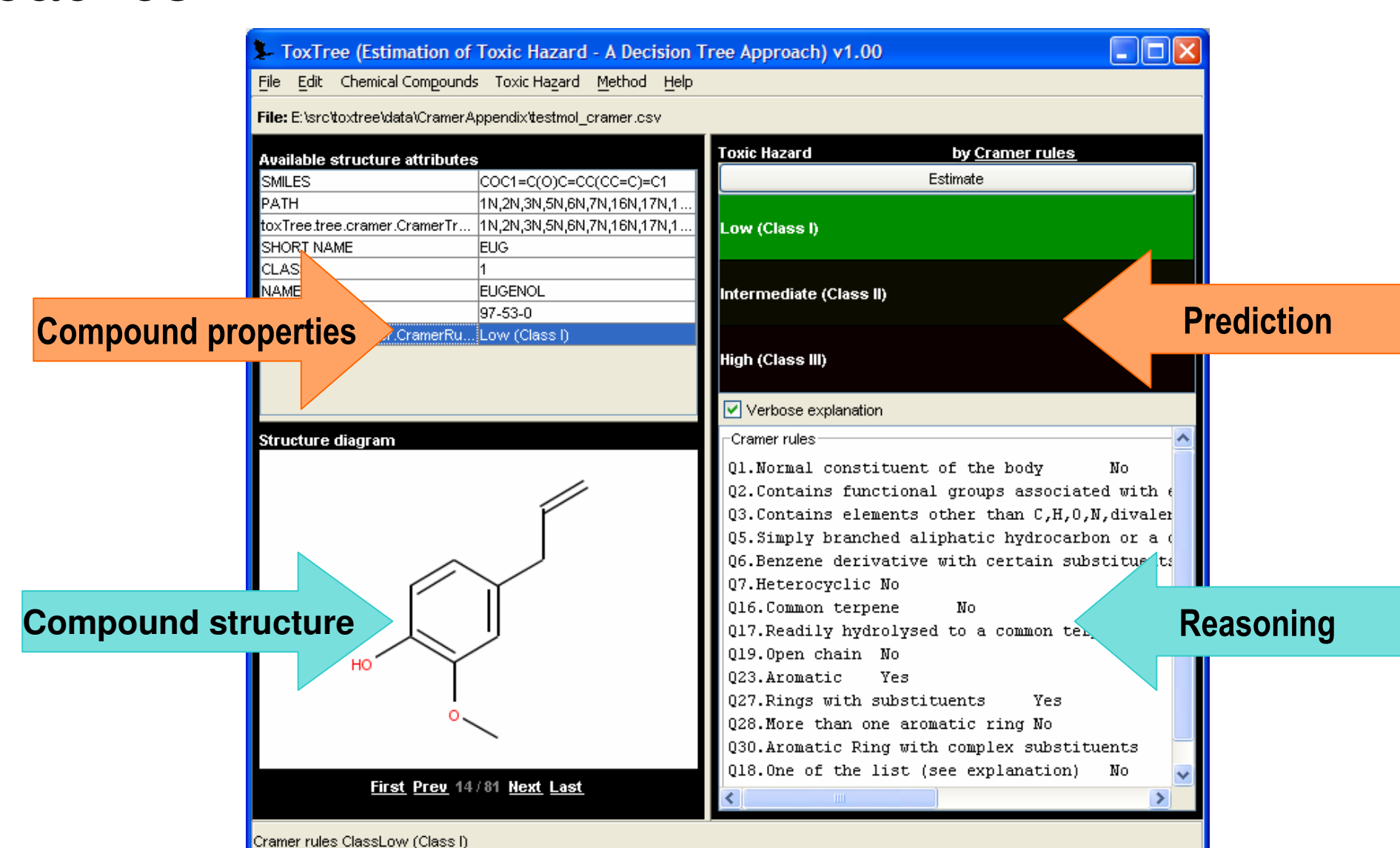
### Working Matrix

Chemical	Prop1	Prop2	Tox1
Parent			
Metabolite1			
Metabolite2			
Metabolite3	...	...	...

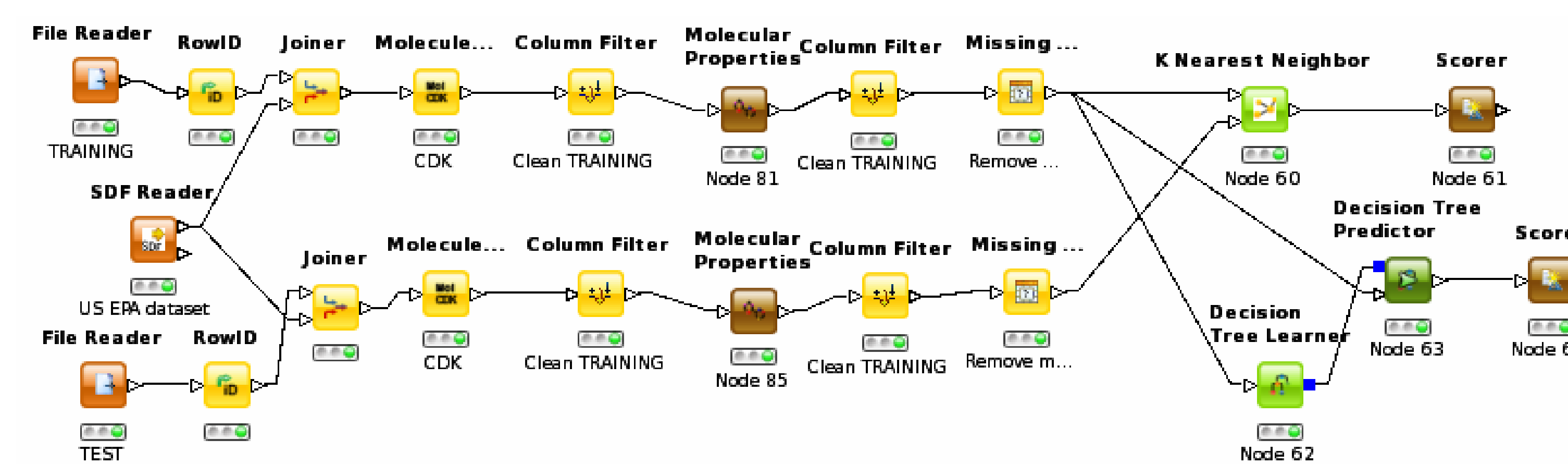


## Some useful tools employed in our organization

•**Toxtree** (freeware, JRC initiative) [4] for classification schemes: it is a flexible, user-friendly, open source application, which is able to estimate toxic hazard by applying decision tree approaches.



•**KNIME** (freeware) [7,8] to build workflows and integrate multiple approaches: KNIME is an open source pipelining platform that enables the user to create data flows visually, execute analysis steps and later investigate the results through interactive views. For example we have used KNIME to: a) pre-process and analyze large amount of data, and then build models; b) perform read-across by means of the k-nearest algorithm.



## Conclusions and remarks

- To optimize the use of non-testing data, an **integrated approach** for the use of multiple models, tools and approaches is required.
- An increasingly wide range of models are being implemented in software tools.
- A **conceptual framework** for integrating non-testing data is provided in the REACH guidance documentation.
- There is a need to facilitate the use of **multiple tools** in an integrated way by using automated workflows
- Acceptance of the non-testing data: **learning-by-doing**

•**OECD QSAR Application Toolbox** (freeware, OECD initiative) [5] for grouping and read-across (category approach): the toolbox includes: a) structures and inventories; b) toxicity and fate data; c) tools to form categories; d) tools to form read-across, trend and limited QSAR analysis; e) small number of QSARs; f) reporting format.

•**Leadscope** (commercial) [6]: cheminformatics platform including databases and QSAR models. Our organization is involved in the Leadscope Toxicity Partnership Program.



## REFERENCES

- [1] REACH guidance, Chapter R.6 "QSARs and grouping of chemicals": [http://guidance.echa.europa.eu/docs/guidance\\_document/information\\_requirements\\_en.htm?time=1247234218](http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_en.htm?time=1247234218)
- [2] Bassan A., Worth A. P., Computational Tools for Regulatory Needs in Computational Toxicology: Risk Assessment for Pharmaceutical and Environmental Chemicals, S. Ekins (editor), Wiley & Sons, Inc. (2007). This chapter gives an overview of tools that could be used within a non-testing strategy
- [3] Bassan A., Worth A. P., The Integrated Use of Models for the Properties and Effects of Chemicals by means of a Structured Workflow, QSAR Comb. Sci., 27, 6-20, (2008)
- [4] Toxtree, <http://ecb.jrc.ec.europa.eu/qsar/qsar-tools/index.php?c=TOXTREE>: the website includes full documentation and references to Toxtree and related databases
- [5] OECD QSAR Application Toolbox, [http://www.oecd.org/document/54/0,3343,en\\_2649\\_34379\\_42923638\\_1\\_1\\_1\\_1,00.html](http://www.oecd.org/document/54/0,3343,en_2649_34379_42923638_1_1_1_1,00.html): this website includes full documentation on the Toolbox
- [6] Leadscope: [www.leadscope.com](http://www.leadscope.com)
- [7] KNIME: [www.knime.org](http://www.knime.org)
- [8] Tiwari A., Sekhar A.K.T., Workflow based framework for life science informatics, Computational Biology and Chemistry 2007, 31:305-319