Integrated Testing Strategies and Decision-Making

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Summary

- Decisions on tests for hazard assessment

- What about risk assessment

- Step 1: Assessing QSAR uncertainty

Comparing tests...

In the framework of Hazard Assessment

1. Assume unknown toxicity of product X

2. To choose among testing alternatives: compare tests

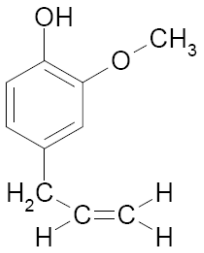
3. Choose the best test or best test battery (parallel) or best test gallery (sequential)

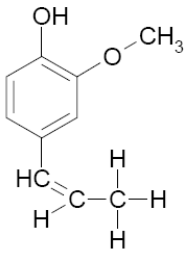
- Tests should be compared on the basis of *performance* (how reliable is the test answer?) and *cost*
  - we need tests' performance data (often lacking)

- If *all chemicals are considered equal* and if *all toxicity profiles are equally likely*, you can evaluate tests only once, updating simply when new tests arrive.

Prior information...

- However :
  - computational chemistry,
  - (Q)SAR modeling,
  - read-across,
  - category grouping,





indicate that chemicals are *not* all the same, and for a given chemical we know that all toxicity profiles are *not* equally likely.

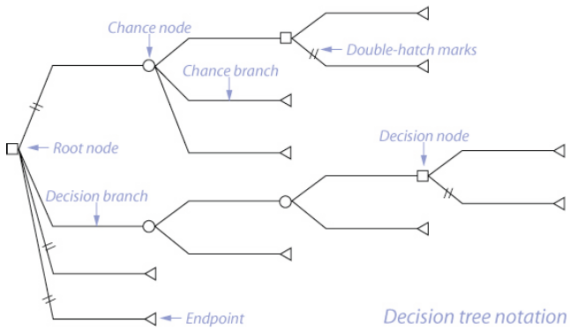
- Ideally they would predict *exactly* the toxicity profile (*no testing would be necessary*) …

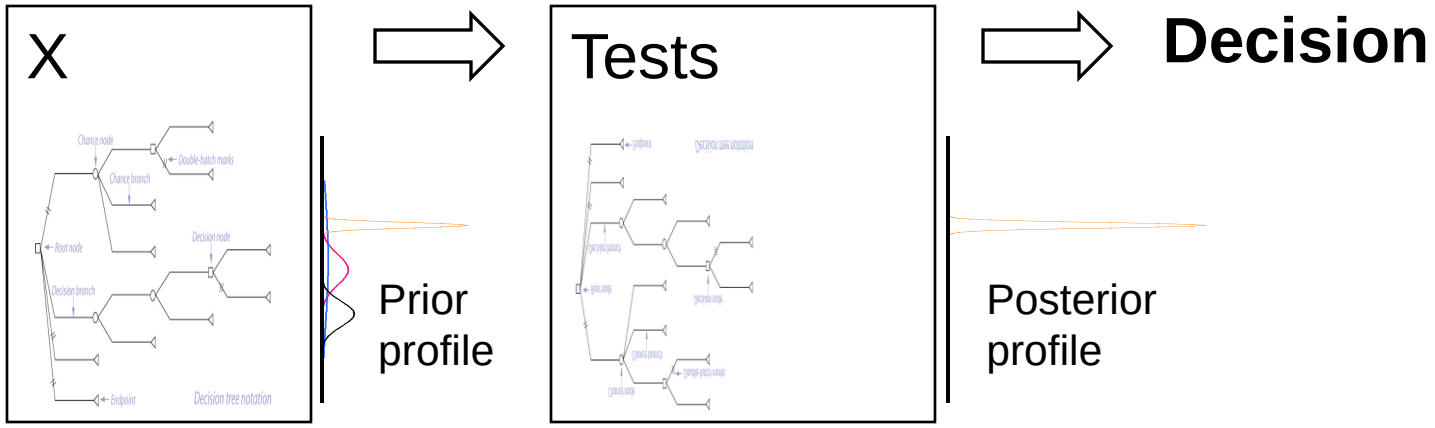
Uncertainty...

- But, toxicity profiles can only be predicted with some *uncertainty*.
  - we need operational measures of uncertainty (not just qualitative)
- Then, formally, we need to *consider and weight all possibilities* about the toxicity of X to evaluate our tests (you may not want to do a cancer test if X is unlikely, or very likely, to be a carcinogen).
- It is possible to simplify the process, but at the risk of being sub-optimal (too costly, not protective enough, *etc.)*

Decisions trees...

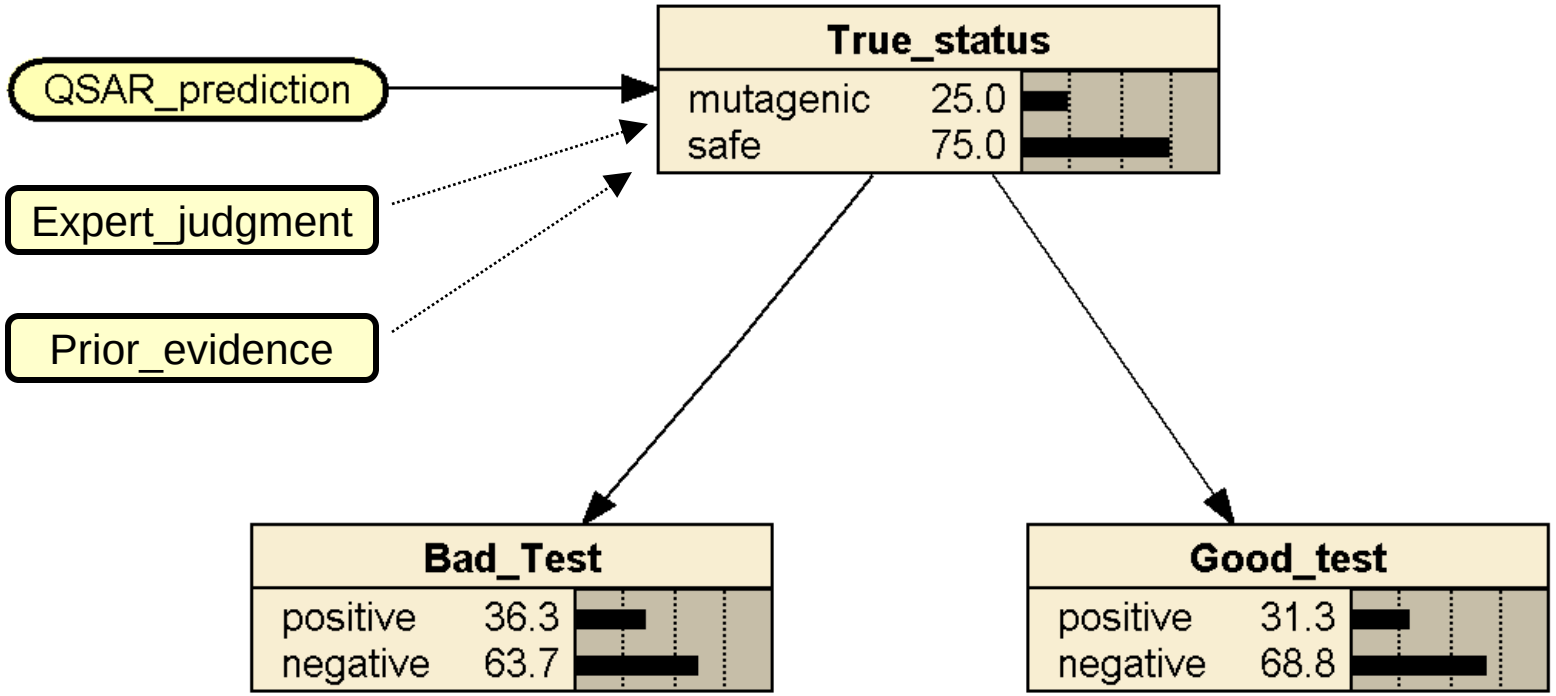
- Trees are just a way to organize, enumerate and weight all the possibilities of :
  - toxicity profiles
  - test outcomes (in particular when a battery is applied)





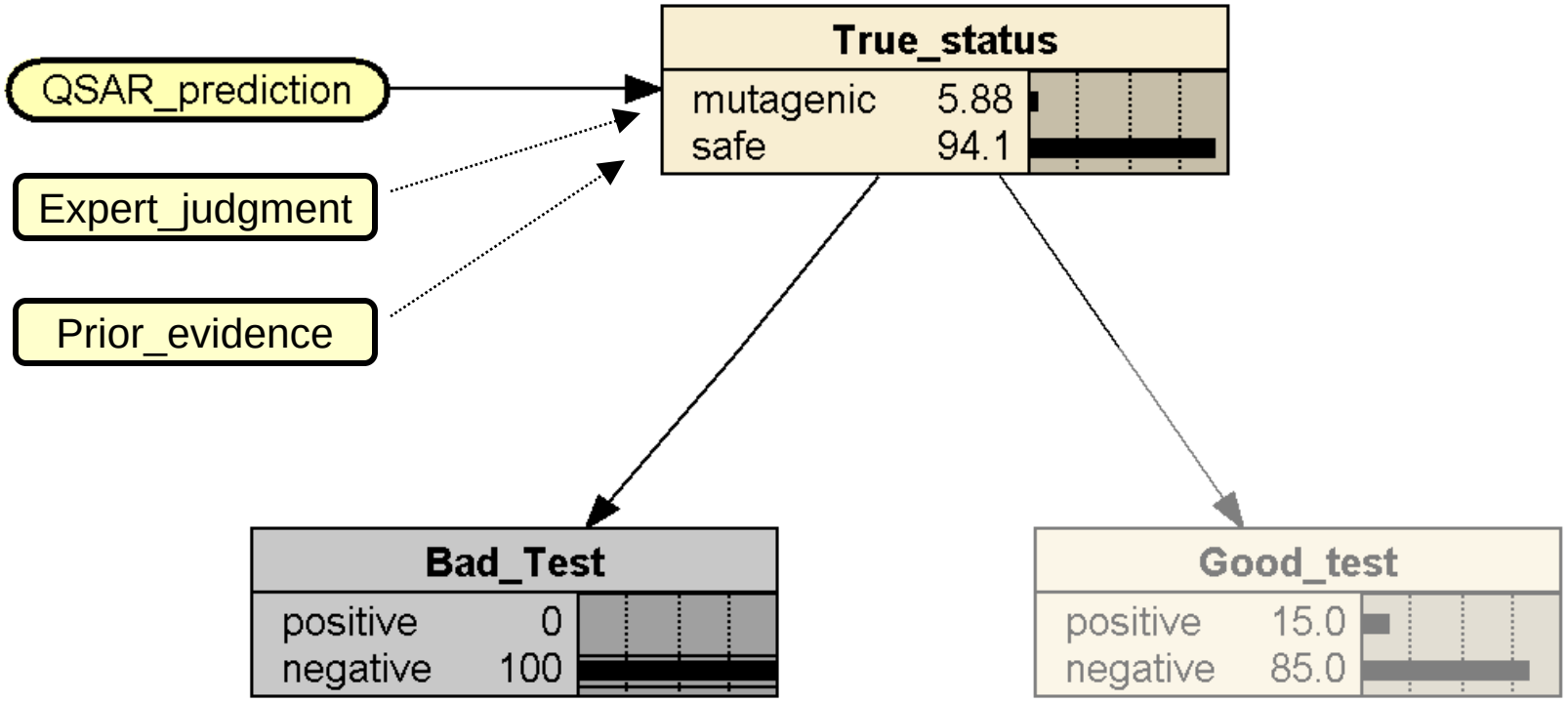
Or Bayesian networks?

- Bayesian networks are a slightly different to organize your thinking and integrate evidence:



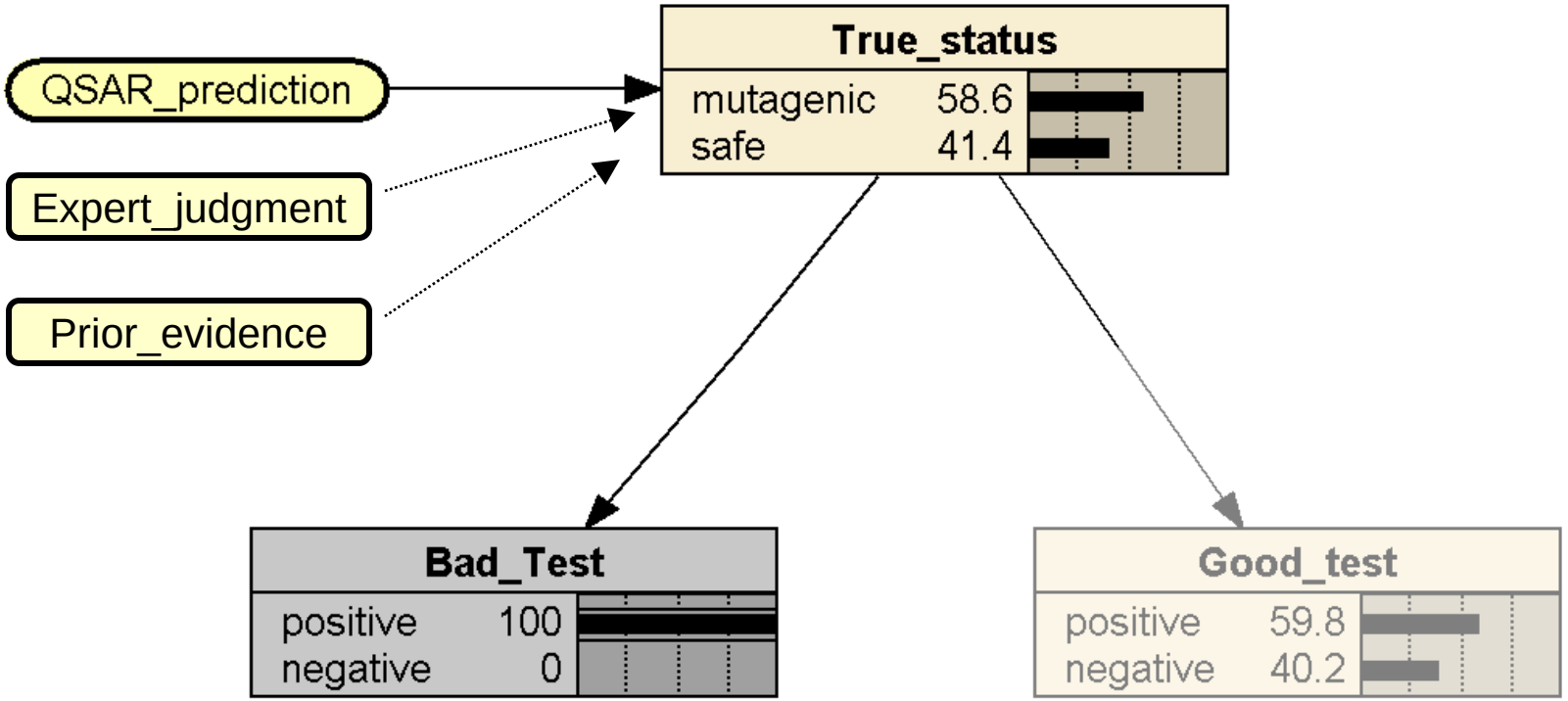
Bayesian networks...

- Bayesian networks can guide your selection of tests



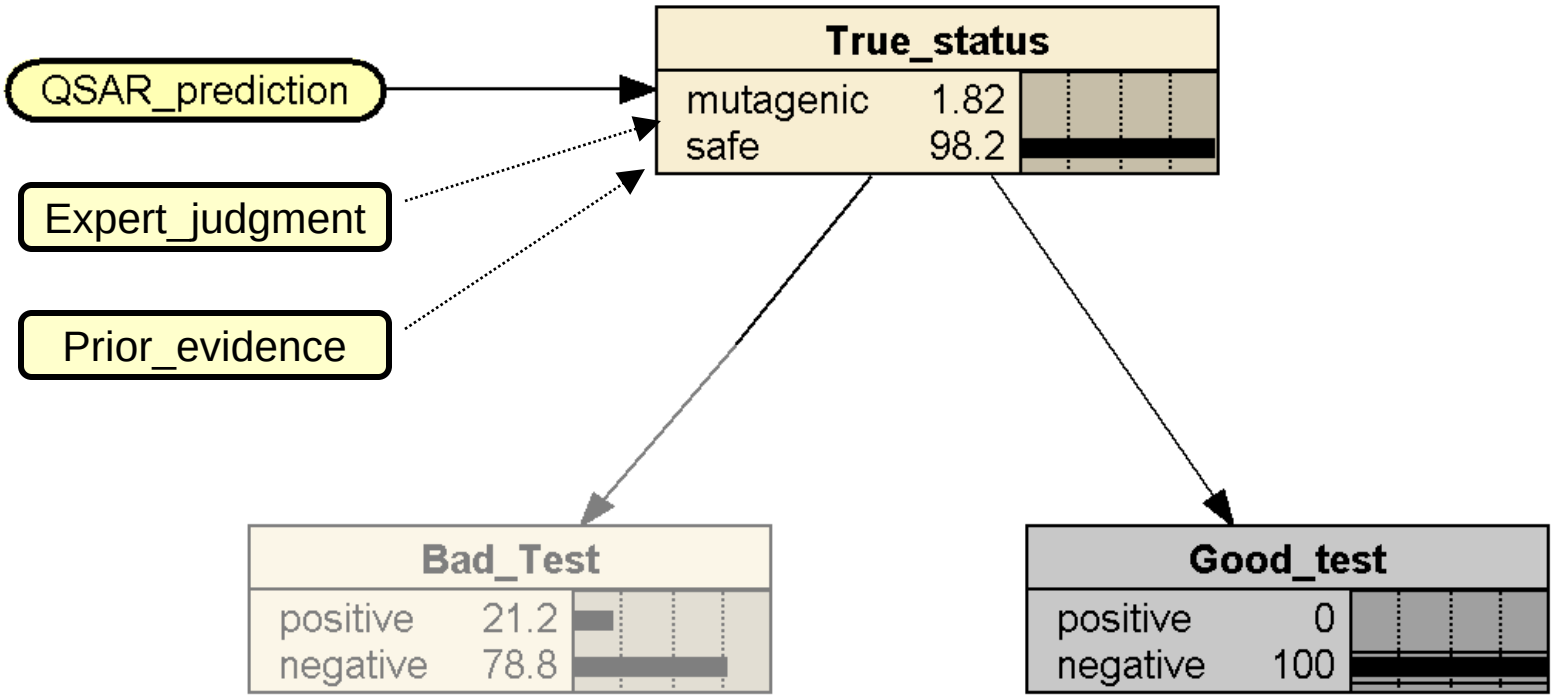
Bayesian networks...

Here, the cheap test will not allow you to conclude



Bayesian networks...

- A more expensive, but better test is preferred:



Bayesian networks...

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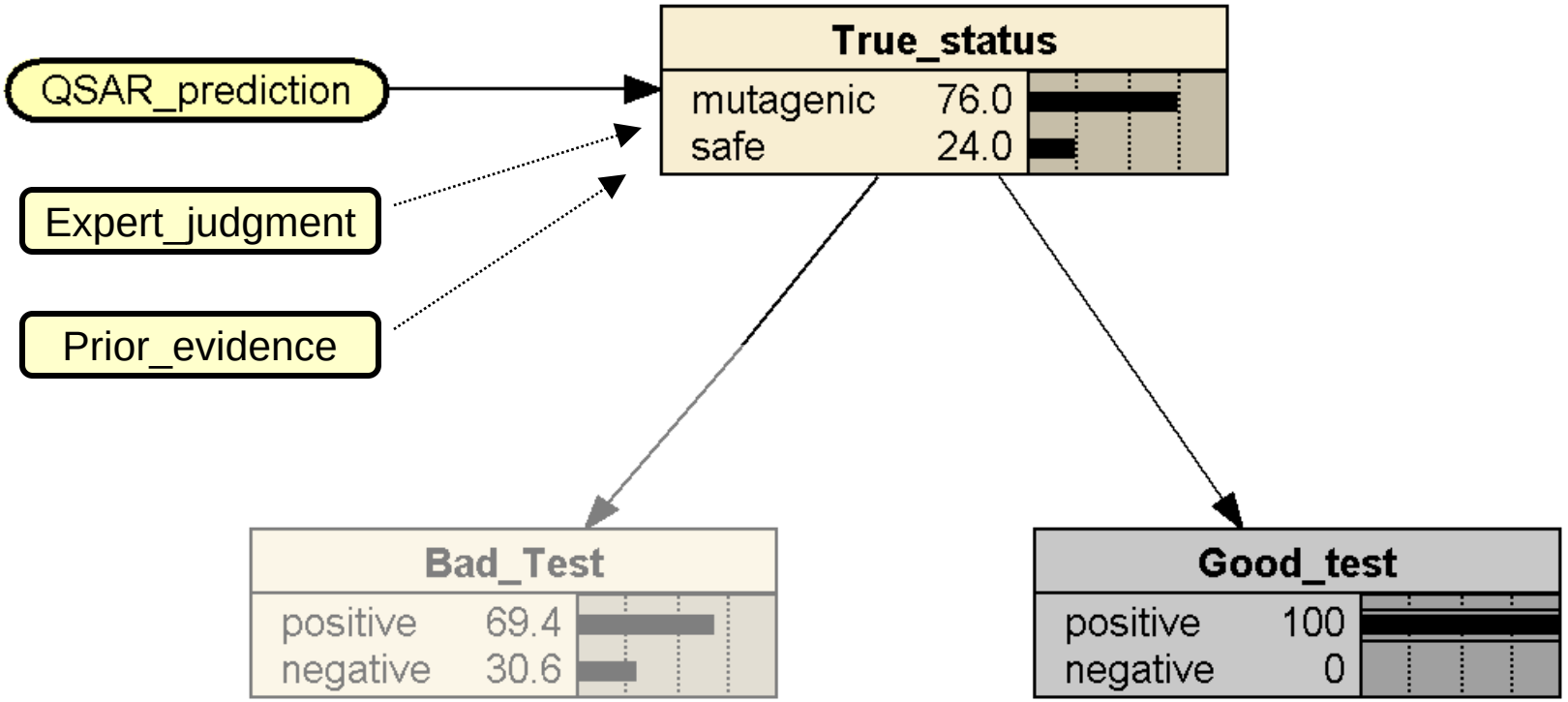

Deciding on tests for hazard assessment

- Enumerating possible profiles and test results can be tedious. Specialized software can help (often using decision trees or BN to speed up problem formulation)
- For each possible "*prior*" profile, the lab tests will produce a "*posterior*" profile (more precise). Test strategies can be compared on the basis of cost and obtained precision (e.g. using "added value of information)
- It may be difficult to estimates costs and aggregate them with precision, but controlling consumer risk and minimizing producer risk can be an option we are exploring

What about Risk Assessment ?

- Risk requires exposure information. Exposure is also a parameter on which you may have control.
- The tests assessed should give you a dose-response relationship (an extension of yes / no answer)
- It's all the more important here to consider all the scenarios and possibilities, but they are continuous and the best way to average over all possibilities is to use Monte Carlo simulations. But the principle is the same as for hazard.

QSAR uncertainty: INERIS' work

- A QSAR modeling method to estimate the probability, and related uncertainty, for query chemicals to be active or inactive, as a function of their similarity to a training set.
- Generalizes the 5 NN approach of Weaver and Gleeson (J Mol Graph Model, 2008, 26:1315)

Five steps

1. A dataset of chemicals with known biological properties is split into 2 categories: active and inactive using a biological criterion.

QSAR uncertainty: INERIS' work

2. A PLS regression is carried out to model the property of interest. It defines a set of orthogonal axes that enables the computation of the Euclidean distance between chemicals.
3. Each molecule of the training set is used to predict the status (active/inactive) of a query molecule and estimate the uncertainty of that prediction. Each active molecule of the training set adds certainty to positive predictions, the converse for inactive molecules.

QSAR uncertainty: INERIS' work

4. Individual contributions to certainty are weighted by the Euclidean distances between the query molecule and the training set molecules (the longer the distance the lower the certainty)
5. Certainty is a Gaussian function centered on each molecule of the training set. The overall certainty attached to a prediction for the query chemical is given by normalized sum of the individual certainties brought by the training set molecules.

QSAR uncertainty: INERIS' work

- Application to a dataset of Duchowicz *et al*. (Eur J Med Chem, 2008) of 78 flavonoids binding to the GABA(A) receptor.
  - Training set: 70 ligands.
  - Test set: 8 ligands.
- We used the same values of the descriptors and the same splitting of datasets.
- To split the training set: active if log10 K_i > 0, inactive otherwise. Gives 28 inactive and 42 active molecules.

QSAR uncertainty: INERIS' work

Results for the test set

Molecule	Probability	Certainty	Prediction by Duchowicz et al.	Experimental result
1	0.42	1	-	+
2	0.41	1	-	+
3	0.77	1	+	+
4	0.19	1	-	-
5	0.27	1	-	-
6	0.10	1	-	-
7	0.20	1	-	-
8	0.31	1	-	-

Conclusion

- We are working to provide concepts and tools to guide decisions about testing strategies.
- In addition to working on QSAR predictions we are evaluating reprotoxicity tests as to their performances.
- The combination of QSAR predictions (with uncertainty attached) and predictive test results (also with their uncertainty) should give improved, more robust decisions.