参考資料5

平成24年10月31日「第3回有害性評価小検討会」資料

# 発がん性等に関する構造活性相関について

Review of QSAR Models and Software Tools for Predicting Genotoxicity and Carcinogenicity
(Institute for Health and Consumer Protection, EC Joint Research Centre) より


**広瀬明彦**

総合評価研究室
安全性生物試験研究センター
国立医薬品食品衛生研究所

# 発がん性及び遺伝毒性のデータベース

| Database (name and link) | Information |
|---|---|
| Benchmark Data Set for In Silico Prediction of Ames Mutagenicity (Hansen et. al., 2009) | Ames mutagenicity databaset for 6500 compounds |
| Carcinogenic Potency Database (CPDB) http://potency.berkeley.edu/cpdb.html | Contains of the results of 6540 chronic, long-term animal cancer tests on 1547 chemicals |
| Danish QSAR database EPA | Searchable database of *predictions* for approx 166,000 chemicals. (based on MulitCase models |
| DSSTox (Distributed Structure-searchable Toxicity) database | Both the CPDB and the online NTP database have been "chemically-indexed" |
| GAP – Genetic Activity Profile Database by US EPA and IARC (Latest update in 2000) | Data on approx 300 chemicals from volumes 1-50 of the IARC Monographs and on 115 |
| Existing Chemicals Examination (EXCHEM) database (Japan) | Ames mutagenicity, chromosomal aberrations and mouse micronucleus assays for more than 250 HPV chemicals |
| Istituto superiore di Sanità database (ISSCAN) | More than 1150 chemical compounds tested with the long-term carcinogenicity bioassay on rodents, mutagenicity data. |
| Monographs on the Evaluation of Carcinogenic Risks to Humans (IARC) | A series of scientific reviews for more than 900 agents, and more than 400 , probable and possible carcinogens. |
| National Toxicology Program (NTP) database | More than 500 two-year, two species, toxicology and carcinogenesis, and more than 2000 genetic toxicity studies, |
| Toxicity Reference Database (ToxRefDB) | studies on 330 of chemicals, many of which are pesticide active ingredients |
| TOXNET database : Carcinogenesis Research Information System database (CCRIS) and the Genetic Toxicology Databank (GENE-TOX) | CCRIS: over 9000 chemical records with animal carcinogenicity, mutagenicity, tumour promotion, and tumor inhibition test results. GENE-TOX: on over 3000 chemicals, from expert peer review of the open scientific literature, |

# 用語の解説

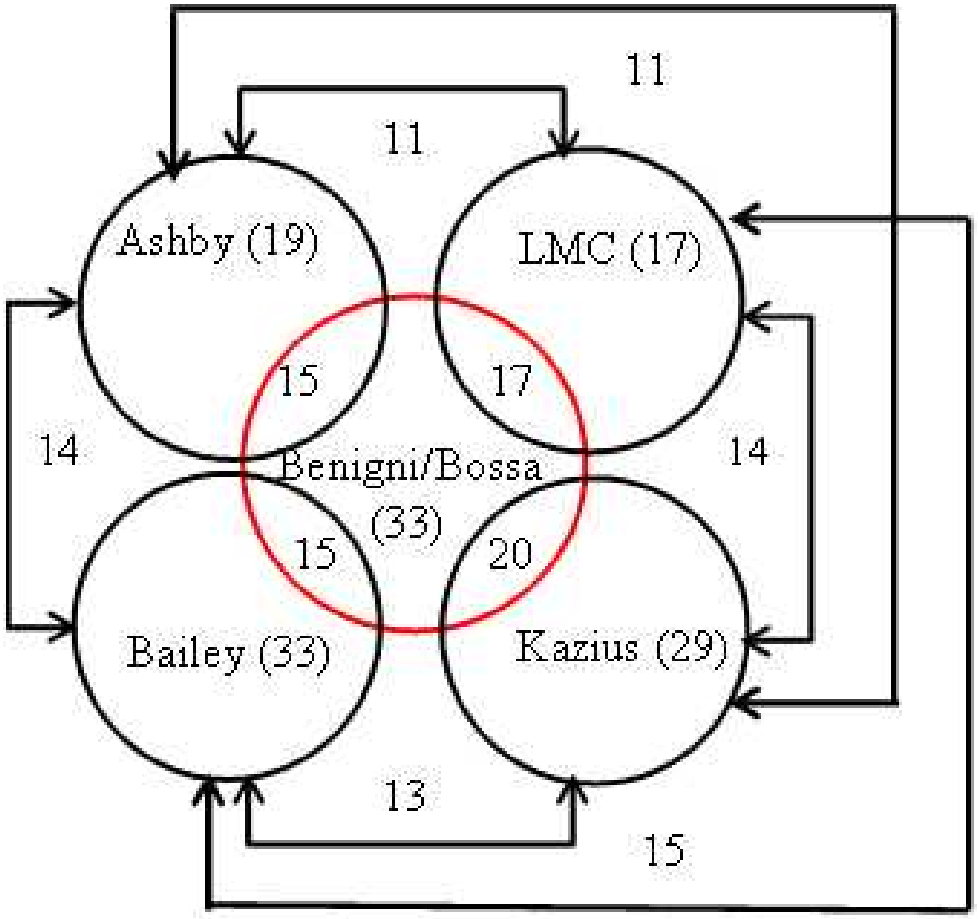
| 日本語 | 英語 | 解説 |
|---|---|---|
| トレーニングセット | training set | 構造活性相関モデルを作成する際に用いられた実測試験データのセット。 |
| 外部 | external validation | 予測性の評価などトレーニングセットに含まれていない化学物質の試験データを用いて、構造活性相関モデルの信頼性を評価すること。 |
| 記述子 | descriptor | 構造活性相関で用いる物質の構造上の特徴又は物理化学的性状のこと。例えば、分子量、部分構造、$LogP_{ow}$などが記述子となる。 本来の定量的構造活性相関では、エネルギーに換算可能な量のみが記述子となる。 |
| エキスパートシステム | expert system | 構造活性相関よる予測手法の一種。統計解析による予測式ではなく、専門家（エキスパート）が有する知見や経験則をルール化し、フローチャート等を用いて行なう予測。エキスパート予測による構造活性相関モデルをシステム化したものをエキスパートシステムという。 |
| 適用領域 | applicability domain | ある構造活性相関モデルが信頼できる予測結果を出すことができる物質の領域。通常、トレーニングセットの物質の構造上の特徴や記述子の範囲で定義される。OECD原則では、構造活性相関モデルの適用領域を明確に定義することが求められている。 |
| 感度 | sensitivity | あるエンドポイントにおいて、陽性か陰性かを予測する構造活性相関モデルで、実際に陽性である物質を予測したとき、それらの中で正しく陽性と予測された物質の割合。 |
| 特異度 | specificity | あるエンドポイントにおいて、陽性か陰性かを予測する構造活性相関モデルで、実際に陰性である物質を予測したとき、それらの中で正しく陰性と予測された物質の割合。 |

NITE構造活性相関に関する用語集より（http://www.safe.nite.go.jp/kasinn/qsar/qsar_pdf/qsar_glossary.pdf）

# 構造アラート(SA)による予測

- Ashby(1985); Ashby and Tennant(1988)：19 SAs
- Bailey et al. (2005): 33 SA for regulatory use
  based on Ashby list and Munro et al. List (1996).
- Kazius et al. (2005): 29 SA based on training set (2401 mutagens and 1936 non-mutagens)
- Laboratory of Mathematical Chemistry (Bourgas, Bulgaria): 17 SA
  (implemented in OASIS TIMES software)
- Benigni and Bossa (2008): 33 SA
  based on the above and OncoLogic (EPA)
  accuracy 78%: mutagenicity; 70%: carcinogenicity
  (implemented in OECD Toolbox)

# 構造アラート(SA)のオーバーラップ



# 構造活性相関モデルのタイプ

| タイプ | 代表的なモデル | 利点 | 欠点 |
|---|---|---|---|
| ルールベース | DEREK<br>HazardExpert<br>ToxTree<br>OECD Toolbox | 多くの文献や知識にサポートされたメカニズムに基づく理由によりサポートされる | アプリカブルドメインはしばしば制限されるか、曖昧になる。その為、統計モデルより精度が低くなる化学物質クラスが存在する |
| 統計アプローチ | MultiCASE<br>TOPKAT<br>Lazar<br>CAESAR | 作用メカニズムが不明な初期的な研究では精度が高い傾向になる | 通常メカニズムに基づく説明が提供されないので、使用者に対して、解析結果の透明性が低くなる |
| ハイブリッド | OASIS TIMES<br>Purdy model(論文のみ) | ルールベースと統計アプローチの利点を併せ持つので総じて精度は高い | アプリカブルドメインが制限される |

# 各ソフトウエアの概略と精度(1)

- CAESAR
  - Support Vector Machine (SVM) classification using 4225 compounds (Kazius-Bursi database) : 92.3% (training set) and 83.2%(test set)
  - two approaches (regression and classification) CPDB (raining and test set)

    Counter-Propagation Artificial Neural Network and MDL descriptors

    91-96% for the training set and 68-74% for the test set.
- DEREK
  - 89SA (mutagenicity), 77SA (chromosome damage), 61SA (carcinogenicity)

    sensitivity: 69% (False nagative : 31%) for 60 pesticides.
- Toxtree
  - the Benigni-Bossa rulebase
  - accuracy of prediction around 70%(carcinogenicity), 78%(mutagenicity)
- HazardExpert
  - toxicophores from the literature, taking into account bioavailability and bioaccumulation
  - 80 NTP chemicals (56 rodent carcinogens; 24 noncarcinogens),
  - concordance: 51%, (sensitivity: 36%; specificity: 81%) for 80 NTP chemicals

# 各ソフトウエアの概略と精度(2)

- Lazar
  - Training set :1447 (CPDB) and 4337 (Kazius/Bursi DB)
  - Leave-one-out accuracy: 86%;
  - other carcinogenicity endpoints accuracy 78 – 95% with applicability domain
- MDL QSAR
  - training set of over 1200 chemicals (pharmaceuticals, industrial chemicals and some natural products)
  - Test set :123 naturally occurring chemicals
  - concordance of 80% (sensitivity:97%, specificity of 53%)
- MultiCASE
  - widely used by authorities and largely in-house modifications
  - DanishEPA reported concordances: 56-100%(different models)
  - Sensitivity: 97%, specificity: 98% (126 chemicals at the optimized system)
  - MCASE model is not readily transferable, and the data used are confidential
- TOPKAT
  - accuracy of predictions: 99.6% (705 carcinogenicity dataset)
  - accuracy of prediction: 40-75% (30-40 chemicals external datasets)

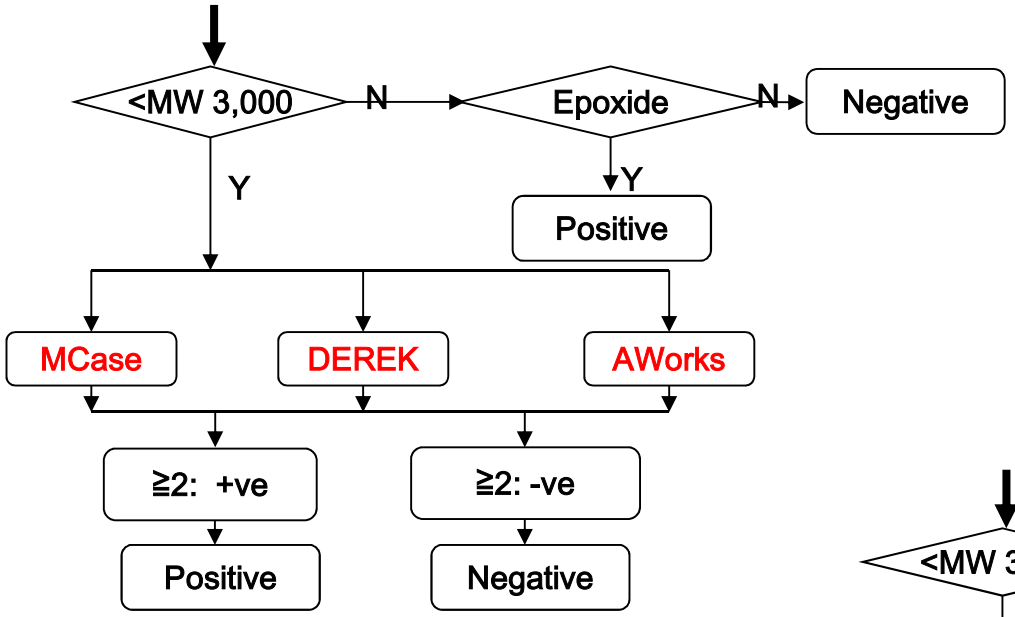
# 各モデルの精度比較研究

- NTP chemicals: 44 chemicals (Benigni and Zito, 2004).
  - CASE, TOPKAT, DfW, COMPACT (computer model)
  - Benigni, Tennant and Ashby, Weisburger and Lijinsky (human expert)
  - overall accuracy: 50-65%, but Tennant and Ashby approach: 75%
- CPDB database: 650 chemical (Mayer et.al. (2008)
  - Comparing carcinogenic prediction with several genotoxic tests
  - OncoLogic, MultiCASE, Ashby-Tennant SA (Computer model)
  - higher concordance frequency (71-88% vs 62-75% for genetic tests)
- 545 Drugs (Physicians Desk Reference 1999-2008) (Snyder (2009)
  - Derek and MCASE/MC4PC
  - Both performance are better than the in vitro genotoxic assays

    high specificity and overall concordance

    low sensitivity of both programs, but it was still higher than vitro assays.
- Battery approach (Matthews et al. 2008)
  - combined use MC4PC, MDL-QSAR, BioEpisteme, Leadscope PDM, Derek.
  - any two programs caused better overall performance than single programs , with a sensitivity ca 85%. Specificity:58%.

# *Combination (Q)SAR approach with three mutagenicity (Q)SAR models for industrial chemical assessments*




**Combination 1 of in silico outcomes**

| Ames test | In silico >++ | In silico >-- | Total |
|---|---|---|---|
| + | 19 | 7 | 26 |
| - | 23 | 147 | 170 |
| | 42 | 154 | 196 |

**Sensitivity 73.1 %**

**Specificity 86.5 %**

**Concordance 84.7 %**

**Applicability: 95.1% (196/206)**

**Combination 2 of *in silico* outcomes**

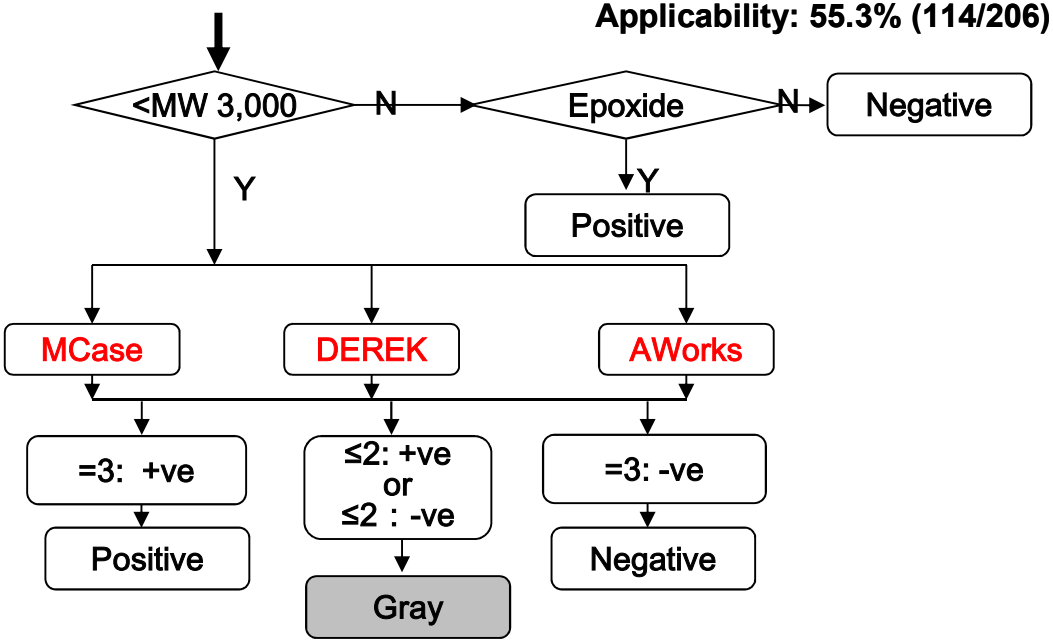
| Ames test | *In silico* +++ | *In silico* - - - | Total |
|---|---|---|---|
| + | 13 | 2 | 15 |
| - | 5 | 94 | 99 |
| | 18 | 96 | 114 |

**Sensitivity 86.7 %**

**Specificity 94.9 %**

**Concordance 93.9 %**

**Applicability: 55.3% (114/206)**






**Acknowledgements:** This work was supported by Health and Labour Sciences Research Grants of MHLW, Japan

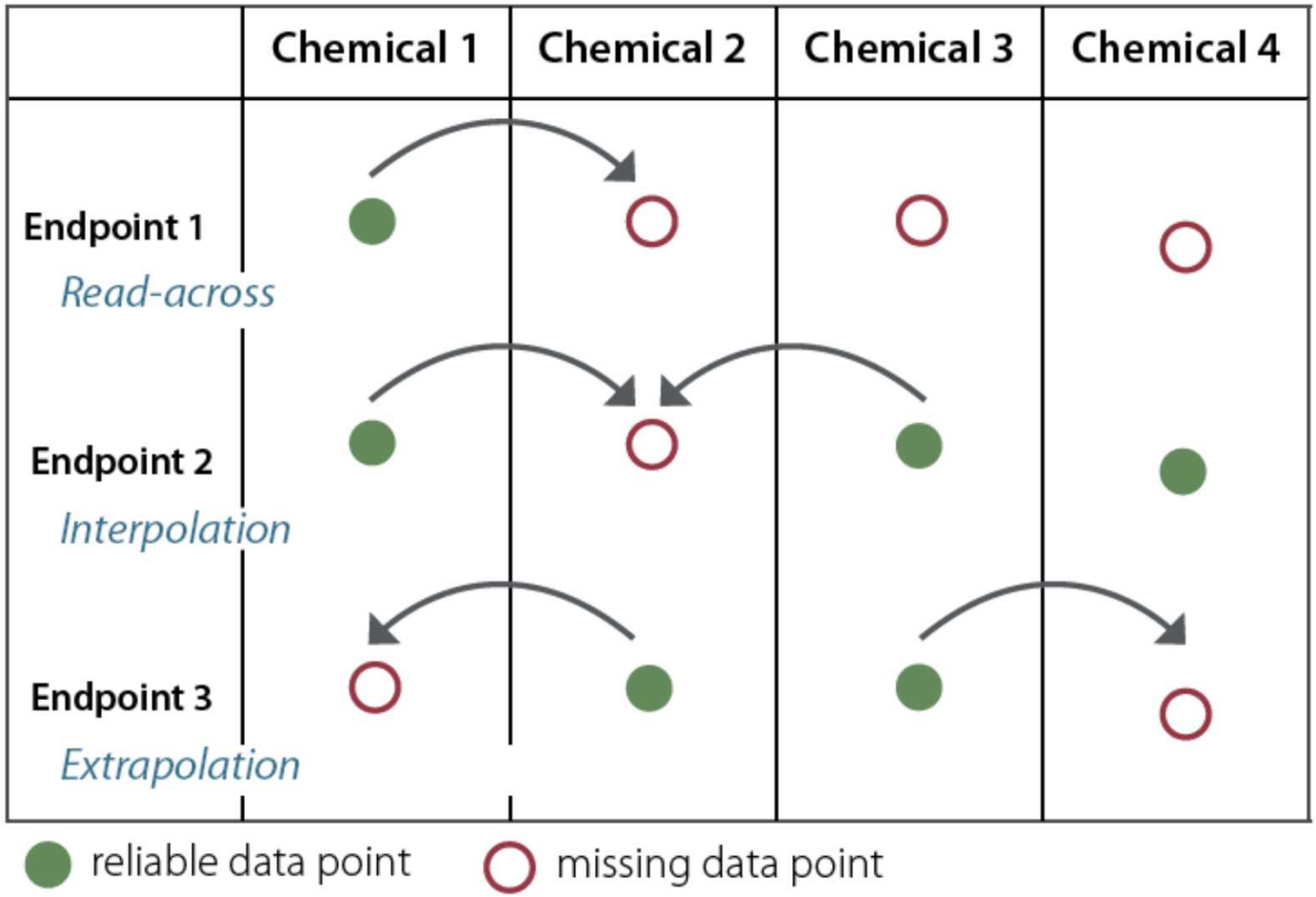
# 各ソフトウエアの概略と精度(3)

- OASIS/TIMES (hybrid approach)

  (for Ames mutagenicity and chromosomal aberration)
  - Expert knowledge was used for SAs and mechanistic basis prediction
  - A pattern recognition approach (COREPA) was used for modulating factors
  - include a liver metabolic simulator
- Oncologic (knowledge-based system)
  - hierarchically ordered rules for description and prediction
  - includes over 40,000 rules based on knowledge and generalisations from more than 10,000 chemicals and c.a. 50 chemical classes
  - requires some chemistry expertise
  - needed to take decisions step-by-step during the prediction
- OECD Tool box
  - implementing two “profilers” connected with genotoxicity and carcinogenicity

    Benigni-Bossa rule base and OASIS DNA binding profiler
  - includes a few databases with experimental data in order to support grouping and read-across

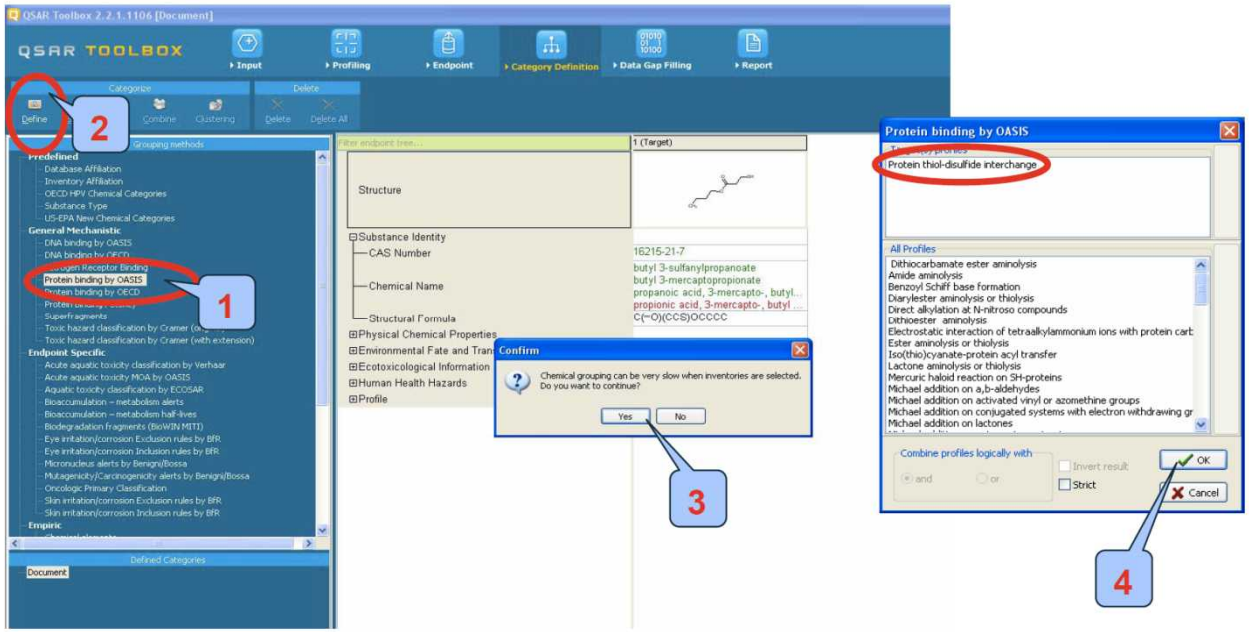
# QSAR/Category approach

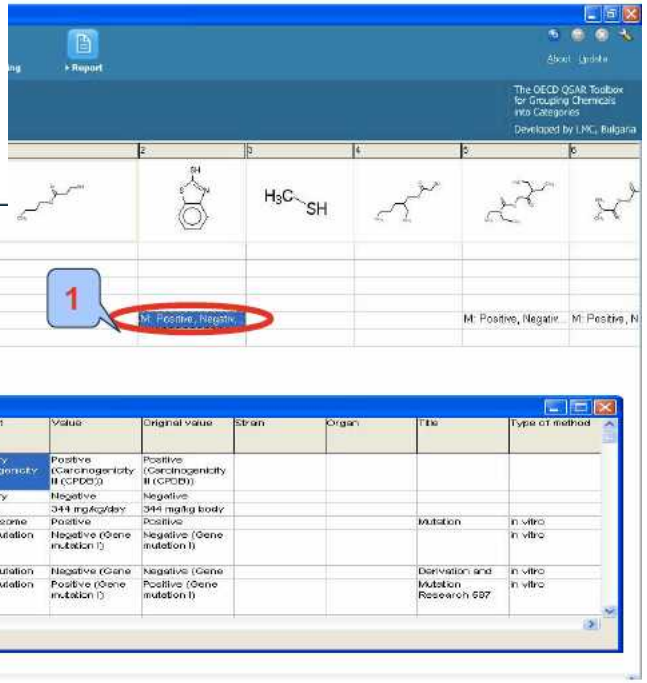



As illustrated above, a chemical category can be represented graphically as a two-dimensional matrix in which category members occupy different columns, and the category endpoints occupy different rows. Data gaps may be filled by read-across from a tested to an untested chemical or by trend analysis.

The OECD QSAR Toolbox for Grouping Chemicals into Categories

# Category definition




1.**Highlight** "Protein binding by OASIS"; 2. **Click** Define, the message that grouping could be slow due to selected inventories appears; 3. **Click** Yes; 4. Confirm the category Protein thiol-disulphide interchange and **click** OK.

**1.Double-click** on the cell with measured data to see detailed information on the data point.

In cooperation:

OECD
BETTER POLICIES FOR BETTER LIVES

ECHA
EUROPEAN CHEMICALS AGENCY

## Donation (for Ver. 2.1) of database, profiler or QSAR from:

The United States Environmental Protection Agency (US-EPA)
Istituto Superiore de Sanita, Italy
European Commission
Environment Canada
Danish Environmental Protection Agency
RIVM, the Netherlands
Ministry of the Environment, Japan
Ministry of Health, Labour and Welfare,Japan
Ministry of Economy, Trade and Industry (METI), Japan
New Energy and Industrial Technology Development Organization (NEDO),Japan
European Centre for Ecotoxicology of Chemicals (ECETOC)
European Chemical Industry Council (CEFIC)
Fraunhofer Institute of Toxicology and Experimental Medicine, Germany
Laboratory of Mathematical Chemistry (LMC),Bulgaria
German Federal Institute for Risk Assessment (BfR)
University of Vienna, Austria
University of Tennessee, Knoxville,
Istituto Superiore de Sanita, Italy; Office of Public Health, Switzerland
Research Institute for Fragrance Materials (RIFM);
International QSAR Foundation
Multicase Inc.; ChemAxon;
Exxon Mobil; Unilever; P&G; L'Oréal; Dow Chemical;