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Prediction of Toxicology from Chemical Structure: DEREK and Other Software

Tox'2017 Hungary

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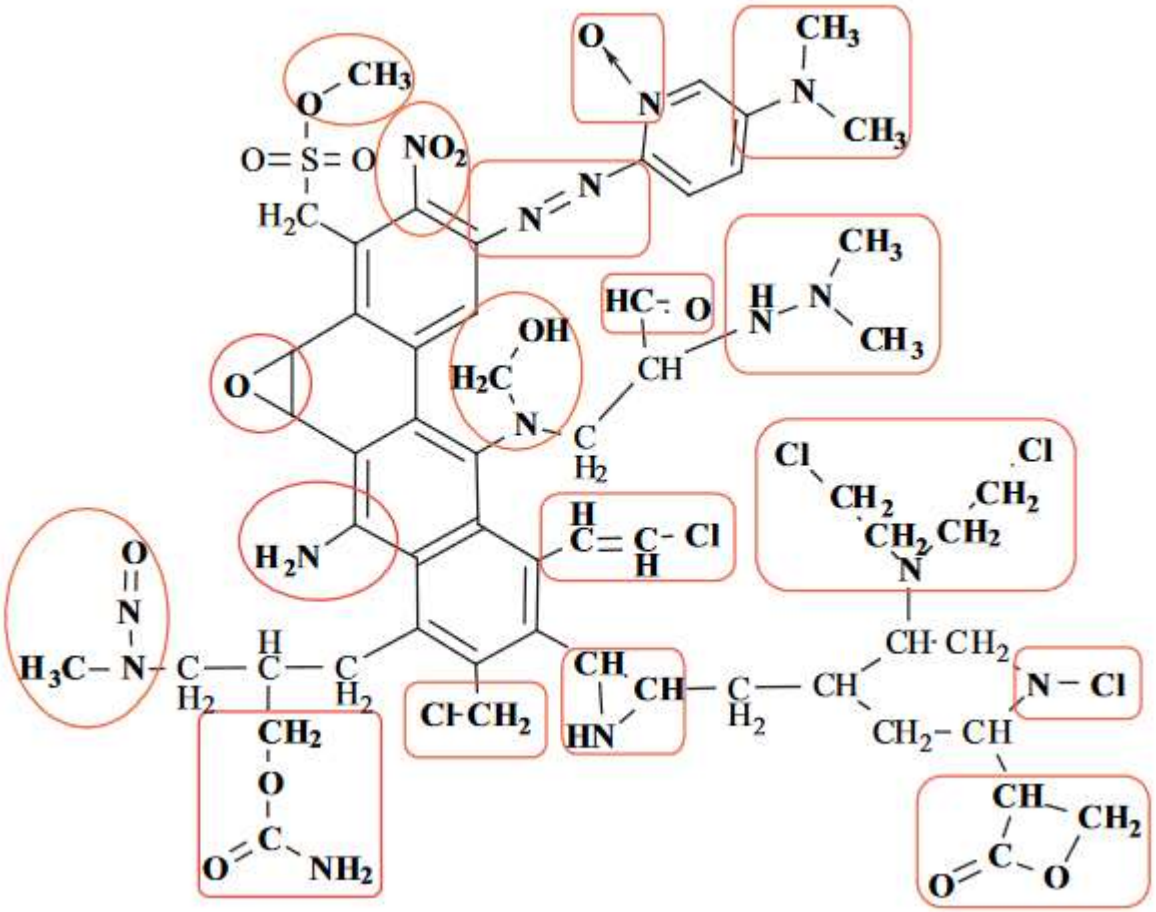
QSAR

- Structure–activity relationship models (QSAR models)



Ashby, J.; Tennant, R.W. Mutat. Res.,1988

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The Objectives for QSARs

"To be able to predict accurately chemical toxicities with in silico software for all toxicological endpoints of interest”

"Substantially reduce, replace and refine the need for animal toxicological testing in establishing the safety of chemical substances”

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QSAR

Regulatory Uses of QSARs

- Pharmaceutical Impurities (USA-FDA, EMA, Japan etc)

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Regulatory Uses of QSARs

- Pharmaceutical Impurities (USA-FDA, EMA, Japan etc)
- Agricultural Chemicals (EFSA, South America, USA-EPA, Asia)

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QSAR

Regulatory Uses of QSARs

- Pharmaceutical Impurities (USA-FDA, EMA, Japan etc)
- Agricultural Chemicals (EFSA, South America, USA-EPA, Asia)
- REACH, K-REACH, Other Chemical regulations

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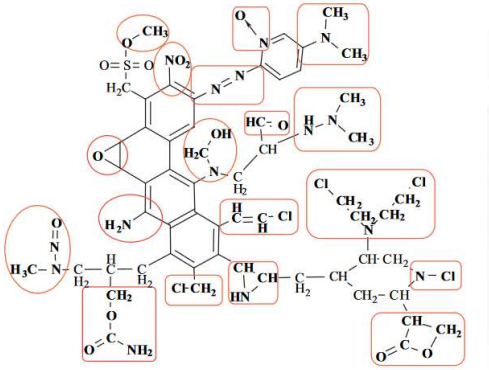
QSAR vs SAR

- Quantitative structure–activity relationship models (QSAR models) are regression models used in the chemical and biological sciences. QSAR regression models relate a set of "predictor" variables (X) to the potency of the response variable (Y). The relationship is mathematical.

- Structure–activity relationship systems (SAR systems) do not use a mathematical approach. These include expert systems, identification of substructures, literature or data-set relationships or other ways to look for some characteristic on the test structure which indicates a potential biological effect.



Both are commonly called "(Q)SAR"

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(Q)SAR Quality

- Mathematical QSARs are based on a 'teaching set' of chemicals with chemical descriptors, plus known endpoints (toxic effects or physicochemical measurements etc).
- The QSAR models are then developed after looking for correlations between the chemical descriptors and the specific endpoint.
- The quality of the data in the 'teaching set' is critical.
- The chemical descriptors need to be extensive but not excessive.
- The degree of correlation needs to be understood.
- All good (Q)SARs in toxicology are evolving continually!
- The real quality of the QSAR is related to the actual relationship between the chemical structure and the endpoint !

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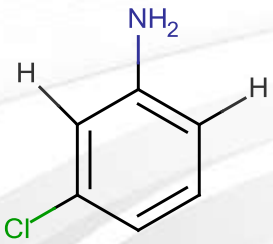
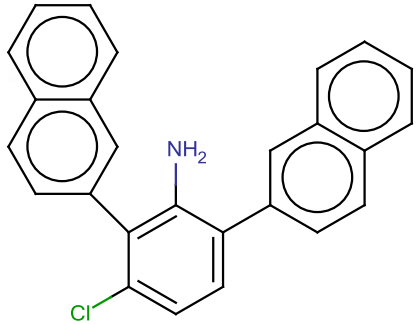
(Q)SAR Quality

- SARs as literature or ”expert” systems are not based on statistical correlations – but are based on Knowledge of Experts
- For Example DEREK is a rule-base system, where approx 1000 rules have been developed for a wide range of endpoints
- The quality of the experts is critical
- The chemical descriptors need to be adequately discriminating.
- The output needs to be understood and put into context!





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DEREK

- The original DEREK expert was Derek Sanderson
- LHASA UK made a software SAR system to try to retain the knowledge of Derek
- Large companies joined a collaboration and shared their expert knowledge to make DEREK into a very useful tool
- The software was originally based on retro-synthesis, but has now been upgraded to NEXUS software

- The organisation is “not-for-profit”, participating companies help improve and build rules
- Most of the world’s biggest Pharma, Agro and Chemical companies, as well as Regulatory agencies and Universities are part of the collaboration
- Updated Rules are issued every 6-month – 1 year

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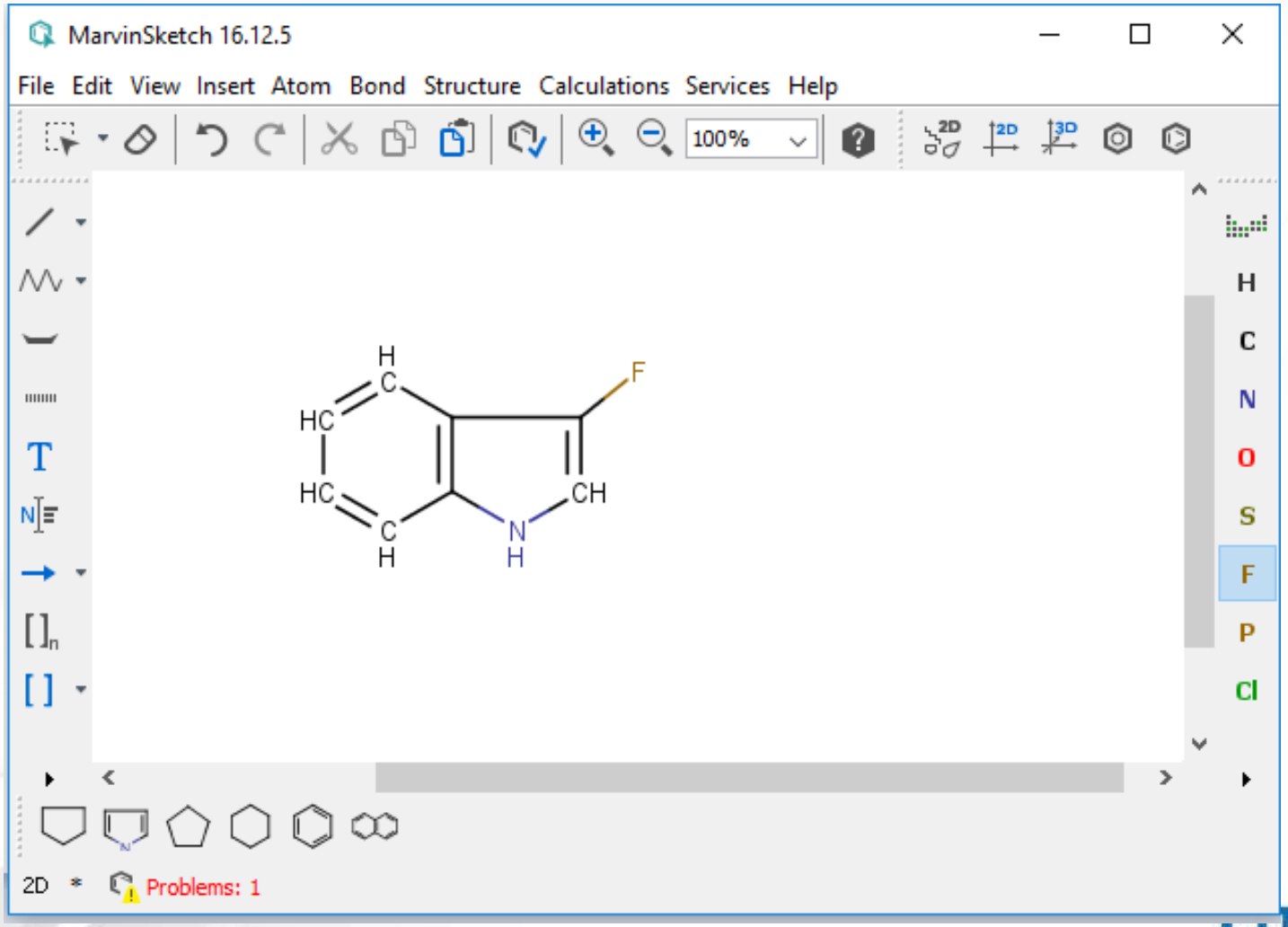
DEREK

- Input is via DRAW or MOL files



DEREK

- Alerts:

Adrenal gland toxicity
alpha-2-mu-Globulin nephropathy
Anaphylaxis
Bladder disorders
Bladder urothelial hyperplasia
Blood in urine
Bone marrow toxicity
Bradycardia
Carcinogenicity
Cardiotoxicity
Cerebral oedema
Chloracne
Cholinesterase inhibition
Chromosome damage in vitro
Chromosome damage in vivo
Cumulative effect on white cell count and immunology
Cyanide-type effects
Developmental toxicity
Hepatotoxicity
HERG channel inhibition in vitro
High acute toxicity
Irritation (of the eye)
Irritation (of the gastrointestinal tract)
Irritation (of the respiratory tract)
Irritation (of the skin)
Kidney disorders
Kidney function-related toxicity
Lachrymation
Methaemoglobinaemia
Mitochondrial dysfunction
Mutagenicity in vivo
Nephrotoxicity
Neurotoxicity
Non-specific genotoxicity in vitro
Non-specific genotoxicity in vivo
Occupational asthma
Ocular toxicity
Oestrogenicity
Peroxisome proliferation
Phospholipidosis
Photo-induced chromosome damage in vitro
Photo-induced non-specific genotoxicity in vitro
Photo-induced non-specific genotoxicity in vivo
Photoallergenicity
Photocarcinogenicity
Photomutagenicity in vitro
Phototoxicity
Pulmonary toxicity
Respiratory sensitisation
Splenotoxicity
Teratogenicity
Testicular toxicity
Thyroid toxicity
Uncoupler of oxidative phosphorylation
Urolithiasis

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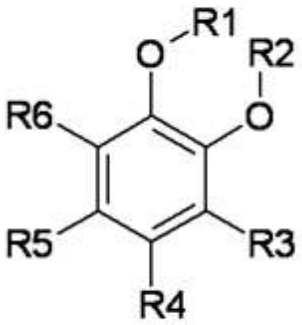
QSAR – Example of DEREK report

Alert overview: 418 Catechol or precursor. Skin sensitisation



Bonds from phenyl ring to R3-R6 may be single or aromatic

R1 = H, acyl
R4, R6 = any except O (not bound to any heteroatoms)

(I) if R2 = H, acyl, CH3, CH2CH3
then R3, R5 = any except O (not bound to any heteroatoms)

(II) if R2 = any other alkyls
then R3, R5 = C (alkene, alkyne or aromatic)

Comments:

This alert describes the skin sensitisation of catechols as well as their ester and ether precursors, as illustrated in toxicophores (I) and (II). These compounds have been reported as moderate to strong sensitisers in the guinea pig maximisation test (GPMT) and in the murine local lymph

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(Q)SAR Prediction Quality

Regulatory decisions using in silico data are made in the absence of some safety information you would like to have (impurities, metabolites, quality of the models used, unknown other endpoints or mechanisms).

Evaluating (Q)SAR systems is not easy. Often a good correlation is found during evaluation, but in real-life situations a less good correlation is found.

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Types of (Q)SAR that might be used for Chemicals

- Physico-chemical properties : e.g. oxidising, explosivity, vapour pressure, LogKow, flash point, etc.

- Absorption, distribution, metabolism

- Degradation, hydrolysis, ecotoxicity (fish, daphnia, algae), bioconcentration (BCF)

- Human health endpoints, e.g. acute toxicity, skin irritation, sensitization, reprotoxicity, endocrine disruption, mutagenicity, genotoxicity, cancer, etc.

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Some Examples of (Q)SAR systems used

- DEREK (Meteor & SANDRA)
- Leadscope
- OECD (Q)SAR Application Toolbox
- Episuite
- Specialist Physical Chemistry Systems

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USA FDA/EPA Use of (Q)SARs

Prediction Suite	Models	Chems	Records
• Carcinogenicity	7	1,584	24,708
• Genetic toxicity	20	8,200	> 27,498
• Reproductive toxicity	9	686	
• Developmental toxicity	27	2,115	51,724
• Behavioral toxicity	3	503	
• Phospholipidosis	1	583	227
• Quantitative MTD	8	1,266	3,925
• Organ specific toxicities		R&D	
• Regulatory dose conc.		R&D	
• Neurotoxicity		R&D	

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QSAR for Agrochemicals

Regulatory Uses of QSARs

EU Agrochemical Companies make QSAR reports for registraton of Actives

- Impurities in the Technical AI
- Metabolites identified in the rat, goat, chicken studies etc.
- Soil metabolites that may enter Ground Water (seen in Lysimeter studies)

- Reports cover mainly the Genotoxic and Neurotoxic potential of each chemical structure based on a (Q)SAR assessment expert report.

•**South American QSAR – Require LD50 and Other Toxicity Endpoint Assessment by QSAR**

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Regulatory Uses of QSARs

- Pharmaceutical Impurities (USA-FDA, EMA, Japan etc)

ICH HARMONISED TRIPARTITE GUIDELINE

ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK

M7

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Regulatory Uses of QSARs

- Pharmaceutical Impurities (USA-FDA, EMA, Japan etc)

- The main issue for Pharmaceuticals is making a Mutagenicity assessment, based on:
  - Chemical Structure
  - Concentration and Daily Intake
  - Duration of Drug use and Patient Population

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QSAR - Introduction

The synthesis of drug substances involves the use of reactive chemicals, reagents, solvents, catalysts, and other processing aids. As a result of chemical synthesis or subsequent degradation, impurities reside in all drug substances and associated drug products

The purpose of this guideline is to provide a practical framework that is applicable to the identification, categorization, qualification, and control of these mutagenic impurities to limit potential carcinogenic risk

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The focus of this guideline is on DNA reactive substances that have a potential to directly cause DNA damage when present at low levels leading to mutations and therefore, potentially causing cancer.

Structure-based assessments are useful for predicting bacterial mutagenicity outcomes based upon the established knowledge.

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A computational toxicology assessment should be performed using (Q)SAR methodologies that predict the outcome of a bacterial mutagenicity assay. **Two (Q)SAR prediction methodologies that complement each other should be applied**. One methodology should be expert rule-based and the second methodology should be statistical-based.

The absence of structural alerts from two complementary (Q)SAR methodologies (expert rule-based and statistical) is sufficient to conclude that the impurity is of no mutagenic concern, and no further testing is recommended.

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Table 1: Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions

Class	Definition	Proposed action for control (details in Section 7 and 8)
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (appropriate TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data	Control at or below acceptable limits (appropriate TTC) or conduct bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance or compounds related to the drug substance (e.g., process intermediates) which have been tested and are non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity or carcinogenicity	Treat as non-mutagenic impurity

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Domain of Applicability – A Very important Part of the Judgement

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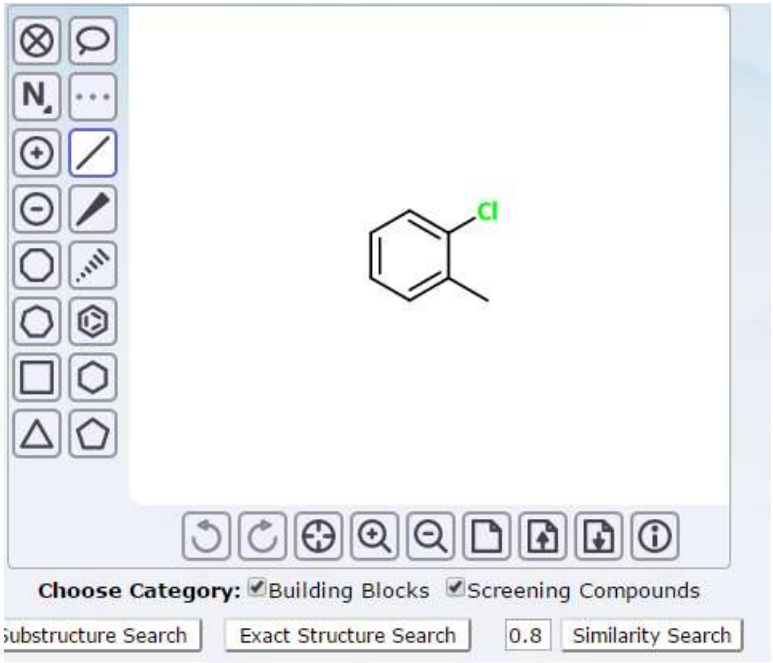

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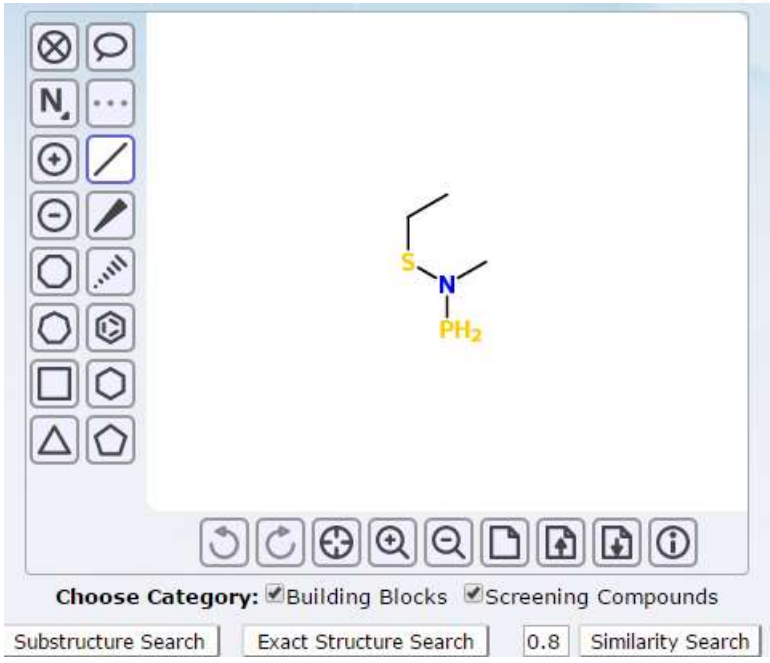

http://www.emolecules.com/

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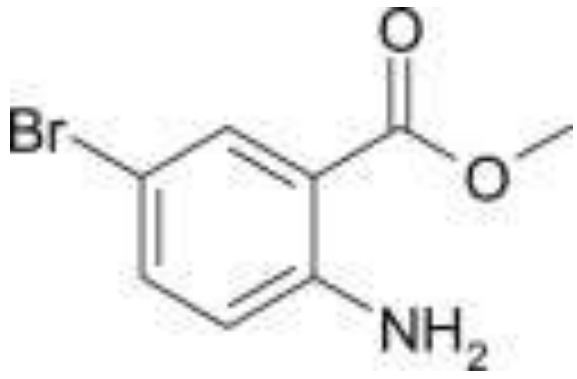
(Q)SAR – Some Examples



predicted to be negative by the expert rule-based methodology and inconclusive by the statistical-based methodology

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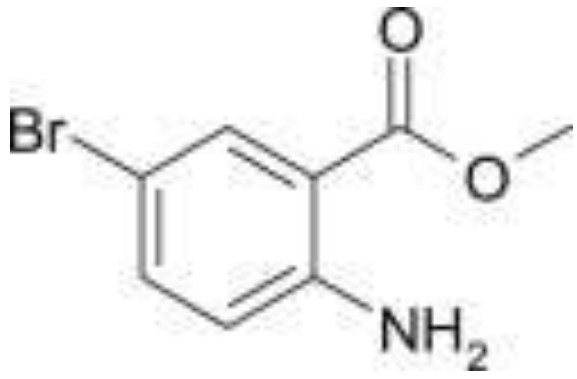
(Q)SAR – Some Examples



predicted to be negative by the expert rule-based methodology and inconclusive by the statistical-based methodology

Primary aromatic amines are mutagenic only in the presence of an activating functional group. Both functional groups (the bromo group in the para position and the carboxylate in the ortho position) are not activating. So it was predicted to be non-mutagenic. This compound has been tested in a standard Ames assay using 5 strains and is non-mutagenic

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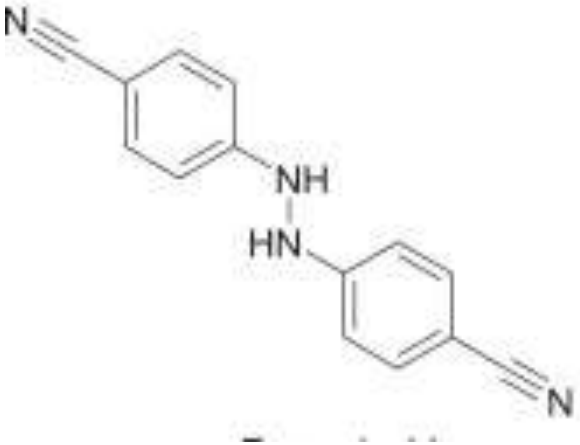
(Q)SAR – Some Examples



predicted to be negative by the expert rule-based methodology and inconclusive by the statistical-based methodology

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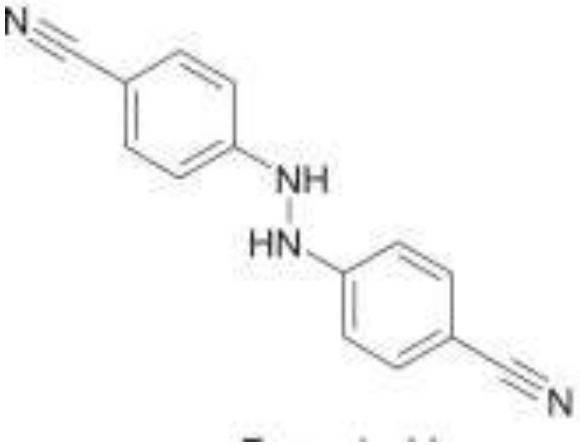
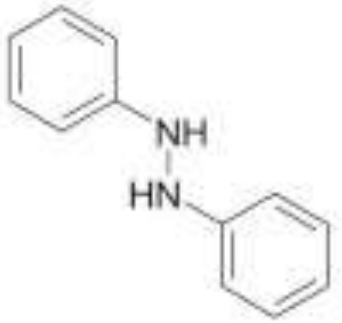
(Q)SAR – Some Examples





Positive analog

predicted to be negative by the expert rule-based methodology and inconclusive by the statistical-based methodology

Contains a hydrazine substructure and specific classes of hydrazines are known to be mutagenic, an analysis based on the evaluation of published Ames assay data for structural analogs was performed. This assessment led to the identification of structural analogs tested in the Ames assay including the analog shown above that was reported to be mutagenic.

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(Q)SAR – Some Examples

Aminoacetonitrile was out-of-domain for the statistical-based models and predicted to be negative by the expert rule-based model.

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(Q)SAR – Some Examples

Analogs

 Negative	 Negative	 Negative
 Negative	 Negative	 Negative
 Negative	 Negative	 Positive

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HOW TO DO (Q)SAR – some advice:

- Look at the chemical structure, make an evaluation about its similarity to other known molecules with good data sets.
- Decide what endpoints are of interest. Some (Q)SAR systems help in this.
- Decide which (Q)SAR systems and endpoints are most appropriate.
- Look carefully at the output and the Domain of Applicability for each (Q)SAR, use expert judgement to decide on the relevance of each.
- Look at substructures, search for known molecules with similar features
- Take all the data from all the outputs, along with literature and in-house data on similar molecules.
- Make a holistic analysis, pulling together all relevant information, for a Weight of Evidence approach for an overall assessment.

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HOW TO DO (Q)SAR – some advice:

•For most REACh type applications, if the Domain of Applicability is good enough the (Q)SAR can be used in the Weight of Evidence to make a judgement. ECHA gives advice on how to do this *(e.g. Non-testing methods, such as SAR, QSAR and read-across approaches, may also provide information on the mutagenic potential of a substance.)*

•QSARs and grouping of chemicals (available at http://echa.europa.eu/web/guest/guidance-documents/guidance-on-informationrequirements-and-chemical-safety-assessment) explains basic concepts of (Q)SARs and gives generic guidance on validation, adequacy and documentation for regulatory purposes.

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HOW TO DO (Q)SAR – some advice:

- (Q)SARs can be very useful for identification of potential issues early – Important for non-regulatory Chemical Discovery/Development.

- (Q)SARs can help reduce animal use when positive findings allow a classification based on the (Q)SAR.

- In some cases, a negative (Q)SAR means that a study is required to prove the negative.

- On a case-by-case basis , sometimes a (Q)SAR approach can be used to fully replace experiments, but this is relatively unusual currently.

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Recap:

- Introduction to (Q)SARs
- Types of Regulatory Use of (Q)SARs
- Types of (Q)SARs that may be used for Chemicals
- DEREK, history and practical use
- Regulatory use of (Q)SARs
- QSAR for Agrochemicals
- Regulations for Pharmaceuticals
- Domain of Applicability
- Examples of (Q)SAR evaluations
- How to do (Q)SAR analysis – some advice
- References

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QSAR - References

ELSEVIER

Regulatory Toxicology and Pharmacology

Volume 77, June 2016, Pages 13-24

Principles and procedures for implementation of ICH M7 recommended (Q)SAR analyses ☆

Alexander Amberg [a], Lisa Beilke [b], Joel Bercu [c], Dave Bower [d], Alessandro Brigo [e], Kevin P. Cross [d], Laura Custer [f], Krista Dobo [g], Eric Dowdy [c], Kevin A. Ford [h], Susanne Glowienke [i], Jacky Van Gompel [j], James Harvey [k], Catrin Hasselgren [d], Masamitsu Honma [l], Robert Jolly [m], Raymond Kemper [n], Michelle Kenyon [g], Naomi Kruhlak [o], Penny Leavitt [f], Scott Miller [d], Wolfgang Muster [e], John Nicolette [p], Andreja Plaper [q], Mark Powley [o], Donald P. Quigley [d], M. Vijayaraj Reddy [r], Hans-Peter Spirkl [a], Lidiya Stavitskaya [o], Andrew Teasdale [s], Sandy Weiner [t], Dennie S. Welch [p], Angela White [k], Joerg Wichard [u], Glenn J. Myatt [d] ✉

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QSAR - References

DEREK

http://www.lhasalimited.org/ich-m7.htm

LEADSCOPE

http://www.leadscope.com/white_papers/ICHM7-WhitePaper-0314.pdf

MULTICASE

http://www.multicase.com/case-ultra

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Thank you for your attention !

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