Filling information gaps with QSAR (Quantitative Structure-Activity Relationship) predictions for 600,000 chemical substances for Reduction, Replacement, Prioritization and Substitution

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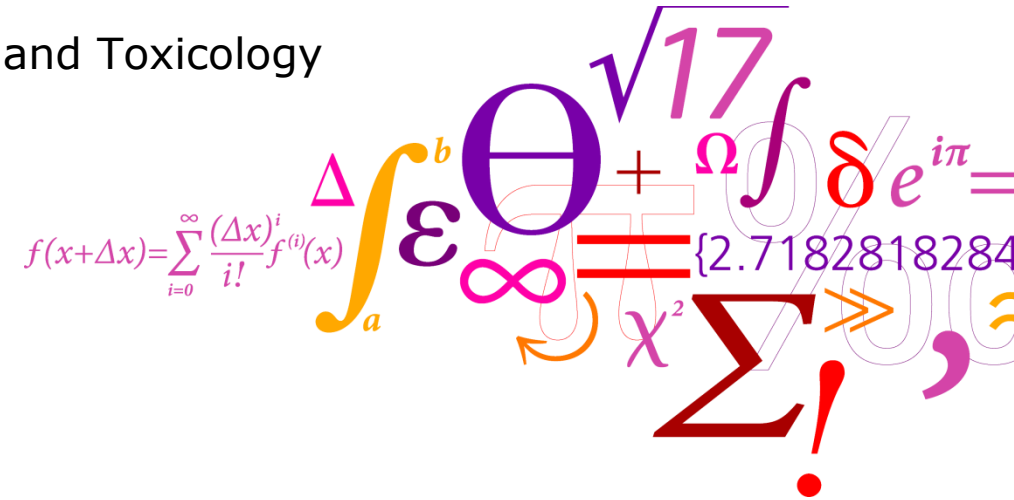
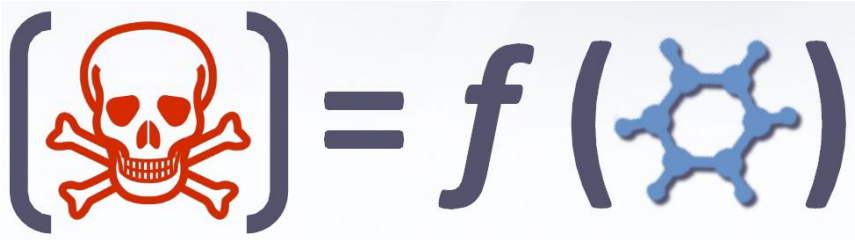
Division of Diet, Disease Prevention and Toxicology



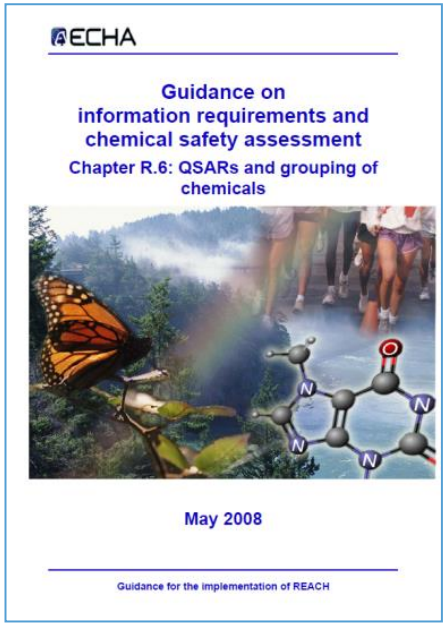
DTU Food
National Food Institute

Definition of QSAR: Quantitative Structure-Activity Relationship

- **A QSAR is a mathematical model** (often a statistical correlation) relating one or more parameters derived from chemical structure to a property or activity, e.g. a toxicological endpoint



See e.g. **EU chemicals legislation, REACH, guidance R.6**: "QSARs and grouping of chemicals" for more information
http://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf

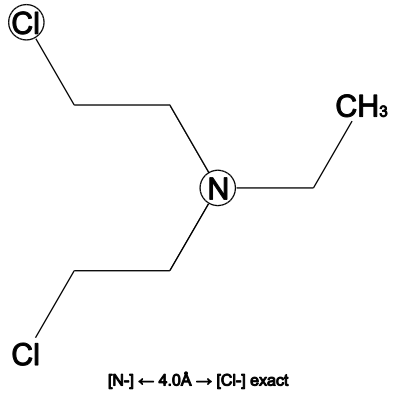


The non-test concept

Non-testing data can be generated by three main approaches:

- **(Q)SARs,** (quantitative) structure-activity relationships
- **read-across,** either by using a category or an analogue approach
- **expert systems**

Non-testing methods are based on the **similarity hypothesis** that molecules of similar structure have similar behaviour



”Pre-computer” QSAR – from 1899

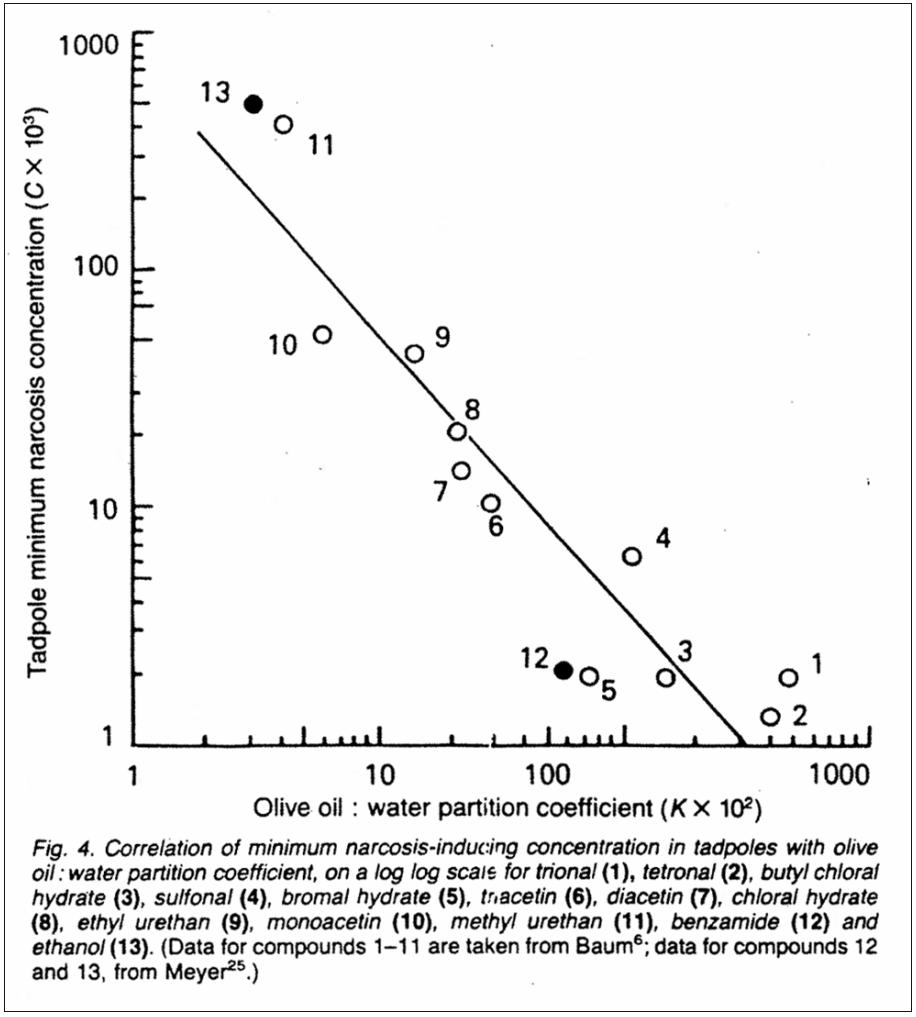


Fig. 4. Correlation of minimum narcosis-inducing concentration in tadpoles with olive oil : water partition coefficient, on a log log scale for trional **(1)**, *tetronal* **(2)**, *butyl chloral hydrate* **(3)**, *sulfonal* **(4)**, *bromal hydrate* **(5)**, *triacetin* **(6)**, *diacetin* **(7)**, *chloral hydrate* **(8)**, *ethyl urethan* **(9)**, *monoacetin* **(10)**, *methyl urethan* **(11)**, *benzamide* **(12)** *and ethanol* **(13)**. (Data for compounds 1–11 are taken from Baum[6]; data for compounds 12 and 13, from Meyer[25].)

Fritz Baum, Arch. Exper. Pathol. Toxikol., 42, p. 119-137, 1899:

QSAR for Tadpole **minimum narcosis concentration** for human anaestetic agents used for surgery

The use of QSAR methods to predict the results of test methods has been a part of chemical engineering for more than 100 years

Today's (Q)SAR computer software

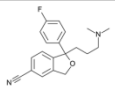
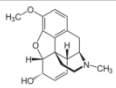
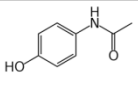
- **Commercial systems** can be licensed (often expensive):
  Leadscope Predictive Data Miner, MC4PC/CASE Ultra, SciQSAR, TOPKAT, ACD Percepta / Tox Suite, Lhasa Derek/Sarah/Meteor Nexus, HazardExpert, OASIS TIMES and COREPA, TerraQSAR, PASS, Molcode Toolbox, Admet Predictor, Symmetry, MultiCASE META etc.

- More and more **free systems** are also available:
  OECD QSAR Application Toolbox, US EPA EPI Suite (EPIWEB), VEGA/CAESAR, Toxtree, Lazar, OSIRIS, T.E.S.T., MetaPrint2D, SMARTCyp, MetaPath, DTU Food/DK-EPA QSAR predictions database etc.

See more e.g. on www.antares-life.eu under Software

QSAR development and use

- Experimental information already obtained for the property (e.g. a toxicity effect): A **training set**
- **Computer software analysis** to find relationships between structural descriptors and modelled property -> **mathematical equations**
- Many different QSAR **techniques** (regression, neural networks, classification methods etc.)

	A	B	C	D	E
1	CAS number	59729-33-8	76-57-3	103-90-2	etc.
2	Structure information				etc.
3	Effect / property information	X	Y	X	etc.

Training set

Analysis -> model

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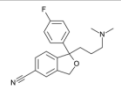
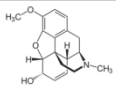
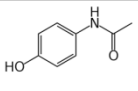
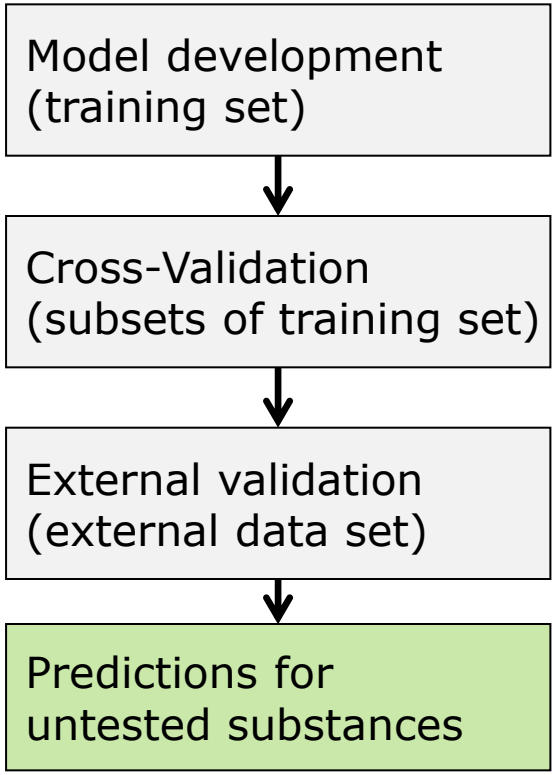
2	Structure information				etc.
3	Effect / property information	X	Y	X	etc.

Training set

Analysis -> model

Example: QSAR model for Ames (Bacterial Reverse Mutation Test)

- **Training set**: 4,102 substances (2,299 Active and 1,803 Inactive)
- Leave-many-out cross-validation: Concordance **86.4%**
- External validation with 1,088 substances: Concordance **88.0%**



A QSAR model can contain many sub-models for different chemical classes

Reliability of QSARs – our experience

- It depends (of course) on the endpoint
  – models are **not better than the underlying data**

- Often the **experimental variance is unknown**

- Concordances most often between **70-85%, in some cases >90%**

- Applicability domain often **30-50% of 72,524 REACH** pre-registered organic chemical substances with known structure

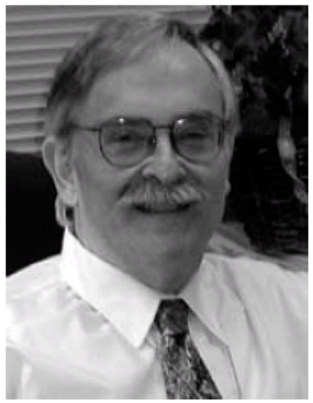
"Essentially, all models are wrong, but some are useful."
George E.P. Box

Current Drug Discovery Technologies, 2004, *1*, 61-76

Assessment of the Health Effects of Chemicals in Humans: I. QSAR Estimation of the Maximum Recommended Therapeutic Dose (MRTD) and No Effect Level (NOEL) of Organic Chemicals Based on Clinical Trial Data[1]

Edwin J. Matthews*, Naomi L. Kruhlak, R. Daniel Benz, and Joseph F. Contrera

U.S. Food and Drug Administration, 5600 Fishers Lane (HFD-901), Rockville, Maryland 20857, USA



ABSTRACT: The primary objective of this investigation was to develop a QSAR model to estimate the no effect level (NOEL) of chemicals in humans using data derived from pharmaceutical clinical trials and the *MCASE* software program. We believe that a NOEL model derived from human data provides a more specific estimate of the toxic dose threshold of chemicals in humans compared to current risk assessment models which extrapolate from animals to humans employing multiple uncertainty safety factors. A database of the maximum recommended therapeutic dose (MRTD) of marketed pharmaceuticals was compiled. Chemicals with low MRTDs were classified as high-toxicity compounds; chemicals with high MRTDs were classified as low-toxicity compounds. Two separate training data sets were constructed to identify specific structural alerts associated with high and low toxicity chemicals. A total of 134 decision alerts correlated with toxicity in humans were identified from 1309 training data set chemicals. An internal validation experiment showed that predictions for high- and low-toxicity chemicals were good (positive predictivity >92%) and differences between experimental and predicted MRTDs were small (0.27–0.70 log-fold). Furthermore, the model exhibited good coverage (89.9–93.6%) for three classes of chemicals (pharmaceuticals, direct food additives, and food contact substances). An additional investigation demonstrated that the maximum tolerated dose (MTD) of chemicals in rodents was poorly correlated with MRTD values in humans (R^2 = 0.2005, n = 326). Finally, this report discusses experimental factors which influence the accuracy of test chemical predictions, potential applications of the model, and the advantages of this model over those that rely only on results of animal toxicology studies.

Maximum Recommended Daily Dose model

Training set

- 1,309 drugs with data from human clinical trials

Cross-validation

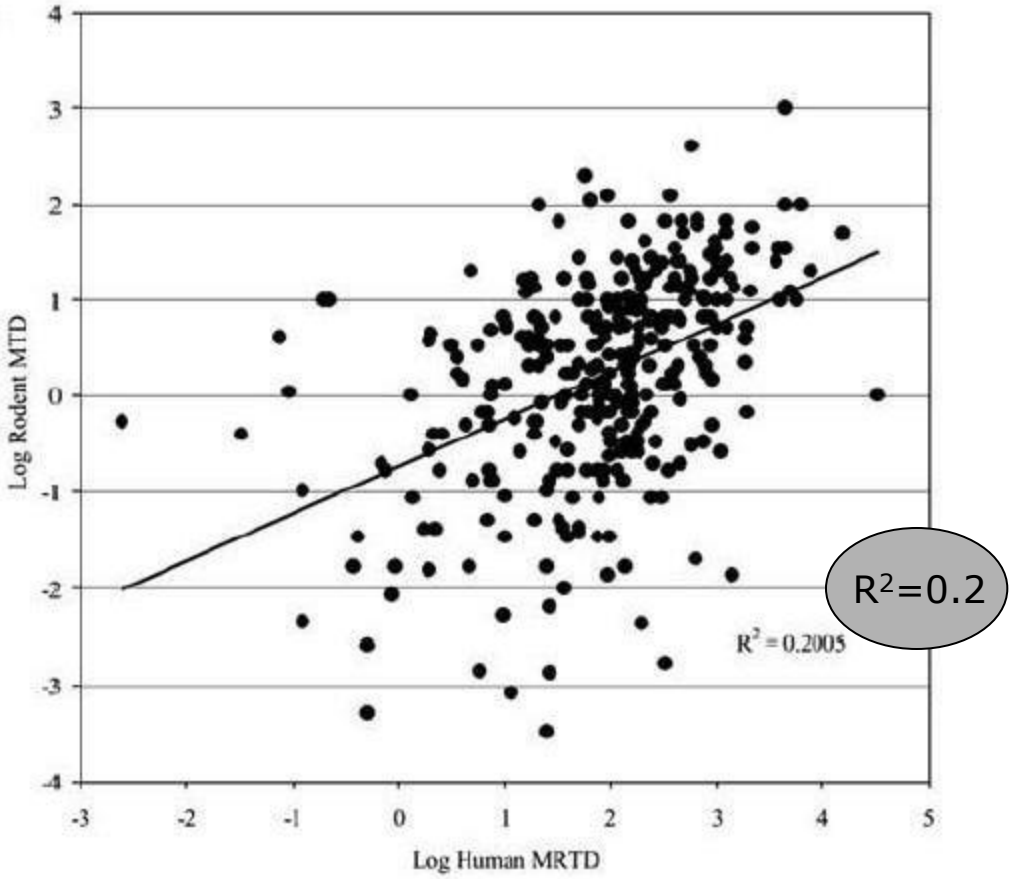
- Sensitivity = 74.0%
- Specificity = 95.2%

DTU version

- 49% of 72,524 REACH substances are within applicability domain

MRDD: estimated upper dose limit beyond which a drug's **efficacy is not increased** and/or undesirable **adverse effects begin to outweigh** beneficial effects. Derived from 3-12 months treatment period.

Fig. (5). Plot of the MRTD values versus the rodent MTD values expressed as logarithms for a set of 326 chemicals.



MTD (Maximum Tolerated Dose) is a dose beyond which toxicity may result in an unacceptable effect on survival in a two year carcinogenicity study. Derived from 18-24 months treatment period in rodents.

MRDD model – in summary

- A (Q)SAR model was made **directly on human data**
- It can be argued that the **predictions** from this (Q)SAR model give a **more accurate estimate of Human toxic dose level** than those derived from repeat-dose tests in rodents
- Once a (Q)SAR model is made predictions can be generated for 72,524 REACH substances in **few hours**
- **Drugs can be a very important source of information** for other types of chemical substances

Clinical trials can identify adverse effects of pharmaceuticals in humans that are poorly assessed in animal toxicology studies (*e.g.* cognitive and mood altering effects, *etc*.).

Other FDA models made on human data

Commercial FDA suites made on clinical data:

- Human Adverse **Hepatobiliary** Effects Suite, 5 models
- Human Adverse **Cardiological** Effects Suite, 13 models
- Human Adverse **Urinary Tract** Effects Suite, 6 models

Replacement – directly or supporting

- In some cases QSAR predictions can be used to **fill data gaps**, replacing experimental tests

- In many cases they can **support assessments** – for example:
  - in development of **read-across** cases
  - to improve **evaluation of reliability of test data**
  - in **weight-of-evidence** approach

- Furthermore, QSARs can provide information **beyond the regulatory standard information requirements**

- Often, many QSAR models exist for the same *in vivo* endpoint and/or for supporting mechanistic endpoints – look at the **whole profile** together with predictions for ADME to increase robustness of prediction

Reduction

- In cases where animal testing is still needed, “pre-experiment” predictions of mechanistic properties of the substance can contribute to **optimize the experimental design to enhance the amount of knowledge** that can be extracted from the experiment without the use of more animals.

Prioritization

Prioritization

- QSAR predictions can contribute to prioritization and target relevant testing, e.g.:
- **between chemicals**, e.g. REACH substance evaluations
- in a **testing strategy** for a chemical and
- in early screening of **new candidate chemicals**, e.g. pharmaceuticals and substitution chemicals (see next slide ☺)

Substitution

Substitution

- **Choosing a good candidate** substance for substitution or for other purposes can save time and financial resources as further investment into a hazardous substance is halted early, and it can **reduce the need for later animal testing**
- QSAR predictions can be made **before organic synthesis** has even taken place; the only thing needed is the molecular structure

Regulatory contexts

(Q)SAR predictions for chemical substances and their metabolites/ transformation products can be used in different regulatory contexts, e.g.

- **EU chemicals Regulation REACH**: Before new tests are carried out data from valid (Q)SARs and data from structurally related substances (read-across approach) shall be assessed
- **EU Cosmetics Regulation**: Ban on cosmetics that contain ingredients tested on animals
- **EU Pesticides Regulation**: Evaluation of the toxicological relevance of metabolites and degradates of pesticide active substances
- **EU Biocides Regulation**: In case of no or limited data for a given endpoint (Q)SARs may be considered
- **Pharmaceuticals guideline** (ICH M7 2014) to assess DNA reactive impurities (cancer risk)

To some extent QSAR applicability domains can be defined to suit the (regulatory) context: Optimisation for high sensitivity vs. high specificity

DTU Food QSAR activities

- **Development and regulatory application** of QSARs >15y
  e.g. in Danish EPA, ECHA, and OECD regi

- **Hundreds of QSARs (DTU or licensed)**
- Physico-chemical properties
- Absorption, distribution, metabolism
- Biodegradation, bioconcentration, aquatic toxicity
- Human health

- Current research to **model molecular and cellular endpoints** which are associated with *in vivo* effects

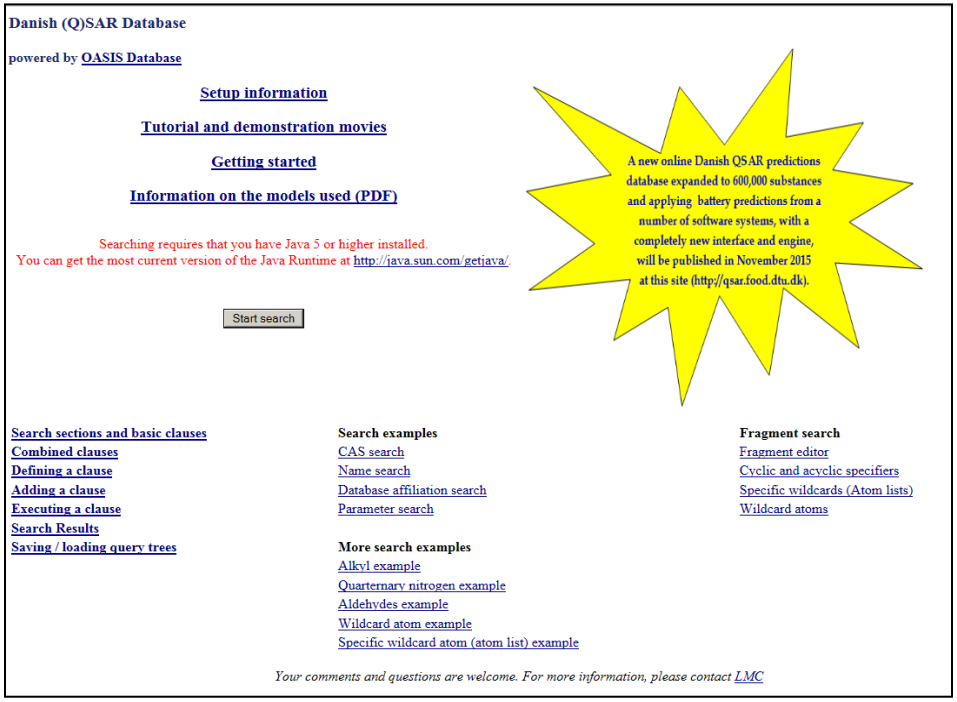
QSAR activities examples

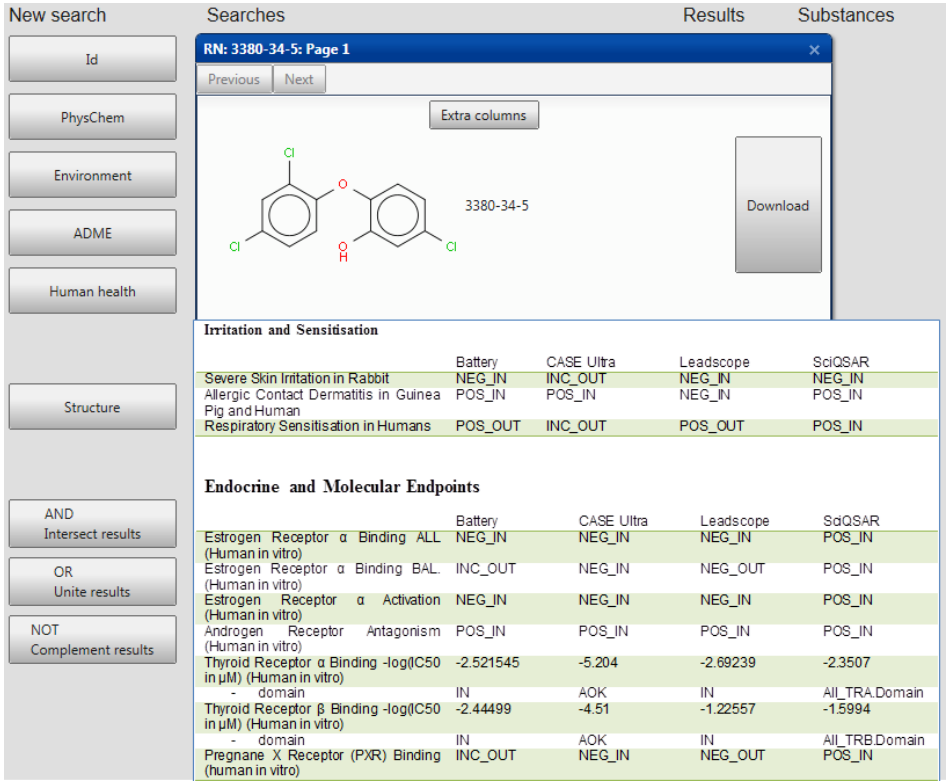
- **Endocrine activity** screening (72k substances, 2014)
- **Cancer, mutagenicity and reproductive toxicity** screening (72k, 2013)
- **Advisory classifications** for 33,835 EU chemicals (2001, 2009, 2010)
- **OECD participation** (validation principles, Toolbox, guidance documents, chemical assessments etc.) (2001-)
- **EU REACH activities** (implementation projects, substance evaluations, cooperation with ECHA etc.) (2003-)

- **Projects** also for DK Research Funds, EU FP7, OECD, Nordic Council of Ministers, US EPA etc.

- Spin-out company **Saxocon** based on DTU Food QSAR patent (hERG cardiotoxicity, 2013)

New Danish QSAR predictions database





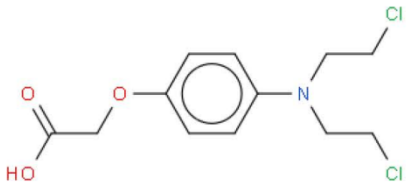
New Danish QSAR predictions database

- **QSAR predictions for >600,000 substances**
- **>200 predictions** for each substance with new versions of models / software
- Includes so-called **battery predictions** where 3 different QSAR systems (technologies) are used for the same training set
- Single substance look-up: **profiling**
- **Screening** across all QSAR predicted properties and structures
- Sort on **chemical similarity** for read-across purposes

Danish (Q)SAR Database, http://qsar.food.dtu.dk Date: 10-11-2015

(Q)SAR predicted profile

Structure (as used for QSAR prediction):



SMILES (used for QSAR prediction): c1(OCC(=O)O)ccc(N(CCCl)CCCl)cc1

ID

EC Number		Registry Number	17528-53-9	PubChem CID	
Chemical Name	Acetic acid, (p-(bis(2-chloroethyl)amino)phenoxy)-				
Molecular Formula	C12 H15 CL2 N1 O3		Molecular weight (g/mole)		292.16

Physical-chemical properties

EPI MPBPVP

Melting Point (deg C)	154.91	Melting Point Experimental (deg C)	
Boiling Point (deg C)	412.44	Boiling Point Experimental (deg C)	
Vapour Pressure (mm Hg)	1.95E-007	Vapour Pressure Experimental (mm Hg)	
Vapour Pressure (Pa)	2.6E-005	Vapour pressure Subcooled Liquid (Pa)	0.000552

EPI HENRYWIN

HLC Bond Method (atm-m3/mole)	5.834E-011	HLC Group Method (atm-m3/mole)	
HLC Via VP/WSol (atm-m3/mole)	2.368E-010	HLC Via VP/WSol (Pa-m3/mole)	2.399E-005
Henrys Law Const. Exp db (Pa-m3/mole)		Henrys Law Const. Exp db (atm-m3/mole)	

HLC: Henry's Law Constant

EPI WSKOW and WATERNT

Water solubility from Kow (mg/L)	316.6	Water solubility from Fragments (mg/L)	484.87
Water solubility Exp (mg/L)		Water solubility Exp Ref	
Log Kow	2.38		
Log Kow Exp		Log Kow Exp Ref	

LogKow: log octanol-water partition coefficient

ACDLabs

pKa Acid	3.4
- Standard deviation (±)	0.5
pKa Base	2.5
- Standard deviation (±)	0.5

pKa estimate 999: no acidic moiety found. pKa estimate -999: no basic moiety found.

ID and physical-chemical properties

4

EPI AEROWIN

Kp (m3/ug) Mackay-based	0.00543	Kp (m3/ug) Koa-based	0.0247
Phi Junge-Pankow-based	0.164	Phi Mackay-based	0.303
Phi Koa-based	0.664		

Kp: particle-gas partition coefficient. Phi: fraction of substance sorbed to atmospheric particulates

EPI KOCWIN

Koc from MCI (L/kg)	73.56	Log Koc from MCI	1.8666
Koc from Kow (L/kg)	29.03	Log Koc from Kow	1.4629

Koc: soil adsorption coefficient of organic compounds. Kow: octanol-water partition coefficient. MCI: first order Molecular Connectivity Index

Level III Fugacity Environmental Partitioning

EPI Level III Fugacity Model	Air	Water	Soil	Sediment
Mass Amount (%)	0.000634	19	80.9	0.103
Half-Life (hr)	1.85	900	1800	8100
Emissions (kg/hr)	1000	1000	1000	0

Persistence time (hr): 1540

Persistence time (days): EPI.Fugacity_Level_III_Persistence_Time_days

Sewage Treatment Plant (STP) overall chemical mass balance using 10,000 hr

EPI STPWIN	Total removal	Biodegradation	Sludge Adsorption	Volatilization
(%)	2.8	0.1	2.7	0

Atmospheric oxidation (25 deg C)

EPI AOPWIN	Hydrolysis	OH	Ozone
Half-Life (d)		0.07712	0
Half-Life (hr)		0.925	
Overall Rate Const. (OH: E-12 cm3/molecule-sec and OZ: E-17 cm3/molecule-sec)		138.6912	

Biodegradation

EPI BIOWIN

Biowin1 (linear model) Probability of Rapid Biodegradation	0.385
Biowin2 (non-linear model) Probability of Rapid Biodegradation	0.0151
Biowin3 Expert Survey Ultimate Biodegradation	2.2589
Biowin3 Expert Survey Ultimate Timeframe	weeks-months
Biowin4 Expert Survey Primary Biodegradation	3.3997
Biowin4 Exp. Survey Primary Timeframe	days-weeks
Biowin5 (MITI linear model) Biodegradation Probability	0.4166
Biowin6 (MITI non-linear model) Biodegradation Probability	0.0501
Biowin7 (Anaerobic Linear) Biodegradation Probability	-0.1551
Petroleum Hydrocarbon Biodegradation Half-Life (days)	

Biowin1 and Biowin2: ≥0.5: "Rapid" <0.5: "Slow"
Biowin3 and Biowin4: 5 ~ hours; 4 ~ days; 3 ~ weeks; 2 ~ months; 1 ~ years.
Biowin5 and Biowin6: ≥0.5: "Readily", <0.5: "Not readily".
Biowin7: ≥0.5: "Fast", <0.5: "Slow"

DK	Exp	Battery	E Ultra	Leadscope	SciQSAR
Not Ready Biodegradability (POS=Not Ready)		POS_OUT	POS_IN	INC_OUT	INC_OUT

Bioaccumulation

EPI BCFBAF

BCF (L/kg wet-wt)	3.162
Log BCF (L/kg wet-wt)	0.5
Whole Body Primary Biotransformation Fish Half-Life (days)	0.2833
BCF Arnot-Gobas (upper trophic) Including Biotransformation (L/kg wet-wt)	20.47
BCF Arnot-Gobas (upper trophic) Zero Biotransformation (L/kg wet-wt)	26.3
BAF Arnot-Gobas (upper trophic) Including Biotransformation (L/kg wet-wt)	20.47
BAF Arnot-Gobas (upper trophic) Zero Biotransformation (L/kg wet-wt)	27.39

BCF: Bioconcentration factor, BAF: Bioaccumulation factor

Environmenal fate, biodegradation, bioaccumulation

Aquatic toxicity

DK	Exp	Battery	Leadscope	SciQSAR
Fathead minnow 96h LC50 (mg/L)			1240.797	4.061821
Domain		OUT	OUT	SC.DYY.Domain
Daphnia magna 48h EC50 (mg/L)		20.72979	19.74153	21.71804
Domain		IN	IN	SC.DYV.Domain
Pseudokirchneriella s. 72h EC50 (mg/L)		5.616287	10.57428	0.6582953
Domain		IN	IN	SC.DWE.Domain

EPI ECOSAR	Fish 96h	Daphnid 48h	Green Algae 96h
LC50 (Fish) or EC50 (Daphnid and Algae) for Most Toxic Class (mg/L)	1102.913	648.364	557.519
Max. Log Kow for Most Toxic Class	5	5	6.4
Most Toxic Class	Neutral Organics-acid	Neutral Organics-acid	Neutral Organics-acid
Note	Chemical may not be soluble enough	Chemical may not be soluble enough	Chemical may not be soluble enough

ECOSAR Classes: EPI.ECOSAR.Classes

ADME

Oral absorption

Equation from literature	
Lipinski's Rule-of-five score (bioavailability)	0
Absorption from gastrointestinal tract for 1 mg dose (%)	95
Absorption from gastrointestinal tract for 1000 mg dose (%)	90

Lipinski scores of 0 or 1: the substance may be bioavailable. Lipinski scores of 2, 3 or 4: the substance may not be bioavailable.

Skin absorption

EPI DERMWIN	
Dermal absorption (mg/cm2/event)	0.00196

Distribution

Equation from literature	
Log brain/blood partition coefficient	0.04230002

Partitioning between the two tissues at equilibrium. >1: high, >0 to <1: medium, >-1 to <0, fair, <-1: low.

Metabolism

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
CYP2C9 substrates (Human clinical data)		NEG_IN	NEG_IN	NEG_OUT	NEG_IN
CYP2D6 substrates (Human clinical data)		NEG_IN	NEG_IN	NEG_IN	NEG_IN

Human Health

Acute toxicity in Rodents

ACDLabs	LD50 (mg/kg/d)	Reliability Index
Rat Oral	110	0.56
Rat Intraperitoneal	55.86	0.4
Mouse Oral	83.06	0.44
Mouse Intraperitoneal	38.44	0.44
Mouse Intravenous	39.71	0.5
Mouse Subcutaneous	75.41	0.81

Reliability index: <0.3 = Not reliable prediction quality; 0.3-0.5 = borderline prediction quality; 0.5-0.75 = moderate prediction quality; >0.75 = high prediction quality.

MRDD in Humans

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
MRDD in Humans ≤ 2.69 mg/kg-bw/d		INC_OUT	POS_OUT	NEG_IN	POS_IN

Model based on data on pharmaceuticals. Maximum recommended daily dose in pharmaceutical clinical trials employing primarily oral route of exposure and daily treatments, usually for 3-12 months.

Aquatic toxicity, ADME (absorption, distribution, metabolism, excretion), Human health acute toxicity

Irritation and Sensitisation

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Severe Skin Irritation in Rabbit		POS_OUT	INC_OUT	NEG_OUT	POS_IN
Allergic Contact Dermatitis in Guinea Pig and Human	NA	POS_IN	POS_IN	NEG_IN	POS_IN
Respiratory Sensitisation in Humans		INC_OUT	INC_OUT	POS_OUT	POS_OUT

Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Estrogen Receptor α Activation (Human *in vitro*)		NEG_IN	NEG_OUT	NEG_IN	NEG_IN
Androgen Receptor Antagonism (Human *in vitro*)		INC_OUT	POS_IN	NEG_IN	NEG_IN
Thyroid Receptor α Binding (Human *in vitro*) (mg/L)		461.6001	46732.69	555.6622	383.4605
domain		IN	OUT	IN	All_TRA.Domain
Thyroid Receptor β Binding (Human *in vitro*) (mg/L)		107.1792	9454.117	96.98415	118.4461
domain		IN	OUT	IN	All_TRB.Domain
Pregnane X Receptor (PXR) Binding (human *in vitro*)	NA	NEG_IN	POS_OUT	NEG_IN	NEG_IN

Developmental Toxicity

	Battery	CASE Ultra	Leadscope	SciQSAR
Teratogenic Potential in Humans	POS_IN	POS_IN	POS_IN	POS_IN

Genotoxicity

Ashby Structural Alerts for DNA Reactivity

	Battery	CASE Ultra	Leadscope	SciQSAR
Ashby Structural Alerts	POS_IN	POS_IN	POS_IN	NEG_IN

Bacterial Reverse Mutation Test (Ames test)

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Ames test in S. typhimurium (*in vitro*)	POS	POS_IN	POS_IN	INC_OUT	POS_IN
- Direct Acting Mutagens (without S9)	NA	NEG_OUT	POS_OUT	NEG_IN	POS_OUT
- Base-Pair Ames Mutagens	NA	POS_IN	POS_IN	POS_IN	INC_OUT
- Frameshift Ames Mutagens	NA	NEG_IN	NEG_IN	NEG_IN	NEG_IN
- Potent Ames Mutagens, Reversions ≥ 10 Times Controls	NA	NEG_OUT	NEG_IN	POS_OUT	INC_OUT

For the four Ames "submodels" (Direct Acting Mutagens (without S9), Base-Pair Ames Mutagens, Frameshift Ames Mutagens, Potent Ames Mutagens) only use the predictions if the main Ames model (Ames test in S. typhimurium (*in vitro*)) is POS_IN.

Other *in vitro* Genotoxicity Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells	NA	POS_IN	POS_IN	POS_IN	POS_IN
Chromosome Aberrations in Chinese Hamster Lung (CHL) Cells		POS_OUT	POS_OUT	POS_IN	NEG_OUT
Mutations in Thymidine Kinase Locus in bMouse Lymphoma Cells		POS_IN	POS_IN	INC_OUT	POS_IN
Mutations in HGPRT Locus in Chinese Hamster Ovary (CHO) Cells		NEG_OUT	INC_OUT	INC_OUT	NEG_IN
Unscheduled DNA Synthesis (UDS) in Rat Hepatocytes		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Syrian Hamster Embryo (SHE) Cell Transformation		NEG_OUT	POS_OUT	NEG_IN	NEG_OUT

HGPRT: Hypoxanthine-guanine phosphoribosyltransferase

Skin irritation, allergy, endocrine activity, developmental toxicity, DNA damage (genotoxicity)

***In vivo* Genotoxicity Endpoints**

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Sex-Linked Recessive Lethal (SLRL) Test in Drosophila m.		POS_IN	POS_IN	POS_IN	POS_IN
Micronucleus Test in Mouse Erythrocytes		POS_IN	POS_OUT	POS_IN	POS_IN
Dominant Lethal Mutations in Rodents		POS_IN	POS_IN	POS_IN	POS_IN
Sister Chromatid Exchange in Mouse Bone Marrow Cells		POS_IN	NEG_OUT	POS_IN	POS_IN
Comet Assay in Mouse		POS_IN	POS_IN	INC_OUT	POS_IN

Carcinogenicity

	CASE Ultra	Leadscope
FDA RCA Cancer Male Rat	POS_OUT	POS_IN
FDA RCA Cancer Female Rat	POS_IN	POS_IN
FDA RCA Cancer Rat	POS_OUT	POS_IN
FDA RCA Cancer Male Mouse	POS_IN	POS_IN
FDA RCA Cancer Female Mouse	POS_IN	POS_IN
FDA RCA Cancer Mouse	POS_IN	POS_IN
FDA RCA Cancer Rodent	POS_IN	POS_IN

FDA RCA: Data from US Food and Drug Administration as part of Research Cooperation Agreement

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Liver Specific Cancer in Rat or Mouse		NEG_IN	NEG_IN	NEG_IN	NEG_IN

DNA damage and cancer

Publication of the new online database

- **Publication 18 November 2015** at: http://qsar.food.dtu.dk
- **Free for everyone to use**
- **User manual** with search examples etc.
- **Model documentations** in international agreed format ("QMRFs")
- **QSAR predictions profile** downloadable as rtf (word)
- **Financial support** from Danish EPA and Nordic Council of Ministers
- Integration with the **OECD QSAR Application Toolbox** planned

Thank you!

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