Technical University of Denmark



#### Danish (Q)SAR Models: A free online DTU QSAR predictor powered by Leadscope

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# Danish (Q)SAR Models: A free online DTU QSAR predictor powered by Leadscope

Nikolai G. Nikolov<sup>1</sup>, Kevin P. Cross<sup>2</sup>, Patrick Quigley<sup>2</sup>, Marianne Dybdahl<sup>1</sup>, Trine K. Reffstrup<sup>1</sup>, Sine A. Rosenberg<sup>1</sup>, Eva B. Wedebye<sup>1</sup>

# <sup>1</sup>Technical University of Denmark, <sup>2</sup>Leadscope Inc.

The QSAR team at the Technical University of Denmark, National Food Institute, has recently published a completely rebuilt version of the Danish (Q)SAR Database (<u>http://qsar.food.dtu.dk</u>) with pre-generated predictions from a large number of QSAR models for over 600,000 chemical structures. A selection of more than 20 of these QSAR models of diverse endpoints encompassing acute toxicity, metabolism, endocrine activity, genotoxicity and sensitization have been implemented in a real-time online predictive system. The system generates predictions on the fly for user-submitted structures and uses Leadscope Enterprise software as a back-end to the web server. All models have undergone robust cross-validation, and documentation in the international QMRF format is available from the website.

Danish (Q)SAR Database: Predictions from >200 (Q)SAR models pre-calculated for >600,000 substances

DTU-developed, commercial and free models
72,000 EU REACH chemical substances and 372,000 NIH MLSMR



- Single substance look-up by ID or structure: profiling
- Screening across all QSARpredicted and experimental properties and structures
- Sort on chemical similarity for

- Battery predictions: 3 QSAR approaches for the same training set
- Database, client and server software developed by DTU Food



# read-across purposes

• Free for everyone to use

# Danish (Q)SAR Models: Online prediction generation from >20 of the Danish (Q)SAR Database models

The Leadscope versions of selected models are made available for real-time prediction. The client/server software is developed by DTU Food and Leadscope Enterprise server is used as a back-end.

# Included models

- Acute aquatic toxicity (Fish, Daphnia, Algae)
- Cytochrome P450 substrates (2C9, 2D6)
- Endocrine (ER binding/agonism, AR antagonism, in vitro)
- <u>Genotoxicity</u> *in vitro* (Ames test in Salmonella t., Chromosome aberrations in CHL, Mutations in Mouse Lymphoma, Mutations in HGPRT Locus in CHO, Unscheduled DNA Synthesis in Rat hepatocyte, SHE Cell Transformation), *in vivo* (Drosophila m. SLRL, Mouse Micronuclei, Rodent Dominant Lethal, Mouse Sister Chromatid Exchange, Mouse Comet Assay)



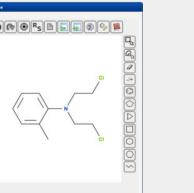
# On-the-fly prediction generation:

- Same prediction and domain call as in the Danish (Q)SAR Database
- Positive prediction probability
- Detailed report with structural alerts and training set analogs

## <u>Chemical structure input</u>

Draw, enter SMILES, MOL/SDF or look up by name:

## Predictions and reports download

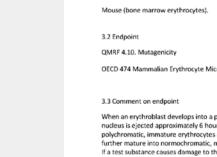


3.3 Comment on endpoint
When an erythroblast develops into a polychromatic (immature) erythrocyte in the bone marrow the main nucleus is ejected approximately 6 hours after mitosis. After 12-24 h in the bone marrow the polychromatic, immature erythrocytes are then released to the peripheral blood where they after 12-24 h further mature into normochromatic, mature erythrocytes by expulsion of their ribosomes.
If a test substance causes damage to the chromosomes or the mitotic apparatus of the erythroblast a micronucleus is formed. Micronuclei are small nuclei produced during cell division and contain lagging chromosome fragments or whole chromosomes. Normally the micronudeus is not ejected along with the main nucleus and can therefore be visualized in the anucleate immature and/or mature erythrocyte. In most species, including humans, the micronucleate drythrocytes in the bone marrow of mice treated with a test substance indicates induction of chromosome damage or damage to the mitotic apparatus by the test substance indicates induction of factors such as absorption, *in vivo* metabolism, pharmacokinetics and DNA-repair processes. This assay is useful for further investigation of an utagenic effect detected in an *in vitro* system.

3.4 Endpoint u

No units, 1 for positives and 0 for negative

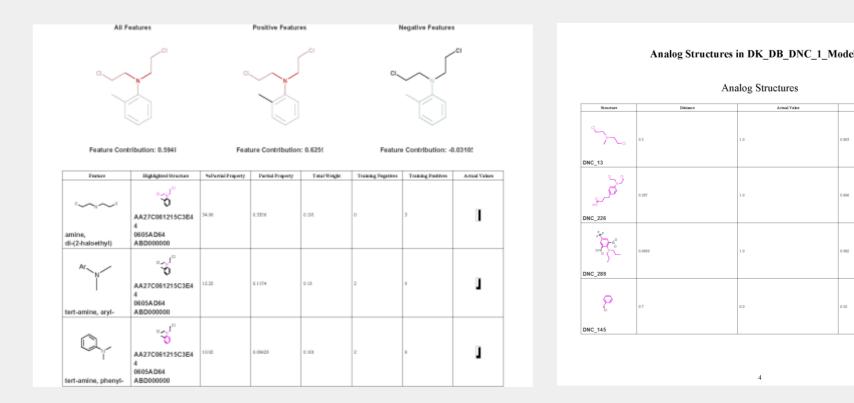
<u>QMRF reports</u>

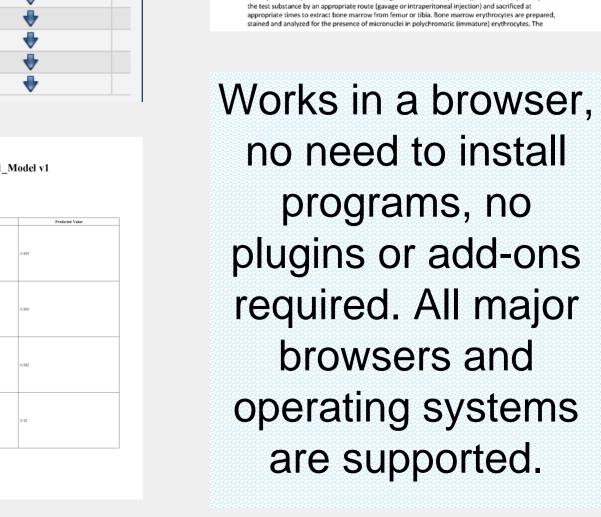


- <u>Acute toxicity</u> (Maximum recommended daily dose, human)
- Skin irritation (Severe skin irritation in Rabbit)
- <u>Respiratory sensitization</u> (human)
- Cardiotoxicity (hERG blocking, in vitro)

Environment         ADME         Endocrine endpoints         Genotoxicity         Other           Ames test				
<ul> <li>Bacterial reverse mutation test (Ames test in S. typhimurium (in vitro))</li> <li>Other in vitro endpoints         <ul> <li>Chromosome Aberrations in Chinese Hamster Lung Cells</li> <li>Mutations in Thymidine Kinase Locus in Mouse Lymphoma Cells</li> <li>Mutations in HGPRT Locus in Chinese Hamster Ovary Cells</li> <li>Unscheduled DNA Synthesis in Rat Hepatocytes</li> <li>Syrian Hamster Embryo Cell Transformation</li> </ul> </li> <li>In vivo endpoints         <ul> <li>Sex-Linked Recessive Lethal Test in Drosophila m.</li> <li>Micronucleus Test in Mouse Erythrocytes</li> <li>Dominant Lethal Mutations in Rodents</li> <li>Sister Chromatid Exchange in Mouse Bone Marrow Cells</li> </ul> </li> </ul>	ADME	Endocrine endpoints	Genotoxicity	Other er
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Model	Probability	Prediction	Report	民
ER alpha binding (human in vitro), all	0.155	NEG_IN		
ER alpha activation (human in vitro)	0.0186	NEG_IN	÷	
Androgen receptor antagonism (human in vitro)	0.138	NEG_IN	+	
Unscheduled DNA Synthesis in Rat Hepatocytes	0.308	NEG_OUT	+	
Micronucleus Test in Mouse Erythrocytes	0.96	POS_IN	+	
Dominant Lethal Mutations in Rodents	0.979	POS_IN	+	
Maximum recommended daily dose (MRDD) in Humans	0.51	POS_OUT		





Publication in 2016 will be announced on the Danish (Q)SAR Database homepage:

Support from the Danish Environmental Protection Agency is acknowledged.

## http://qsar.food.dtu.dk