



Miljøministeriet
Miljøstyrelsen

Danish EPA past and recent experience with use of QSAR predictions

LIFE Concert REACH
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DK EPA use of (Q)SAR predictions – introduction

Generally, two types of use of QSAR predictions:

1. Support to **Single substance evaluation**, e.g. under REACH:

- Dossier evaluation (LT fish, EOGRTS, Mutagenicity)
- Substance evaluation
- and initial/supportive SVHC (PBT, CMR and ED) evaluation

Substance profile relating to physicochemical properties, environmental fate, ADME, local toxicity, long term toxicity (CMR), short and long term ecotoxicity

2. **Screening** for substances of specific concern

- under REACH: CORAP / SVHC (e.g. regarding PBT, CMR, ED)
- **complex search** required (AND/OR/NOT based prediction algorithms)

An example of WoE use of (Q)SAR predictions: The Danish self-classification list



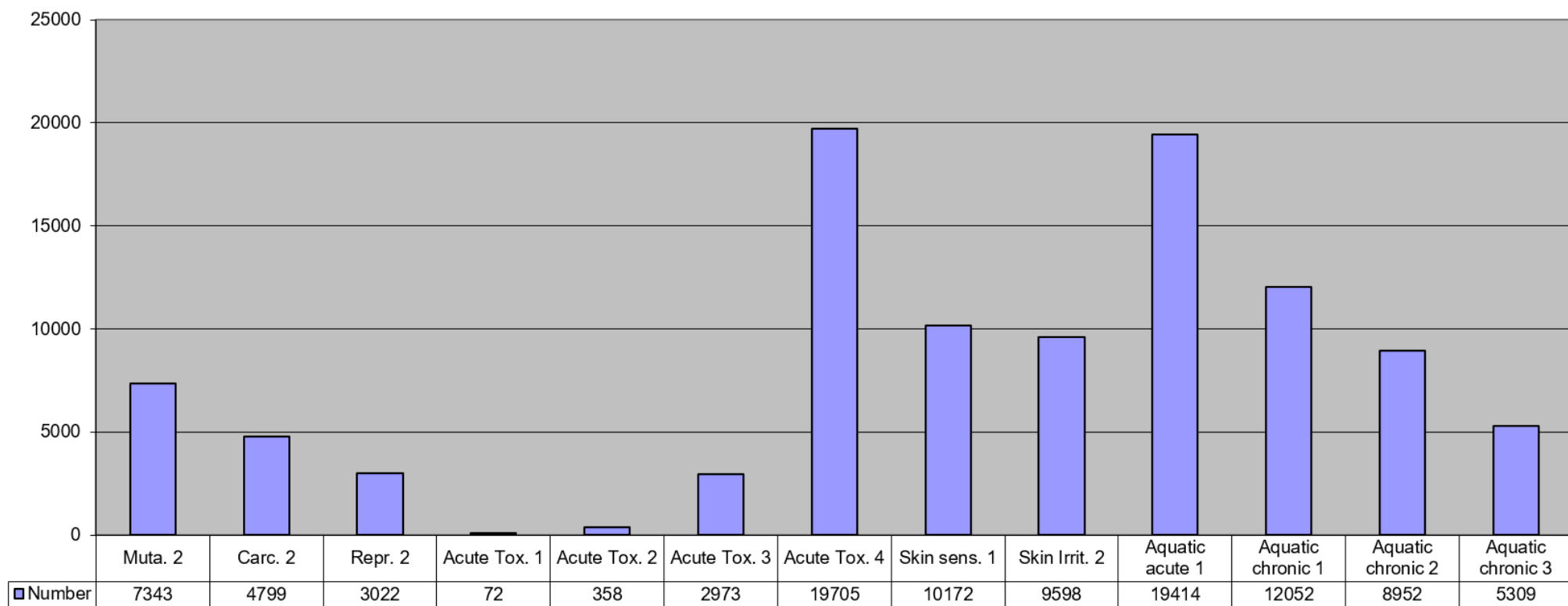
- Project done by DTU QSAR team for Danish EPA 2016-2018
- Algorithms for **WoE combinations** of QSAR predictions decided together with the DK EPA
- EU Classification, Labelling and Packaging (CLP) Regulation criteria
- Screening of **76,313 REACH** substances, excluding as far as possible all with harmonized classification (3,704 excluded)
- Assigns "advisory classifications"
- Classifications are now included in the DK (Q)SAR Database
- **Publication** on the Danish EPA homepage as a searchable database and file for download:
<https://eng.mst.dk/chemicals/chemicals-in-products/assessment-of-chemicals/the-advisory-list-for-self-classification-of-hazardous-substances/>

Included dangerous properties

Dangerous property	Classification	Wording of CLP classification
Mutagenicity	Muta. 2	Suspected of causing genetic defects
Carcinogenicity	Carc. 2	Suspected of causing cancer
Reproductive toxicity	Repr. 2	Suspected of damaging fertility or the unborn child
Acute oral toxicity	Acute Tox. 1	Fatal if swallowed
	Acute Tox. 2	Fatal if swallowed
	Acute Tox. 3	Toxic if swallowed
	Acute Tox. 4	Harmful if swallowed
Sensitisation by skin contact	Skin Sens. 1	May cause an allergic skin reaction
Respiratory sensitisation	Resp. Sens. 1	May cause allergy or asthma symptoms or breathing difficulties if inhaled
Skin irritation	Skin Irrit. 2	Causes skin irritation
Danger to the aquatic environment	Aquatic Acute 1	Very toxic to aquatic life
	Aquatic Chronic 1	Very toxic to aquatic life with long lasting effects
	Aquatic Chronic 2	Toxic to aquatic life with long lasting effects
	Aquatic Chronic 3	Harmful to aquatic life with long lasting effects

Advisory list for self-classification 2018

- in total 54,163 substances



Why an Advisory self-classification list?

- All chemical substances and preparations marketed in the EU must be classified and labelled according to **Regulation (EC) No. 1272/2008**
- Annex VI to the regulation includes **harmonised legally binding classifications** for certain substances or groups of substances
- Harmonised classifications in the EU presently cover <10,000 substances. For the remaining, it is the **obligation of producers / importers** to self-classify substances
- **Lack of data** on hazardous properties of chemicals makes it **difficult for companies to meet their obligations** to self classify the chemicals they import or produce
- To address this issue, DK-EPA in **2001, 2009 and 2010 published lists for self-classification** of substances based on DTU QSAR screening



Danish (Q)SAR Database



QSAR TOOLBOX



- Advisory self-classification list based on predictions from DK (Q)SAR Database
- QSAR predictions for **650,000 substances**, including **80,000 EU REACH industrial chemical substances**
- **>200 predictions** for each substance in DTU-developed, commercial and free models covering a wide range of hazardous properties relevant for human health and the environment
- Database and internet solution **developed by DTU Food** and published 23rd November 2015, freely available at: <https://qsar.food.dtu.dk>



Danish (Q)SAR Database



QSAR TOOLBOX

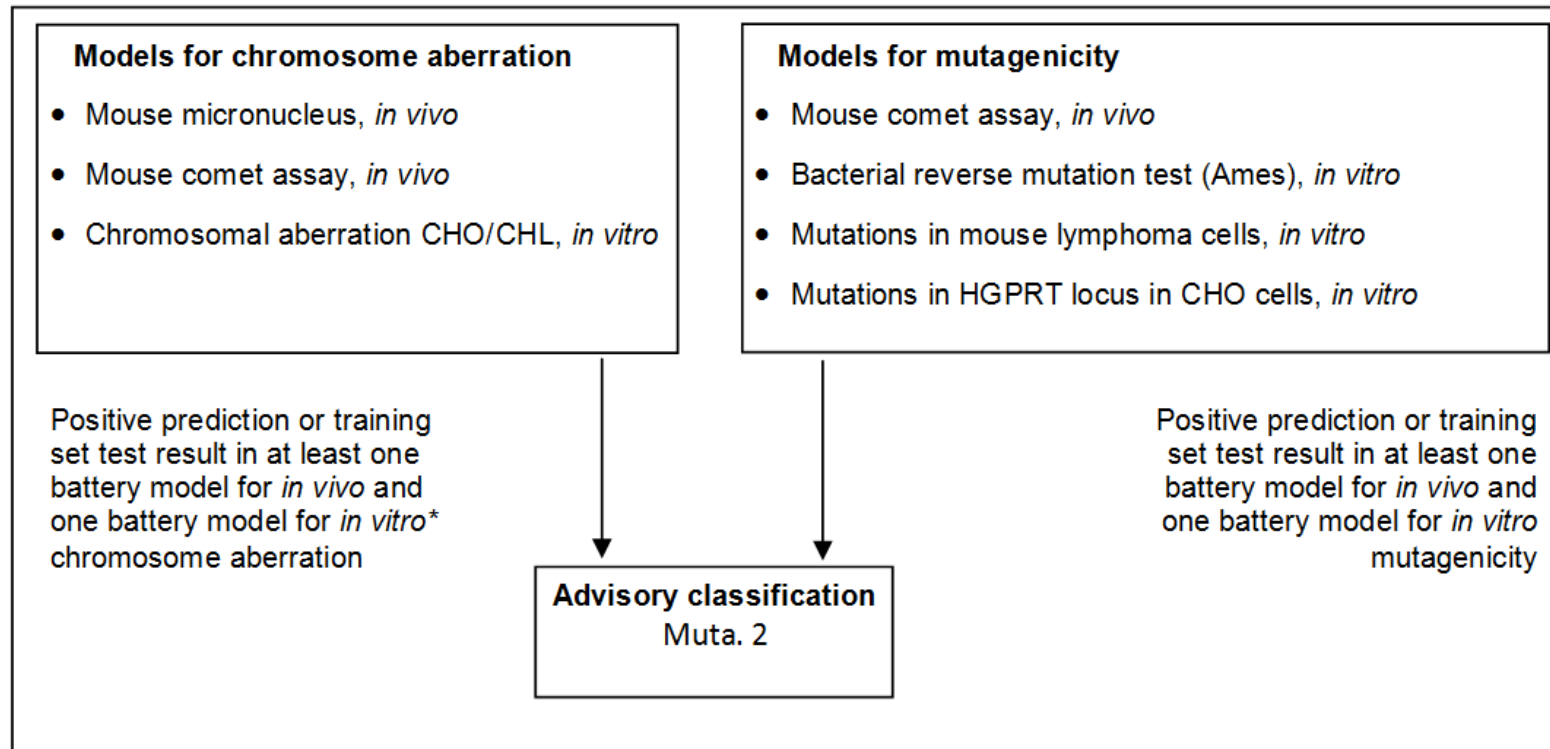


VEGAHUB

- Includes so-called **battery predictions** where 3 different QSAR systems (technologies) are used for the same training set
- All DTU models validated and documented in the **QSAR Model Reporting Format (QMRF)** and available in the system
- Plus extra **VEGA** predictions which have now been included for all 650,000 substances in the database in the EU Concert REACH project

Example of endpoint

Muta. 2 Suspected of causing genetic defects (7,323)

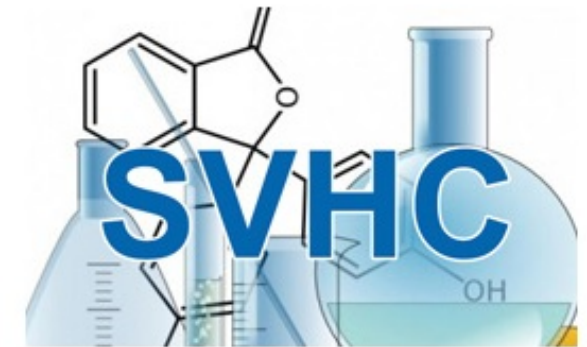
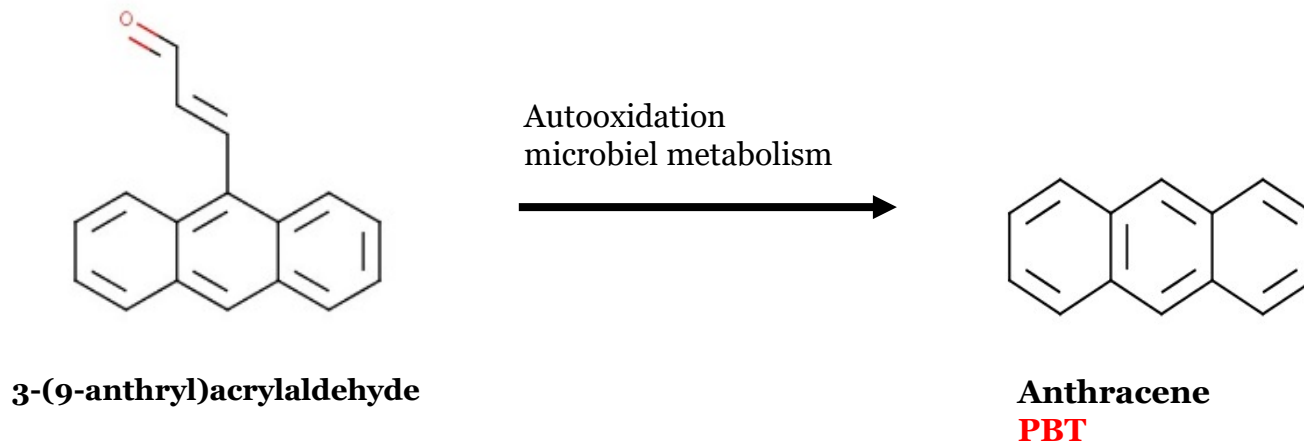


*Training set data was not used for the chromosomal aberrations in CHO cells models as this was proprietary information in the commercial model.

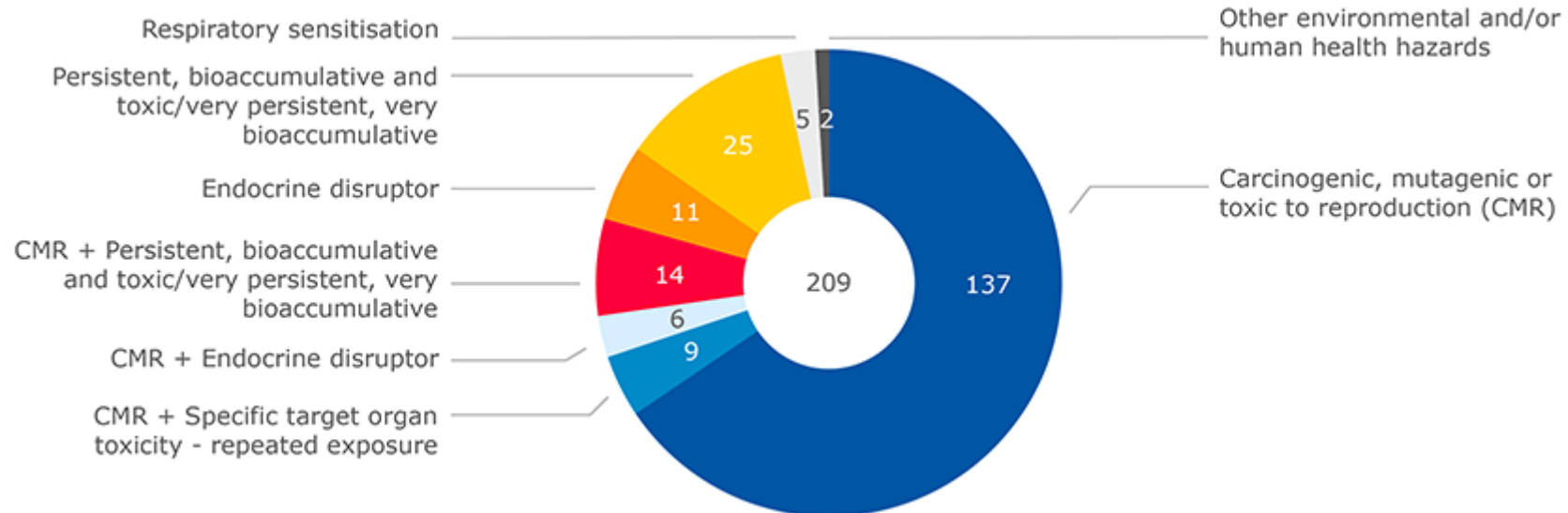
Figure 2: Schematic diagram illustrating the systematic evaluation applied to assign advisory classifications for mutagenicity.

PBT/PMT precursor screening

- ~13,000 REACH monoconstituent registered chemicals screened for being precursors to known PBT/PMTs
- PBT, vPvB, PMT, vPvM from SVHC and SINLIST
- Combination of abiotic and biotic simulators in Toolbox (autooxidation, microbial metabolism, hydrolysis)



Substances on the Candidate List (2020)



Persistency focus in the screening! (although other endpoints could be considered)

Initial precursor results

- 130 potential precursors identified
- Hits mostly from metabolism and ‘first and second generation’ simulation
- Further analysis needed (e.g. quantification with CATALOGIC and assessment of identified pathways)



Simulator(s)	SVHC	SIN LIST*	Total
Autooxidation (A)	0	0	0
Hydrolysis (H)	0	13	13
Metabolism (M)	14	96	110
AH	0	1	1
AM	1	4	5
HA	0	0	0
HM	5	22	27
MA	0	28	28
MH	1	33	34
AHM	0	2	2
AMH	0	3	3
HAM	0	3	3
HMA	0	5	5
MAH	0	10	10
MHA	0	2	2
Total unique substances having one or more PBT/PMT metabolite	15	115	130

*Only substances not already on the SVHC list

Thanks!

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