Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*

OECD QSAR Toolbox

and

CADASTER

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OECD QSAR Toolbox: http://www.qsartoolbox.org/

OECD QSAR Toolbox - timeline

- 2004: OECD members countries recognize a need focus on regulatory use and application of (Q)SARs

- 2005: Setubal (P): criteria for evaluation/validation of (Q)SARs
- 2006: Report on potential user needs / mock-up screens *(RIVM)*
- 2007: Several beta versions 0.x distributed, tested, commented
- 2008: v1.0 released, Proof of Principle *(OECD, ex-ECB, ECHA)*
- 2010: v2.0, extended (data, models, profiles) *(ECHA)*
  - focus on category formation

- 2012: v3.0, expansion of data, models, profiles
  - chemical speciation, metabolism, mixtures
  - chronic effects data and profiles,
  - Adverse Outcome Pathways

CADASTER

- aims at providing the practical guidance to integrated risk assessment by carrying out a full hazard and risk assessment for chemicals belonging to four compound classes (for REACH).

- Hazard assessment:
  - Information requirements — REACH Annex VII-X
  - Existing data
  - QSAR predictions
  - Read across & Category Approaches
  - Weight of Evidence analysis
  - Exposure Based Waiving

  } REACH Annex XII

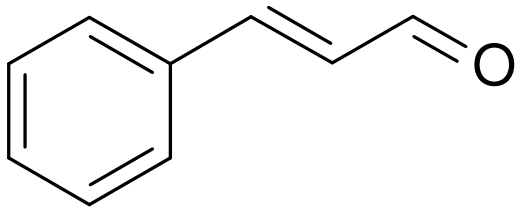
  - Testing Proposal

Existing Data / WoE data

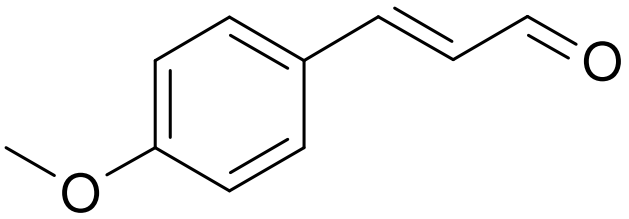
- QSAR Toolbox contains
  - structure identity information
  - regulatory inventories
  - (eco)toxicological datasets
- Can be used as a “one stop” database
- No quality assessment of tox data
- Focus on regulatory endpoints, but other data also available
- Aggregation of data on different levels

Example Existing Data:

- fragrance substances
- cinnamaldehyde, and
- para-methoxy cinnamaldehyde
- fish toxicity



cinnamaldehyde
CAS RN 104-55-2



4-methoxy cinnamaldehyde
CAS RN 1963-36-6

The QSAR Toolbox

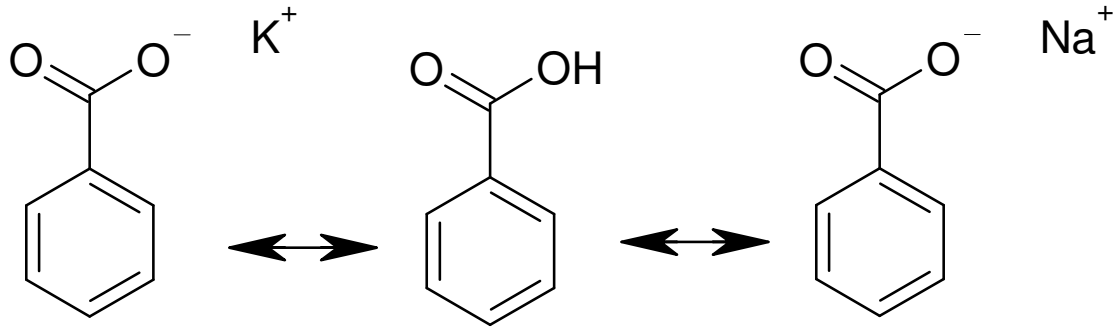
- Available Models (QSARs):
  - EPA EPISUITE models
  - 4 ex-ECB fish tox models
  - Bintein fish Bioconcentration
  - Chemaxon pKa models
  - BfR skin/eye irritation
  - DANISH EPA QSAR Database models
  - some MultiCASE models (HIA, ERBA, logP, WS, pKa, bacterial tox)

  - EXAMPLE: QSAR predictions for cinnamaldehydes

Read Across

- select similar substances
- assume similar properties

- Useful for (very) similar substances, e.g.



- Useful for yes/no endpoints, absence of effect
  - e.g. skin sensitizer, reproductive toxicity

Example of READ ACROSS in Toolbox

- 4-methoxycinnamaldehyde
- fish toxicity, LC50, 96 hours
- use most similar substances – profile: protein binding potency

What is a category (1)? (OECH, HPV program)

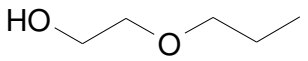
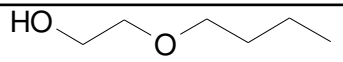
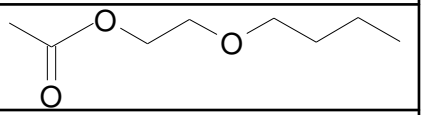
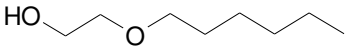
- Officially
  - *"a group of chemicals whose physicochemical and human health and/or environmental toxicological properties and/or environmental fate properties are likely to be similar or follow a regular pattern as a result of structural similarity (or other similarity characteristic)"* (OECD & REACH)

- Historically, inclusion of chemicals in a category depended on
  - Commercial interests
  - Data availability
  - Similarity in toxicological properties (!)

- Result
  - Categories do not reflect any toxicological relevance

What is a category (2)?

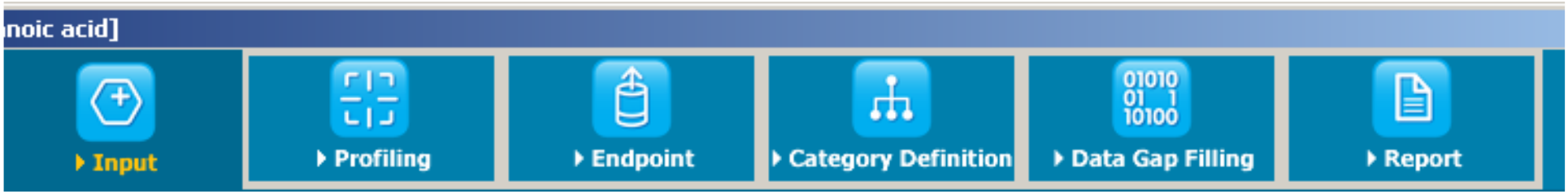
- OECD category of monoethylene glycol ethers

Category member	Abbreviation	Structure
Ethylene glycol propyl ether	EGPE	
Ethylene glycol butyl ether	EGBE	
Ethylene glycol butyl ether acetate	EGBEA	
Ethylene glycol hexyl ether	EGHE	

- Category definition?
- Category boundaries?
- Category characteristics?

CATEGORY APPROACH – in OECD QSAR Toolbox

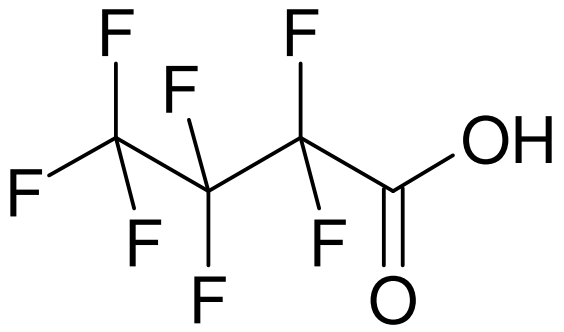
Essentially a mechanism based (pre-)QSAR approach:



- Enter chemical of interest (Input)
- Characterize your target substance (Profiling)
- Retrieve all available data (Endpoint)
- Establish a Category (training set) using mechanistical information (profiles) (Category Definition)
- Filter dataset (Data Gap Filling)
- Apply Read Across, Trend Analysis (= category)
- Or export dataset for more advanced QSAR modelling
- Document all steps leading to prediction (Report)

Example:

- (per)fluorinated compounds
- Bioaccumulation
- PFOS, PFOA shown to have high affinity for binding to B-lipoproteins, albumin, and liver fatty acid-binding protein
- → Protein binding profile (category)



perfluorobutanoic acid (PFBA)
CAS RN 375-22-4

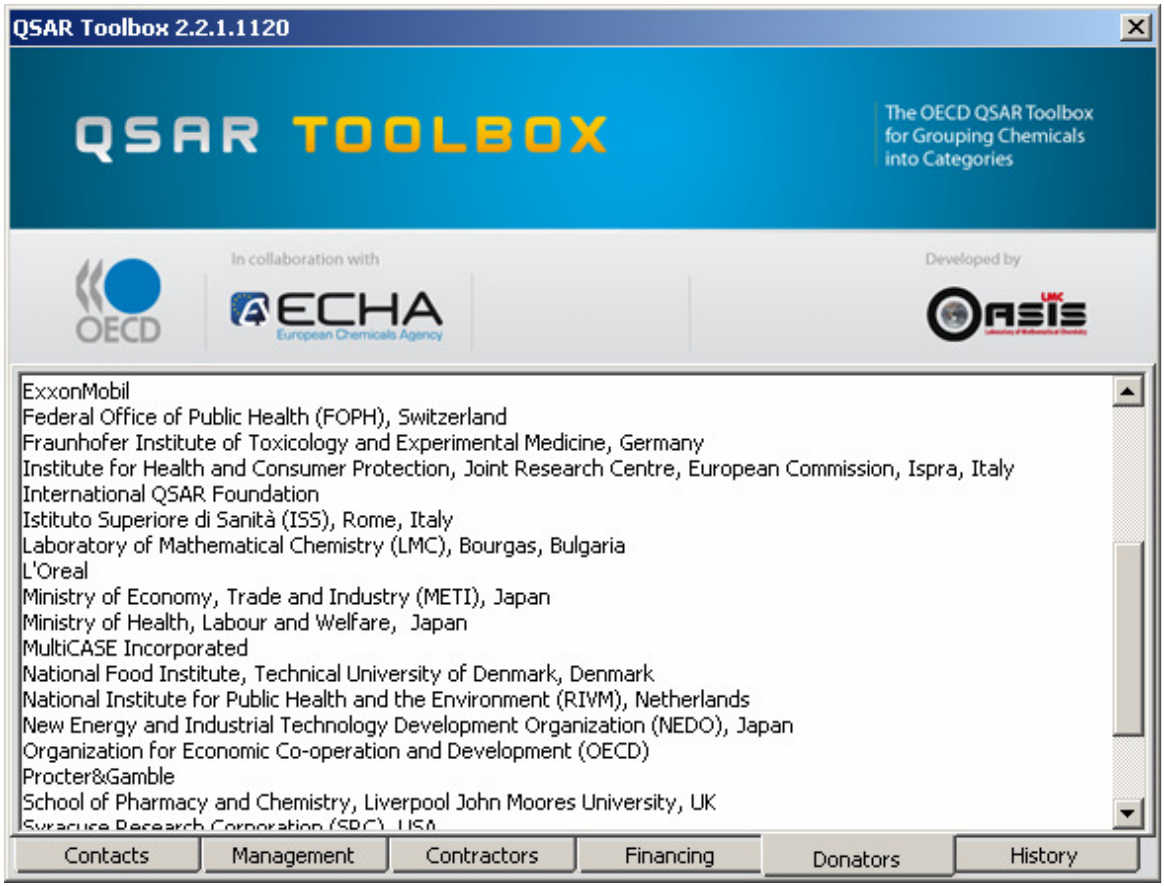
QSAR Toolbox - CADASTER

- import own datasets
- compare data
- reproduce own QSARs
- compare results
- create your own profiles

- donate datasets

- donate QSARs

- donate QSAR domain information → profile



Read Across, Category approach, QSARs

Your results are clear and irrefutable, Dr. Gardner.
Obviously, our agency can't approve this.

Thanks for your attention