OECD QSAR Toolbox in support of PBT identification under REACH

Webinar: OECD QSAR Toolbox applications for REACH and beyond

30 November 2021

Doris Hirmann
Scientific officer
Computational assessment unit
European Chemicals Agency

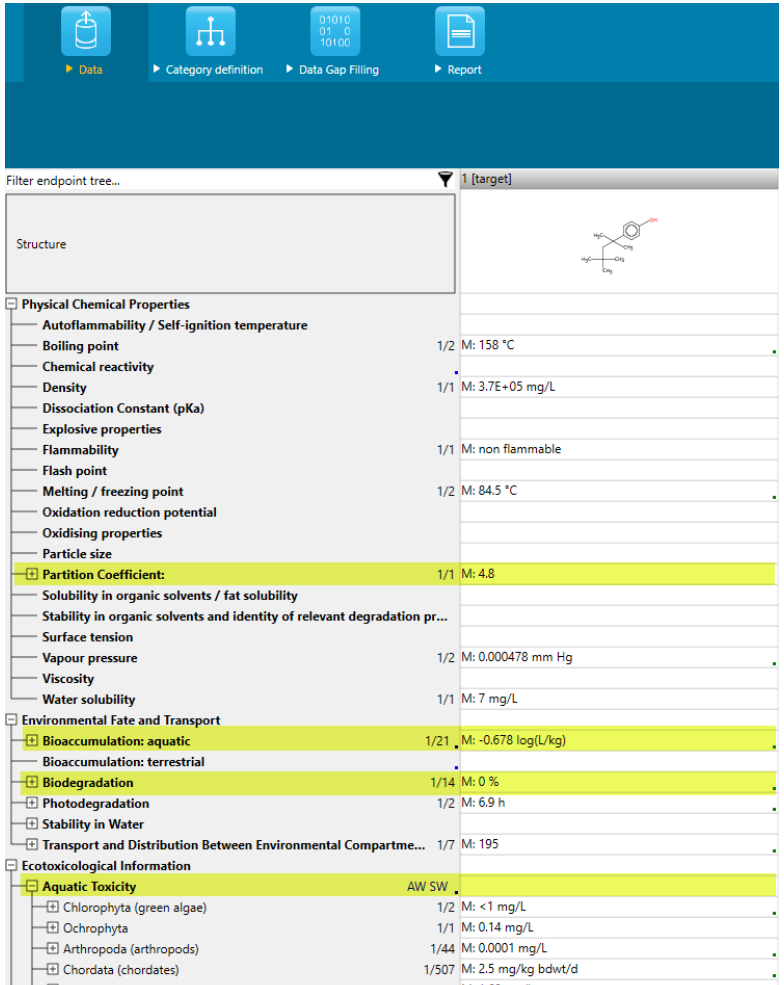
Overview

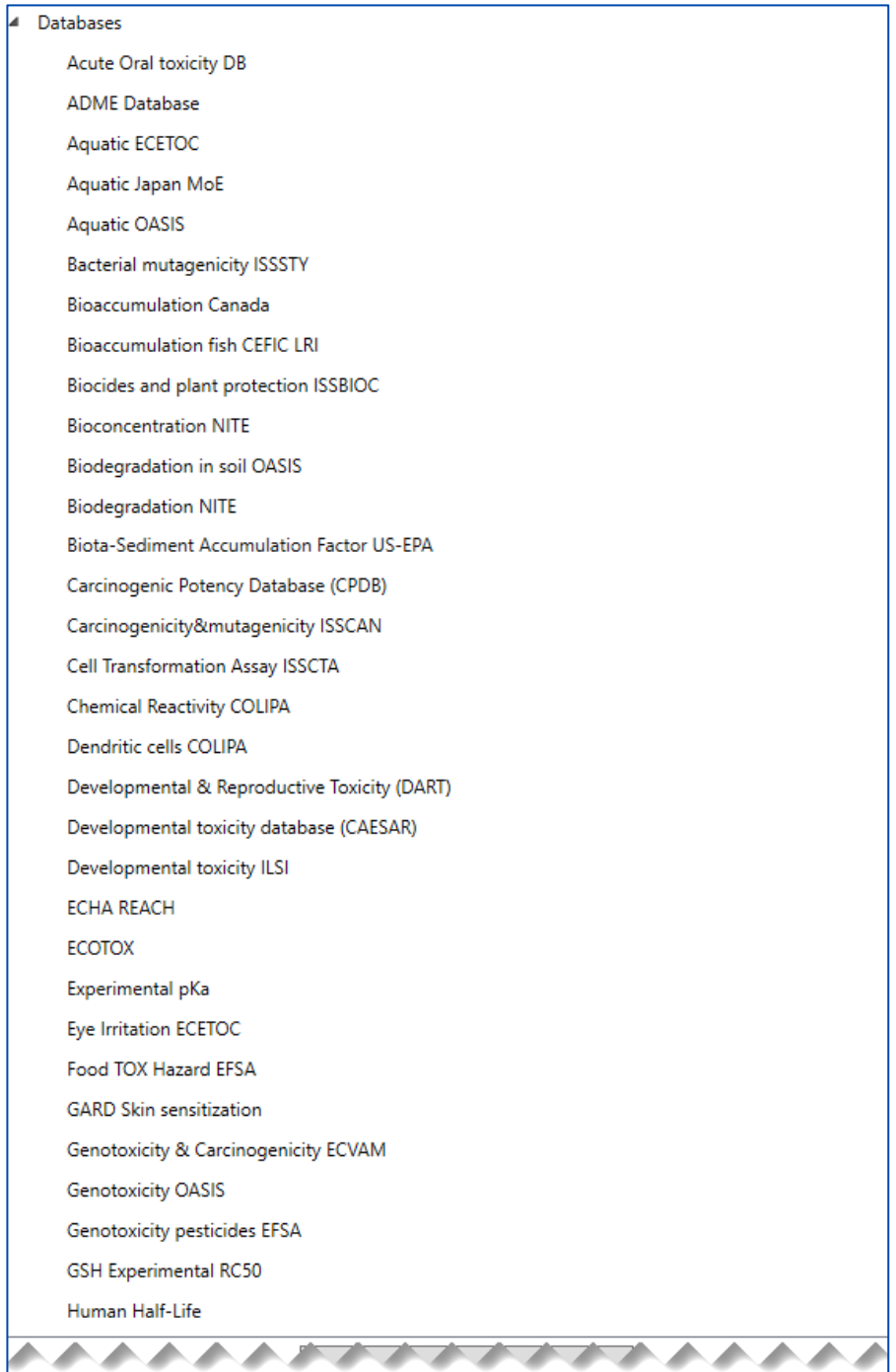
- Gathering relevant information in the QSAR Toolbox
- ECHA PBT screening profiler
- Precursor search with QSAR Toolbox
  - Bisphenols
  - PFAS

Gathering relevant information in the QSAR Toolbox

Information in QSAR Toolbox

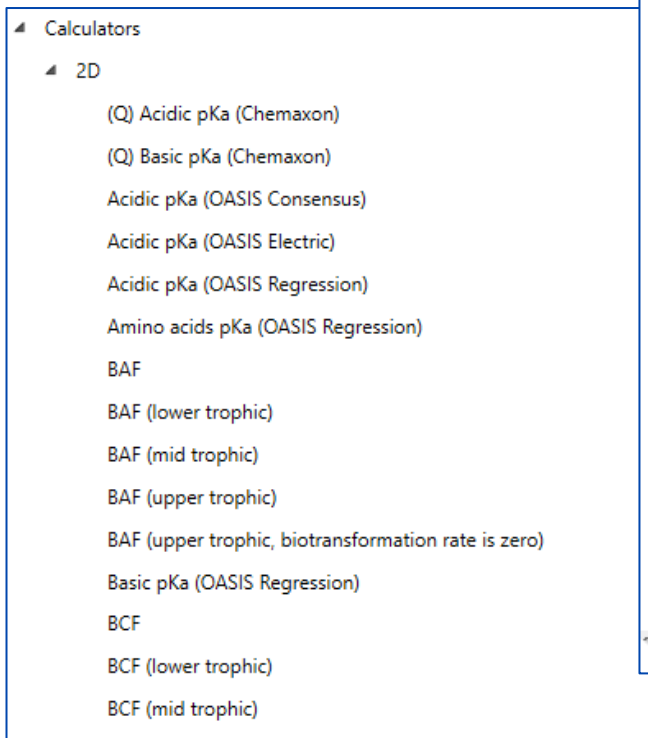
- 50+ databases

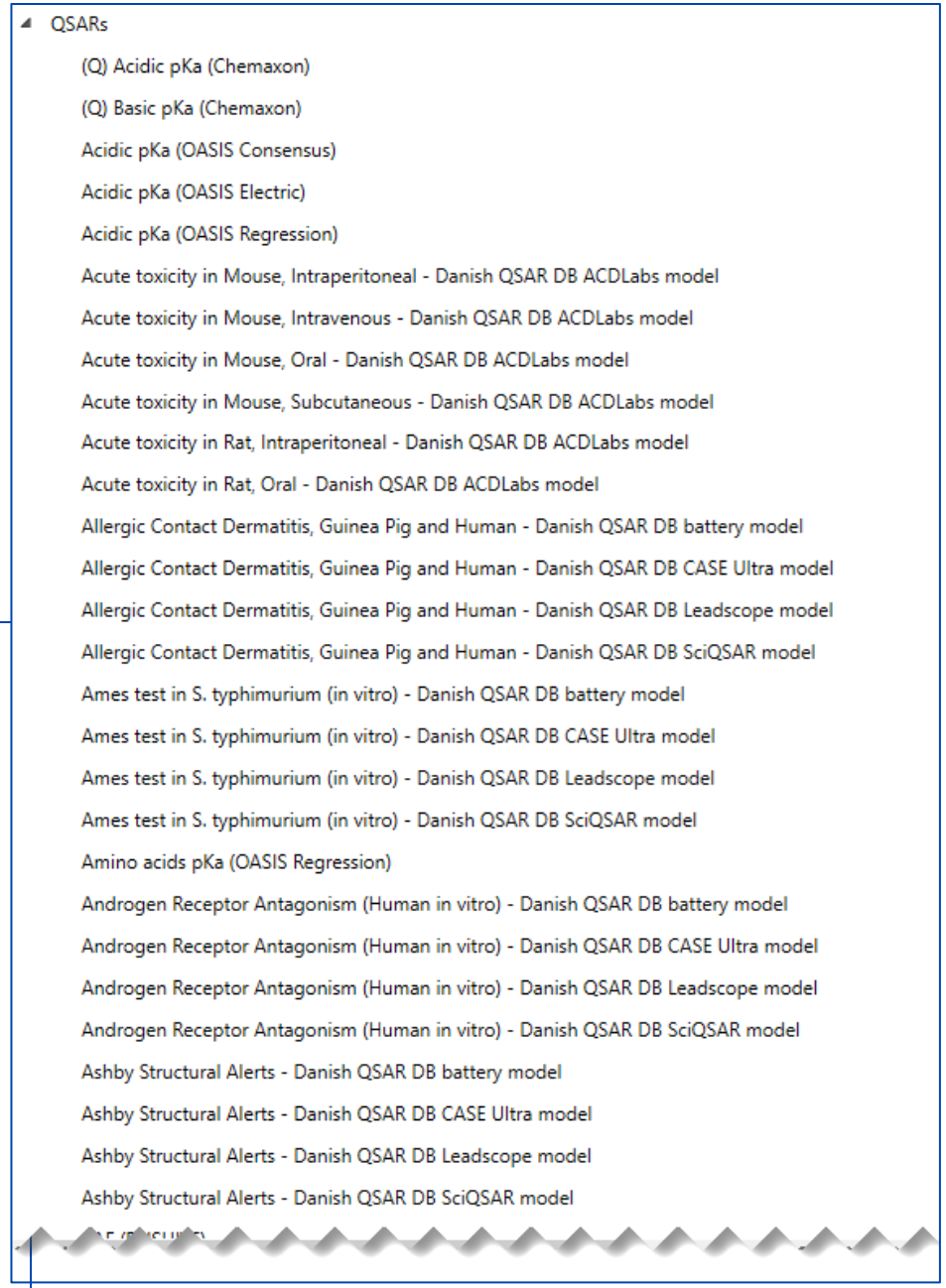




Information in QSAR Toolbox

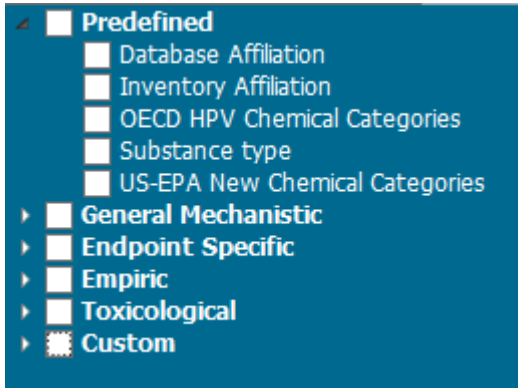
- 50+ databases
- Predictions of properties from parameter calculators and (Q)SARs

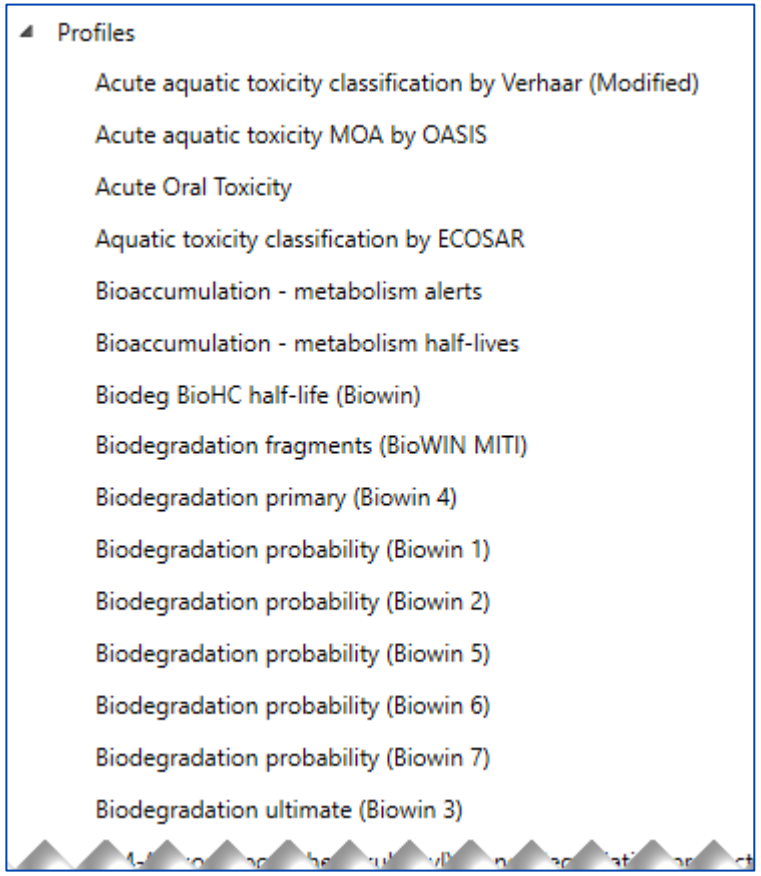




Information in QSAR Toolbox

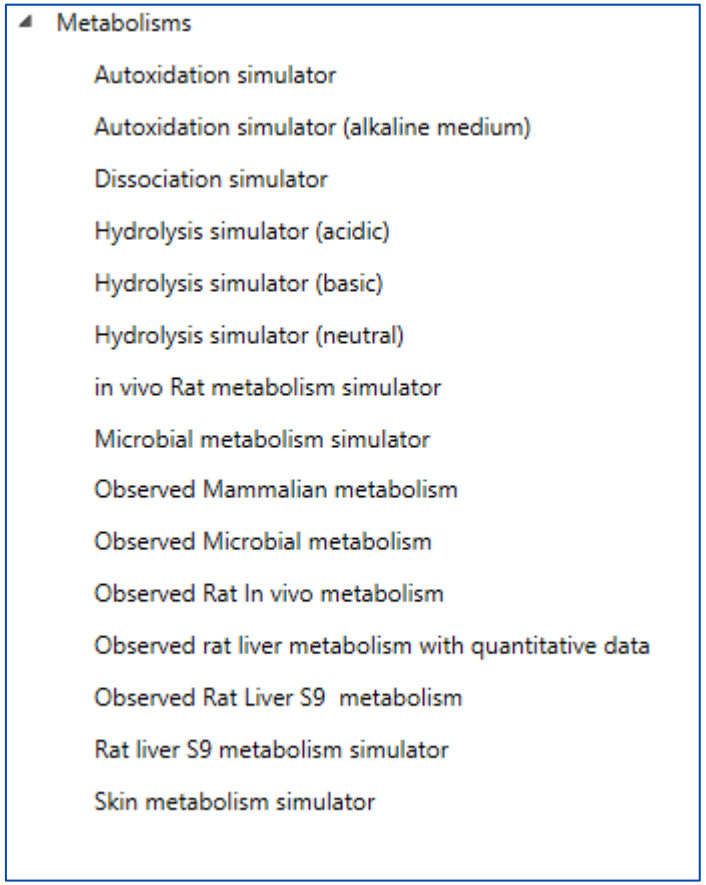
- 50+ databases
- Predictions of properties from parameter calculators and (Q)SARs
- Profiling: Knowledge on structural alerts





Information in QSAR Toolbox

- 50+ databases
- Predictions of properties from parameter calculators and (Q)SARs
- Profiling: Knowledge on structural alerts
- Metabolism simulators: Potential degradation products of concern



=> Efficient screening of PBT/vPvB properties with ECHA PBT screening profiler

ECHA PBT screening profiler

ECHA PBT screening profiler

- Published in April 2021 to support authorities and registrants in assessing the PBT/vPvB potential of individual or groups of substances
- It combines experimental data and (Q)SAR predictions and considers applicability domain if possible
- Profiler rules according to PBT/vPvB criteria in REACH Annex XIII and REACH R.11 PBT guidance
- Includes also indication of potential for bioaccumulation in terrestrial mammals and other air-breathers

Installation:

QSAR **Tool**box 4.4.1 Repository Client

or

https://repository.qsartoolbox.org/

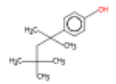
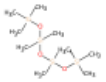
ECHA
ECHA P screening (BETA)

ECHA
ECHA B screening (BETA)

ECHA
ECHA T (ENV) screening (BETA)

Example output

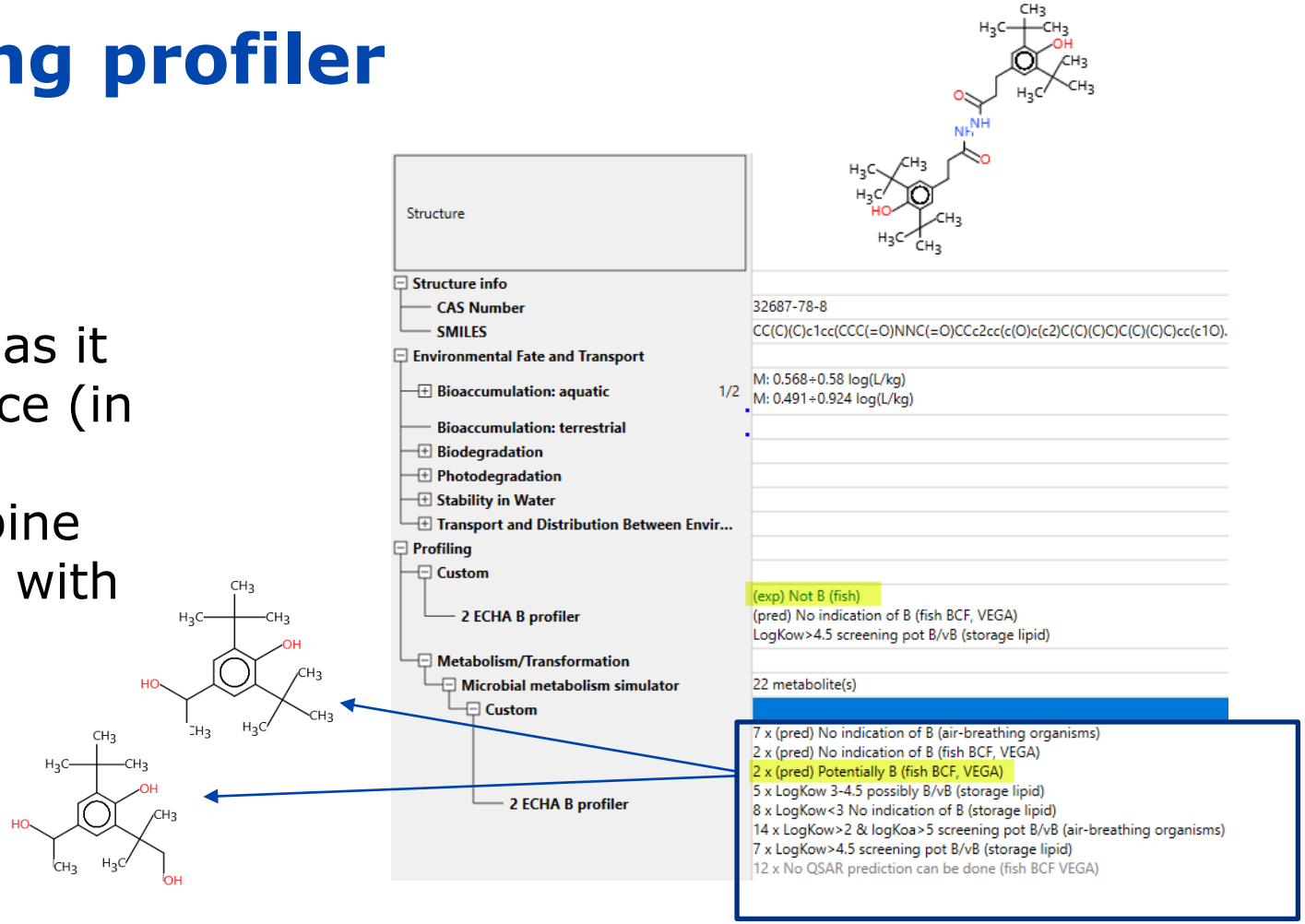
Profiler results

Filter endpoint tree...		1 [target]	2 added by user
Structure			
Partition Coefficient:	2/4	M: 4.8	M: 5.4
Environmental Fate and Transport			
Bioaccumulation: aquatic			
OECD Guideline 305 (Bioconcentration: Flow-through Fish Test)	2/9	M: 261 dimensionless	M: 3.21 log(L/kg) M: 3.21 log(L/kg) M: 3.25 log(L/kg) M: 3.25 log(L/kg) M: 3.58 log(L/kg)
Biodegradation			
Biodegradation in Sewage Treatment...			
Biodegradation in soil	1/10		M: 1.2 d
Biodegradation in water and sediment...			
% Degradation	1/5	M: 0 %	
Half-life	2/7	M: ≥8÷≤13 d M: ≥13÷≤23 d M: >20 d M: ≥8÷≤50 d M: 60 d	M: 53 d M: 192 d
Biodegradation in Water: Screening...	1/4	M: 0 %	
Ecotoxicological Information			
Aquatic Toxicity	AW SW		
Chlorophyta (green algae)	2/4	M: <1 mg/L	M: >0.0022 mg/L
Arthropoda (arthropods)	2/47	M: 0.0001 mg/L	M: >0.0049 mg/L
Chordata (chordates)	2/514	M: 2.5 mg/kg bdwt/d	M: >0.0053 mg/L
Profiling			
Custom			
1 ECHA P profiler		(exp) P (pred) Potentially P/vP (BIOWIN, VEGA and/or Danish QSAR DB)	(exp) vP (pred) Potentially P/vP (BIOWIN) / No QSAR prediction can be done (VEGA/Danish QSAR DB)
2 ECHA B profiler		(pred) No indication of B (fish BCF, VEGA) LogKow>2 & logKoa>5 screening pot B/vB (air-breathing organisms) LogKow>4.5 screening pot B/vB (storage lipid)	(exp) B (fish) (pred) No indication of B (air-breathing organisms) LogKow>4.5 screening pot B/vB (storage lipid) No QSAR prediction can be done (fish BCF VEGA)
3 ECHA T profiler (ENV)		(exp) No indication of T (from available long term studies: fish, daphnids and algae) (exp) No indication of T (from available short term studies: fish, daphnids and algae) (pred) No indication of T (Danish QSAR DB, acute) (pred) No indication of T (ECOSAR LC50 fish) (pred) No indication of T (VEGA, acute)	(exp) T (pred) No acute aquatic effects expected (ECOSAR, max logKow exceeded) No QSAR prediction can be done (Danish QSAR DB) No QSAR prediction can be done (VEGA) Water solubility low: effects may not show in short term toxicity tests; long-term tests likely more adequate

ECHA PBT screening profiler

Assessment of relevant degradation products

Not included int the profiler as it will decrease the performance (in terms of calculation speed). However, the user can combine ECHA PBT screening profiler with simulators.



Profiler highlights bioaccumulation potential for predicted transformation products

ECHA PBT screening profiler

Current limitations:

- Works with QSAR Toolbox version 4.4, VEGA addin needs update to work for v4.5
- the profiler for B does not take into account ionisability of the substance and related uncertainties with the predicted B potential coming with that

Send feedback to: ECHA PBT EG <pbt_wg@echa.europa.eu>

Precursor search with QSAR Toolbox

Aim: identify substances which can transform in a substance of concern

Precursor

↓ Transformation reaction, e.g. biodegradation, metabolism

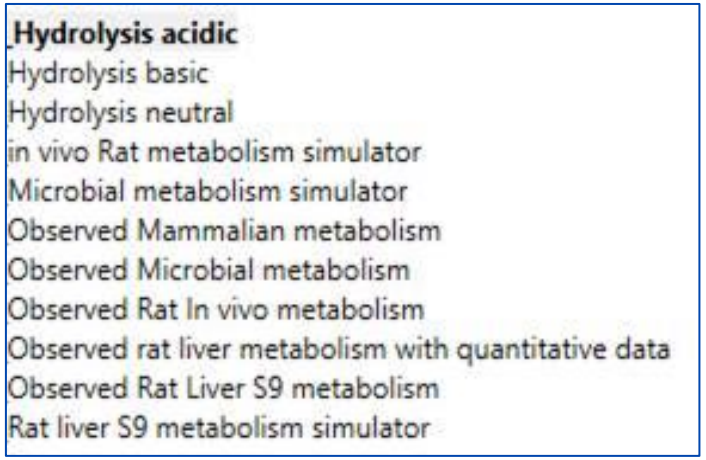
Substance of concern

Precursors search – example Bisphenols

Precursor screening for different types of Bisphenols to support substance evaluation work

- Input: list of different bisphenol group derivatives
- Creation of customised profilers in the QSAR Toolbox
- Application of relevant simulators to predict potential degradation or transformation products

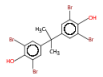
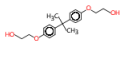
Tutorial: https://qsartoolbox.org/wp-content/uploads/2020/04/Tutorial_5_Building-custom-profiler.pdf



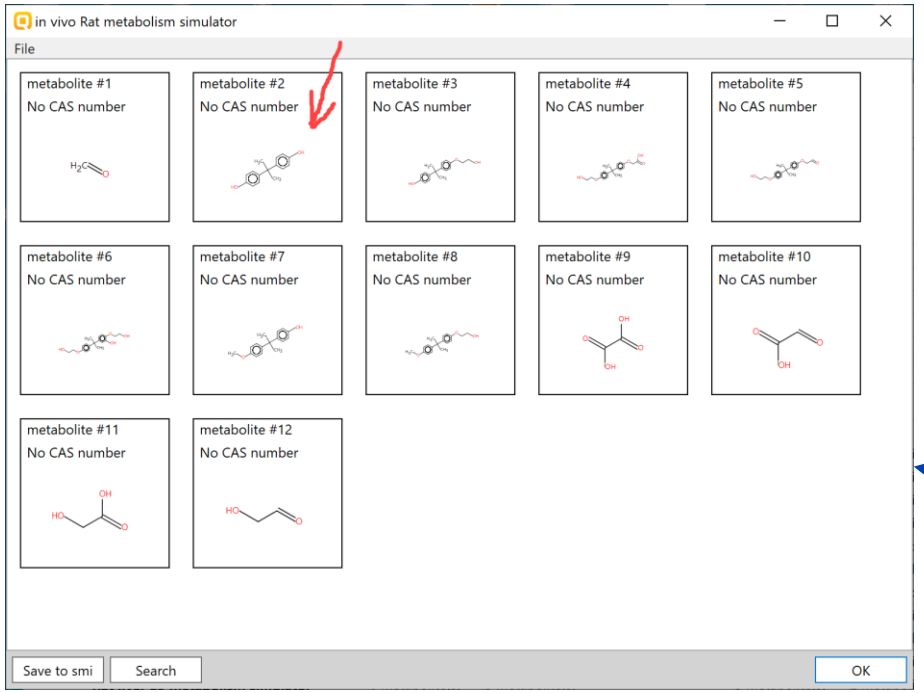
Precursors of Bisphenols

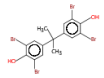
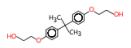
- Identification of target structures within all transformation products and giving alert which simulator identified the target

Potential precursor

Filter endpoint tree...	1	2	3
Structure			
Structure info			
Parameters			
Physical Chemical Properties			
Environmental Fate and Transport			
Ecotoxicological Information			
Human Health Hazards			
Profiling			
Custom			
BPA	(N/A)	BPA_in vivo Rat metabolism simulator	(N/A)
Metabolism/Transformation			
Hydrolysis simulator (acidic)	0 metabolite(s)	0 metabolite(s)	0 metal
Hydrolysis simulator (basic)	0 metabolite(s)	0 metabolite(s)	0 metal
Hydrolysis simulator (neutral)	0 metabolite(s)	0 metabolite(s)	0 metal
in vivo Rat metabolism simulator	0 metabolite(s)	12 metabolite(s)	6 metal
Microbial metabolism simulator	37 metabolite(s)	102 metabolite(s)	131 me
Observed Mammalian metabolism	Not tested	Not tested	Not tes
Observed Microbial metabolism	Not tested	Not tested	Not tes
Observed Rat In vivo metabolism	3 metabolite(s)	Not tested	Not tes
Observed rat liver metabolism with qu...	Not tested	Not tested	Not tes
Observed Rat Liver S9 metabolism	Not tested	Not tested	Not tes
Rat liver S9 metabolism simulator	0 metabolite(s)	5 metabolite(s)	5 metal

BPA among the predicted metabolites



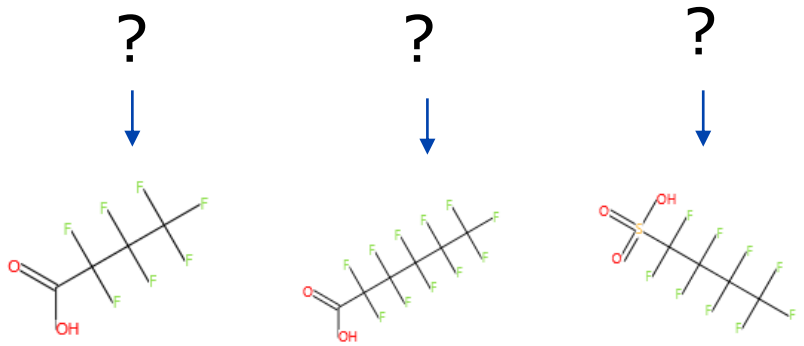
Filter endpoint tree...	1	2	3
Structure			
Structure info			
Parameters			
Physical Chemical Properties			
Environmental Fate and Transport			
Ecotoxicological Information			
Human Health Hazards			
Profiling			
Custom			
BPA	(N/A)	BPA_in vivo Rat metabolism simulator	(N/A)
Metabolism/Transformation			
Hydrolysis simulator (acidic)	0 metabolite(s)	0 metabolite(s)	0 metal
Hydrolysis simulator (basic)	0 metabolite(s)	0 metabolite(s)	0 metal
Hydrolysis simulator (neutral)	0 metabolite(s)	0 metabolite(s)	0 metal
in vivo Rat metabolism simulator	0 metabolite(s)	12 metabolite(s)	6 metal
Microbial metabolism simulator	37 metabolite(s)	102 metabolite(s)	131 me
Observed Mammalian metabolism	Not tested	Not tested	Not tes
Observed Microbial metabolism	Not tested	Not tested	Not tes
Observed Rat In vivo metabolism	3 metabolite(s)	Not tested	Not tes
Observed rat liver metabolism with qu...	Not tested	Not tested	Not tes
Observed Rat Liver S9 metabolism	Not tested	Not tested	Not tes
Rat liver S9 metabolism simulator	0 metabolite(s)	5 metabolite(s)	5 metal

Precursor search with customised profilers

- Efficient screening of large lists of input structures (imported, or databases / inventories in QSAR Toolbox)
- Results can be exported in text file / excel
- Verification step recommended to confirm that degradation is relevant and target structures are formed in sufficient quantity

Precursor search – example PFAS

Screening for potential precursor substances Perfluorobutyric acid (PFBA), perfluorohexanoic acid (PFHxA), and perfluorobutanesulfonic acid (PFBS)



Aim: identify potential precursors from list of per- and polyfluoroalkyl substances (PFAS) to support PFAS restriction work

- Input for restriction report on Undecafluorohexanoic acid, its salts and related substances;

Method

- QSAR Toolbox v4.1: pre-processing step to retrieve all compounds with the substructure $CF_3(CF2)_2$ in any database or inventory in the QSAR Toolbox, plus ca 400 structures from an internal screening exercise
- Customised profilers were created to identify target structures within all transformation products of the pre-selected compounds.
- Transformations were based on the simulators for hydrolysis (neutral, acidic and basic), and microbial biodegradation.

Findings

From about 1000 structures, 55 were identified as potential precursors for PFBA, 48 for PFBS and 73 for PFHxA.

Learnings

QSAR Toolbox contains databases with relevant substances and simulators to predict potential degradation products of large data sets.

Probability and quantity of predicted degradation products are not part of the QSAR Toolbox predictions.

Supporting information strengthens the findings from the screening.

Thank you!

Subscribe to our news at echa.europa.eu/subscribe

Follow us on Twitter
@EU_ECHA

Follow us on Facebook
Facebook.com/EUECHA