

OECD QSAR Toolbox in support of PBT identification under REACH

Webinar: OECD QSAR Toolbox
applications for REACH and beyond

30 November 2021

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Overview

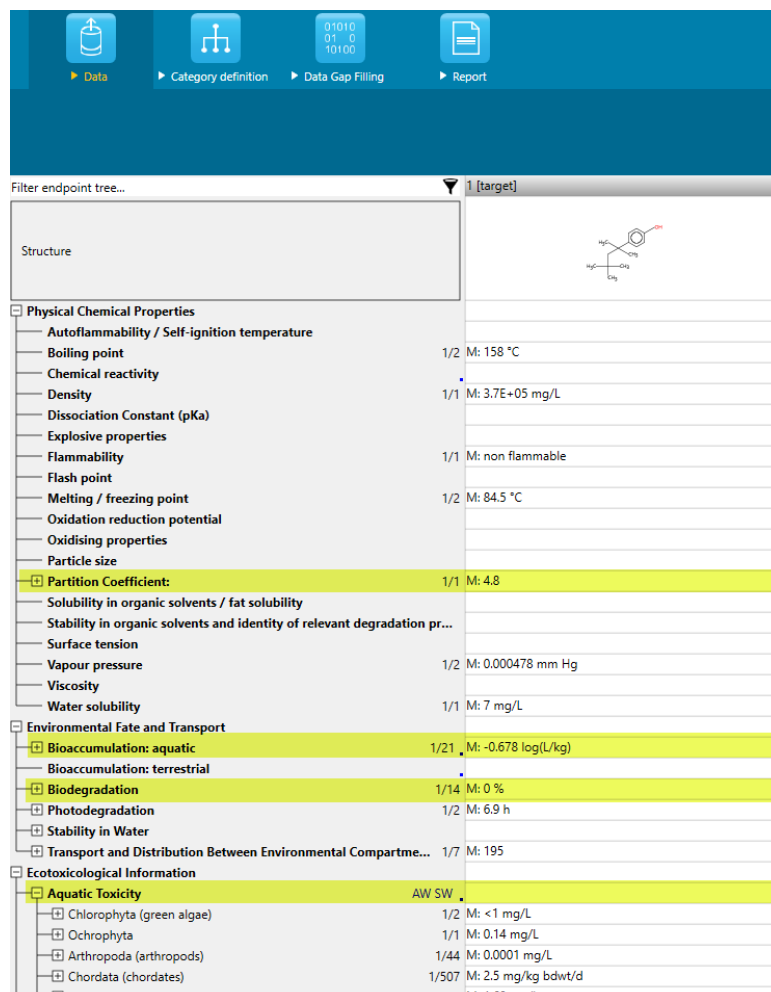
- Gathering relevant information in the QSAR Toolbox
- ECHA PBT screening profiler
- Precursor search with QSAR Toolbox
 - Bisphenols
 - PFAS

Gathering relevant information in the QSAR Toolbox



Information in QSAR Toolbox

- 50+ databases



The screenshot shows the QSAR Toolbox interface with a chemical structure and a list of properties. The interface includes a top navigation bar with icons for Data, Category definition, Data Gap Filling, and Report. Below this is a filter endpoint tree and a structure viewer. The main area displays a list of properties with their corresponding values and methods.

Property	Value	Method
Autoflammability / Self-ignition temperature		
Boiling point	158 °C	M
Chemical reactivity		
Density	3.7E+05 mg/L	M
Dissociation Constant (pKa)		
Explosive properties		
Flammability	non flammable	M
Flash point		
Melting / freezing point	84.5 °C	M
Oxidation reduction potential		
Oxidising properties		
Particle size		
Partition Coefficient	4.8	M
Solubility in organic solvents / fat solubility		
Stability in organic solvents and identity of relevant degradation pr...		
Surface tension		
Vapour pressure	0.000478 mm Hg	M
Viscosity		
Water solubility	7 mg/L	M
Environmental Fate and Transport		
Bioaccumulation: aquatic	-0.678 log(L/kg)	M
Bioaccumulation: terrestrial		
Biodegradation	0 %	M
Photodegradation	6.9 h	M
Stability in Water		
Transport and Distribution Between Environmental Compartme...	195	M
Ecotoxicological Information		
Aquatic Toxicity	AW SW	
Chlorophyta (green algae)	<1 mg/L	M
Ochrophyta	0.14 mg/L	M
Arthropoda (arthropods)	0.0001 mg/L	M
Chordata (chordates)	2.5 mg/kg bw/d	M

Databases

- Acute Oral toxicity DB
- ADME Database
- Aquatic ECETOC
- Aquatic Japan MoE
- Aquatic OASIS
- Bacterial mutagenicity ISSSTY
- Bioaccumulation Canada
- Bioaccumulation fish CEFIC LRI
- Biocides and plant protection ISSBIOC
- Bioconcentration NITE
- Biodegradation in soil OASIS
- Biodegradation NITE
- Biota-Sediment Accumulation Factor US-EPA
- Carcinogenic Potency Database (CPDB)
- Carcinogenicity&mutagenicity ISSCAN
- Cell Transformation Assay ISSCTA
- Chemical Reactivity COLIPA
- Dendritic cells COLIPA
- Developmental & Reproductive Toxicity (DART)
- Developmental toxicity database (CAESAR)
- Developmental toxicity ILSI
- ECHA REACH
- ECOTOX
- Experimental pKa
- Eye Irritation ECETOC
- Food TOX Hazard EFSA
- GARD Skin sensitization
- Genotoxicity & Carcinogenicity ECVAM
- Genotoxicity OASIS
- Genotoxicity pesticides EFSA
- GSH Experimental RC50
- Human Half-Life

Information in QSAR Toolbox

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

Calculators

2D

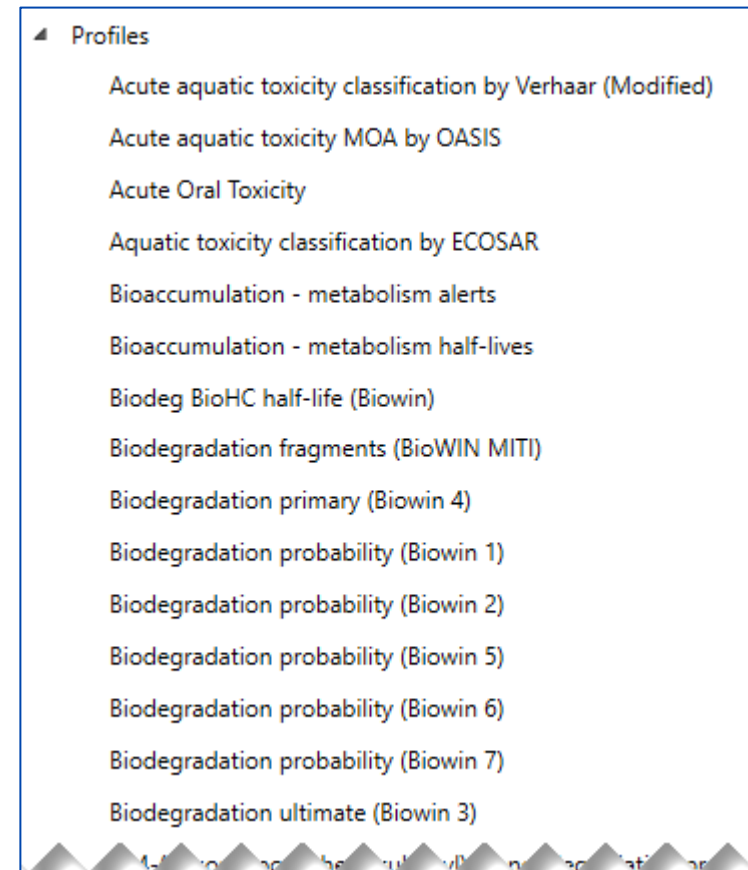
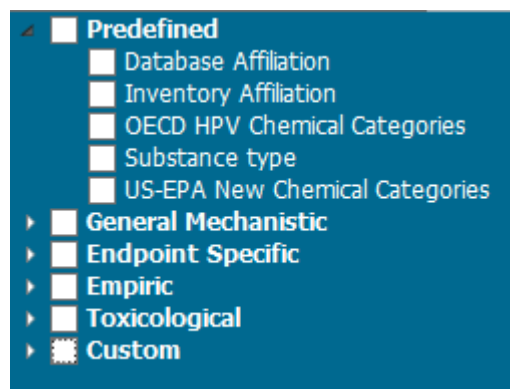
- (Q) Acidic pKa (Chemaxon)
- (Q) Basic pKa (Chemaxon)
- Acidic pKa (OASIS Consensus)
- Acidic pKa (OASIS Electric)
- Acidic pKa (OASIS Regression)
- Amino acids pKa (OASIS Regression)
- BAF
- BAF (lower trophic)
- BAF (mid trophic)
- BAF (upper trophic)
- BAF (upper trophic, biotransformation rate is zero)
- Basic pKa (OASIS Regression)
- BCF
- BCF (lower trophic)
- BCF (mid trophic)

QSARs

- (Q) Acidic pKa (Chemaxon)
- (Q) Basic pKa (Chemaxon)
- Acidic pKa (OASIS Consensus)
- Acidic pKa (OASIS Electric)
- Acidic pKa (OASIS Regression)
- Acute toxicity in Mouse, Intraperitoneal - Danish QSAR DB ACDLabs model
- Acute toxicity in Mouse, Intravenous - Danish QSAR DB ACDLabs model
- Acute toxicity in Mouse, Oral - Danish QSAR DB ACDLabs model
- Acute toxicity in Mouse, Subcutaneous - Danish QSAR DB ACDLabs model
- Acute toxicity in Rat, Intraperitoneal - Danish QSAR DB ACDLabs model
- Acute toxicity in Rat, Oral - Danish QSAR DB ACDLabs model
- Allergic Contact Dermatitis, Guinea Pig and Human - Danish QSAR DB battery model
- Allergic Contact Dermatitis, Guinea Pig and Human - Danish QSAR DB CASE Ultra model
- Allergic Contact Dermatitis, Guinea Pig and Human - Danish QSAR DB Leadscope model
- Allergic Contact Dermatitis, Guinea Pig and Human - Danish QSAR DB SciQSAR model
- Ames test in *S. typhimurium* (in vitro) - Danish QSAR DB battery model
- Ames test in *S. typhimurium* (in vitro) - Danish QSAR DB CASE Ultra model
- Ames test in *S. typhimurium* (in vitro) - Danish QSAR DB Leadscope model
- Ames test in *S. typhimurium* (in vitro) - Danish QSAR DB SciQSAR model
- Amino acids pKa (OASIS Regression)
- Androgen Receptor Antagonism (Human in vitro) - Danish QSAR DB battery model
- Androgen Receptor Antagonism (Human in vitro) - Danish QSAR DB CASE Ultra model
- Androgen Receptor Antagonism (Human in vitro) - Danish QSAR DB Leadscope model
- Androgen Receptor Antagonism (Human in vitro) - Danish QSAR DB SciQSAR model
- Ashby Structural Alerts - Danish QSAR DB battery model
- Ashby Structural Alerts - Danish QSAR DB CASE Ultra model
- Ashby Structural Alerts - Danish QSAR DB Leadscope model
- Ashby Structural Alerts - Danish QSAR DB SciQSAR model

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

Metabolisms
Autoxidation simulator
Autoxidation simulator (alkaline medium)
Dissociation simulator
Hydrolysis simulator (acidic)
Hydrolysis simulator (basic)
Hydrolysis simulator (neutral)
in vivo Rat metabolism simulator
Microbial metabolism simulator
Observed Mammalian metabolism
Observed Microbial metabolism
Observed Rat In vivo metabolism
Observed rat liver metabolism with quantitative data
Observed Rat Liver S9 metabolism
Rat liver S9 metabolism simulator
Skin metabolism simulator


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 Toolbox 4.4.1 Repository Client](#) >

or

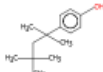
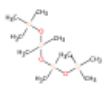
<https://repository.qsartoolbox.org/>



ECHA
ECHA P
screening
(BETA)

ECHA
ECHA B
screening
(BETA)

ECHA
ECHA T (ENV)
screening
(BETA)

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	M: 261 dimensionless	M: 3.21 log(L/kg)
OECD Guideline 305 (Bioconcentration: Flow-through Fish Test) 2/9		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 %	M: 53 d
	M: ≥8÷≤13 d	M: 192 d
	M: ≥13÷≤23 d	
Half-life 2/7	M: >20 d	
	M: ≥8÷≤50 d	
	M: 60 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

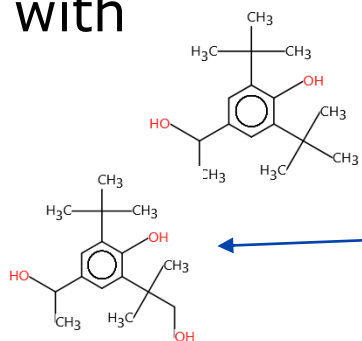
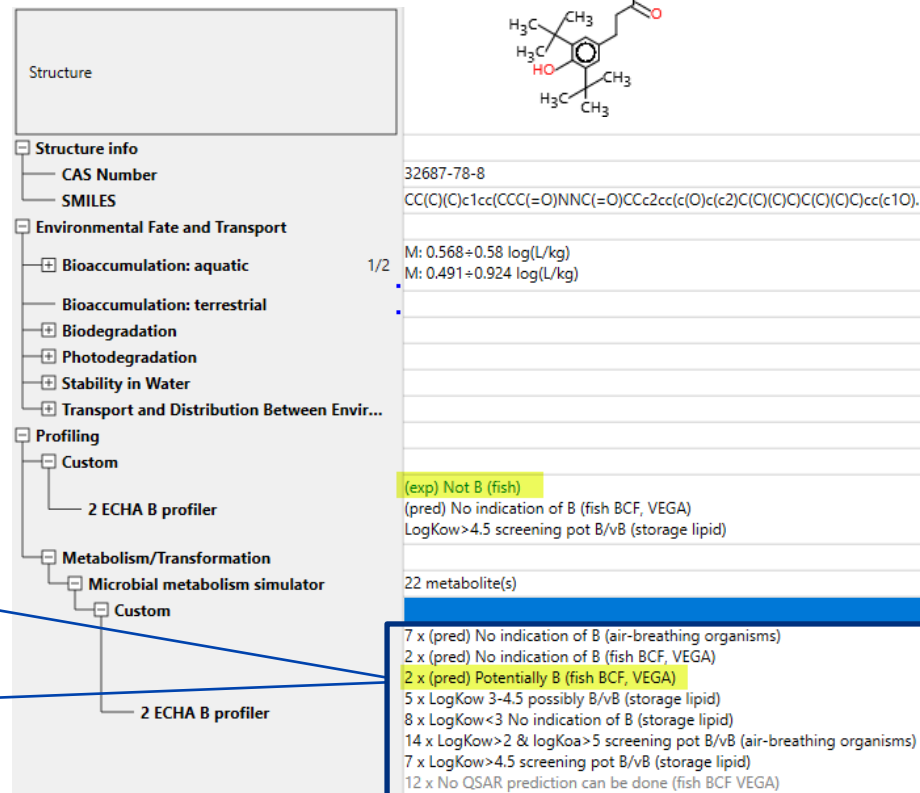
Profiler results

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

Structure

Structure info

- CAS Number: 32687-78-8
- SMILES: CC(C)(C)c1cc(CCC(=O)NNC(=O)CCc2cc(c(O)c(c2)C(C)C)C(C)C)cc(c1O)

Environmental Fate and Transport

- Bioaccumulation: aquatic: 1/2
 - M: 0.568+0.58 log(L/kg)
 - M: 0.491+0.924 log(L/kg)
- Bioaccumulation: terrestrial
- Biodegradation
- Photodegradation
- Stability in Water
- Transport and Distribution Between Envir...

Profiling

- Custom
 - 2 ECHA B profiler
- Metabolism/Transformation
 - Microbial metabolism simulator
 - Custom: 22 metabolite(s)

(exp) Not B (fish)
(pred) No indication of B (fish BCF, VEGA)
LogKow>4.5 screening pot B/vB (storage lipid)

7 x (pred) No indication of B (air-breathing organisms)
2 x (pred) No indication of B (fish BCF, VEGA)
2 x (pred) Potentially B (fish BCF, VEGA)
5 x LogKow 3-4.5 possibly B/vB (storage lipid)
8 x LogKow<3 No indication of B (storage lipid)
14 x LogKow>2 & logKoa>5 screening pot B/vB (air-breathing organisms)
7 x LogKow>4.5 screening pot B/vB (storage lipid)
12 x No QSAR prediction can be done (fish BCF VEGA)

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

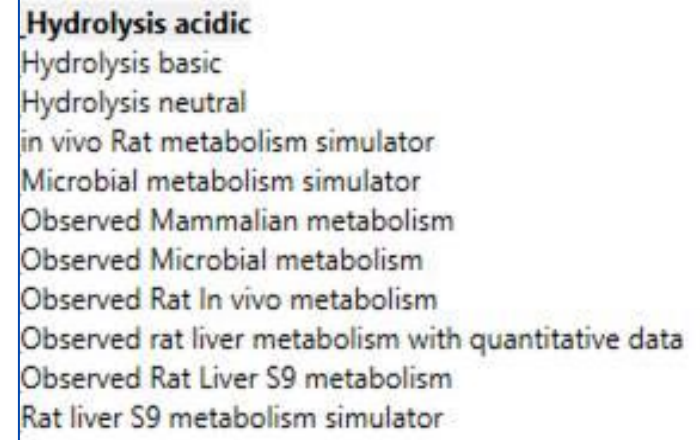
Substance of concern

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



Hydrolysis acidic
Hydrolysis basic
Hydrolysis neutral
in vivo Rat metabolism simulator
Microbial metabolism simulator
Observed Mammalian metabolism
Observed Microbial metabolism
Observed Rat In vivo metabolism
Observed rat liver metabolism with quantitative data
Observed Rat Liver S9 metabolism
Rat liver S9 metabolism simulator

Precursors of Bisphenols

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

Filter endpoint tree...

Structure

Structure info

Parameters

Physical Chemical Properties

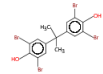
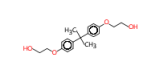

Environmental Fate and Transport

Ecotoxicological Information

Human Health Hazards

Profiling

- Custom
 - BPA
- Metabolism/Transformation
 - Hydrolysis simulator (acidic)
 - Hydrolysis simulator (basic)
 - Hydrolysis simulator (neutral)
 - in vivo Rat metabolism simulator
 - Microbial metabolism simulator
 - Observed Mammalian metabolism
 - Observed Microbial metabolism
 - Observed Rat In vivo metabolism
 - Observed rat liver metabolism with qu...
 - Observed Rat Liver S9 metabolism
 - Rat liver S9 metabolism simulator


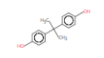
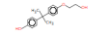
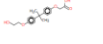
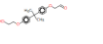

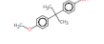
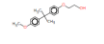
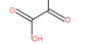
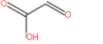

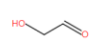
	1	2	3
Structure			
Structure info			
Parameters			
Physical Chemical Properties			
Environmental Fate and Transport			
Ecotoxicological Information			
Human Health Hazards			
Profiling			
Custom			
BPA	(N/A)	BPA_in vivo Rat metabolism simulator	(N/A)
Metabolism/Transformation			
Hydrolysis simulator (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

Potential precursor

BPA among the predicted metabolites

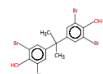
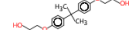

in vivo Rat metabolism simulator

File

metabolite #1 No CAS number 	metabolite #2 No CAS number 	metabolite #3 No CAS number 	metabolite #4 No CAS number 	metabolite #5 No CAS number 
metabolite #6 No CAS number 	metabolite #7 No CAS number 	metabolite #8 No CAS number 	metabolite #9 No CAS number 	metabolite #10 No CAS number 
metabolite #11 No CAS number 	metabolite #12 No CAS number 			

Save to smi Search OK

Filter endpoint tree...

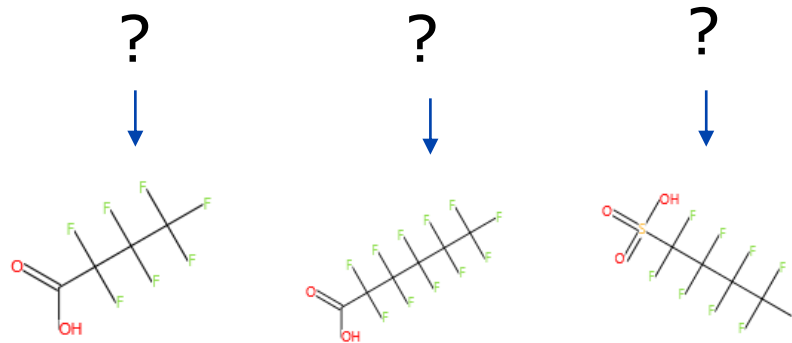
	1	2	3
Structure			
Structure info			
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Environmental Fate and Transport			
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Observed rat liver metabolism with qu...	Not tested	Not tested	Not tes
Observed Rat Liver S9 metabolism	Not tested	Not tested	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 $\text{CF}_3(\text{CF}_2)_2$ 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!

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