Substituting harmful chemicals.

The challenge of perfluorinated compounds

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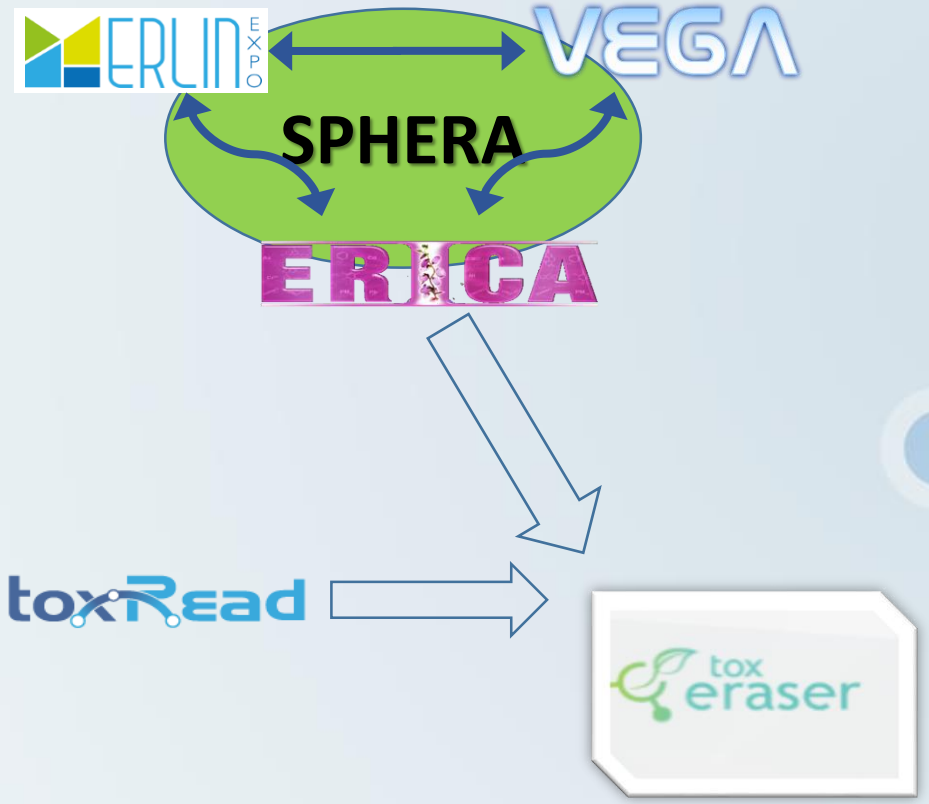
The LIFE VERMEER project



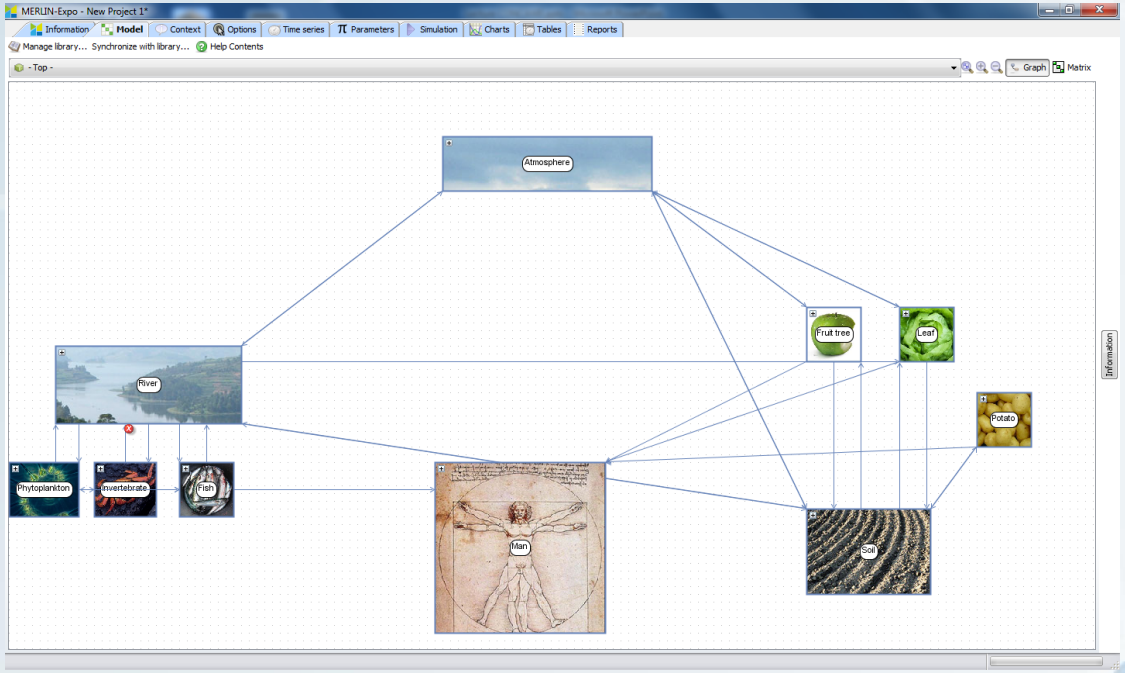
Integrating **VEGA**, **ToxRead**, **MERLIN-Expo**, and **ERICA** in a platform for risk assessment and substitution of risky substances

Towards substitution:

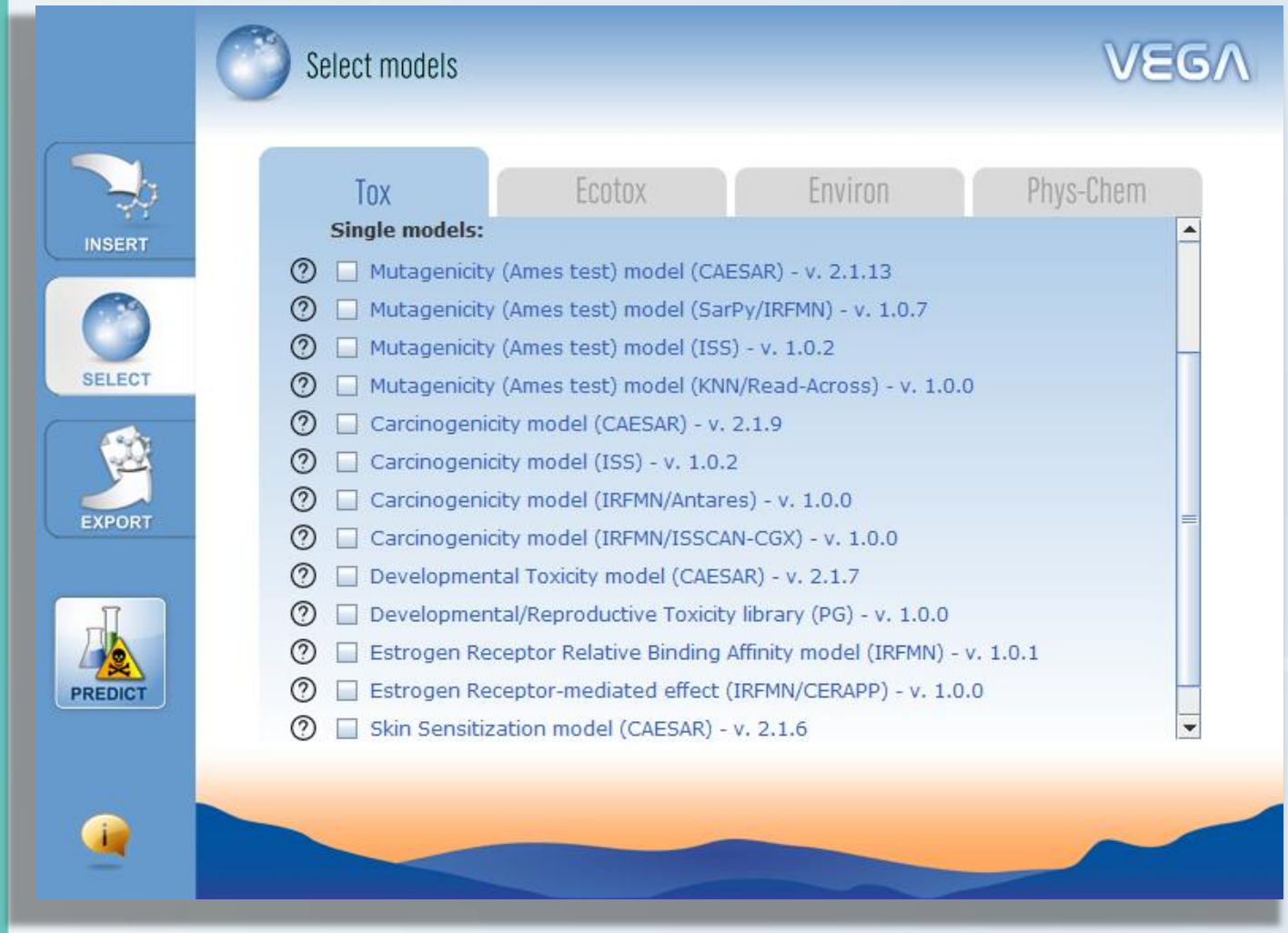
1. Identification of the risky substances
2. Identification of possible substitutes
3. Application to **6** case studies

LIFE16
ENV/IT/000167

Modelling Exposure to chemicals for Risk assessment: a comprehensive Library of multimedia and PBPK models for Integration, prediction, uNcertainty and sensitivity analysis.



VEGA predictive models



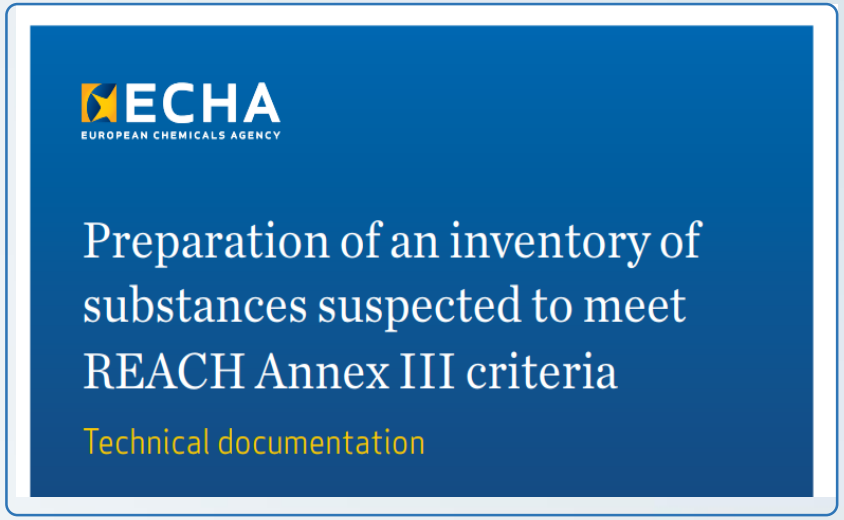
80 models regarding properties on:

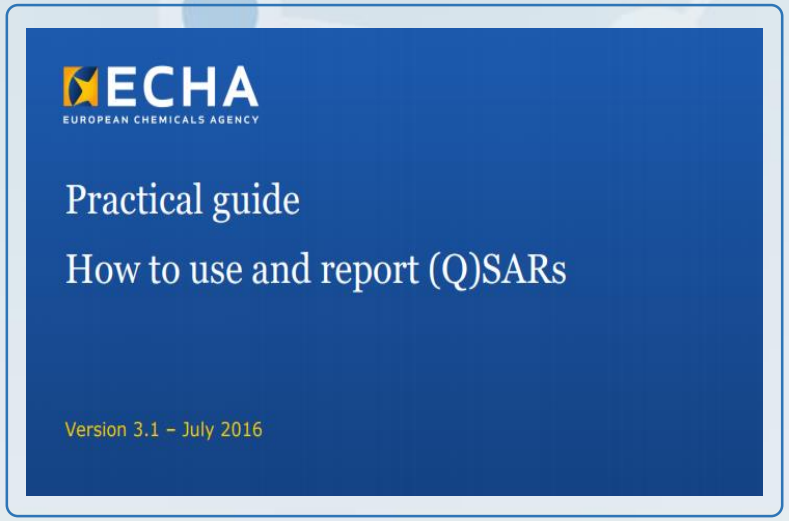
- Human toxicity
- Eco-toxicity
- Environmental
- Physico-chemical
- Toxicokinetics

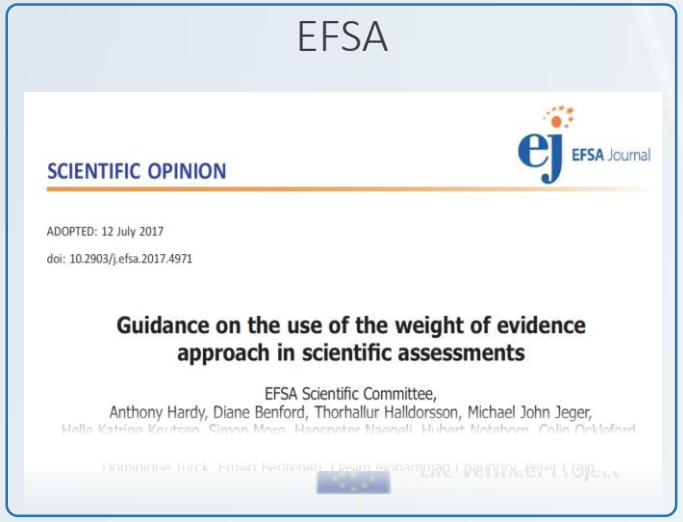
www.vegahub.eu

Regulatory use

- OECD
- ECHA
- EFSA
- Docked to the OECD QSAR Toolbox
- Projects from Italian Health and Environmental Ministries
- Used by German UBA for prioritization and substance evaluation







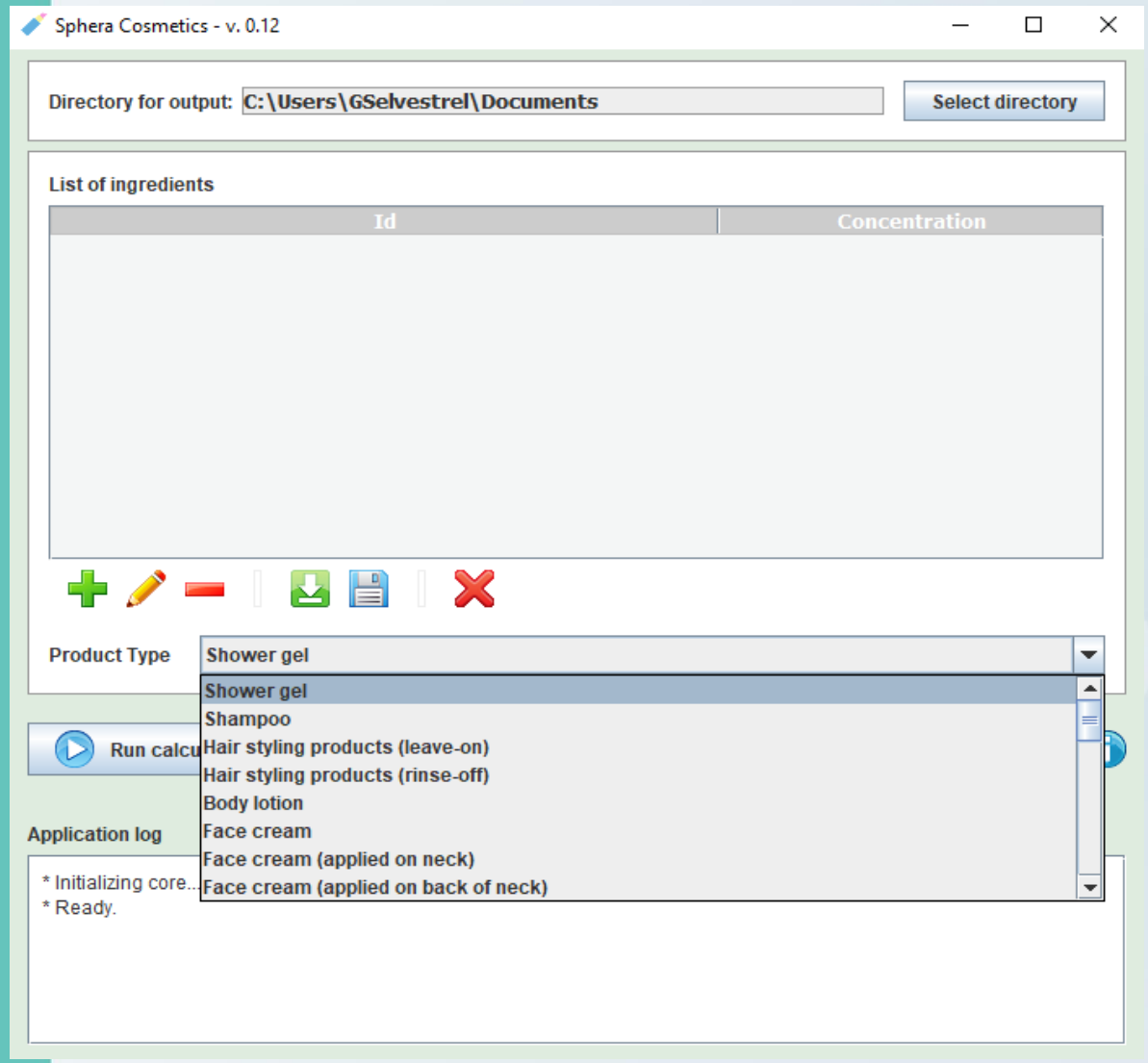
Six tools for specific targets

- Cosmetics
- FCM
- Solvents
- Biocides
- Oil
- Dispersants

life Sphera

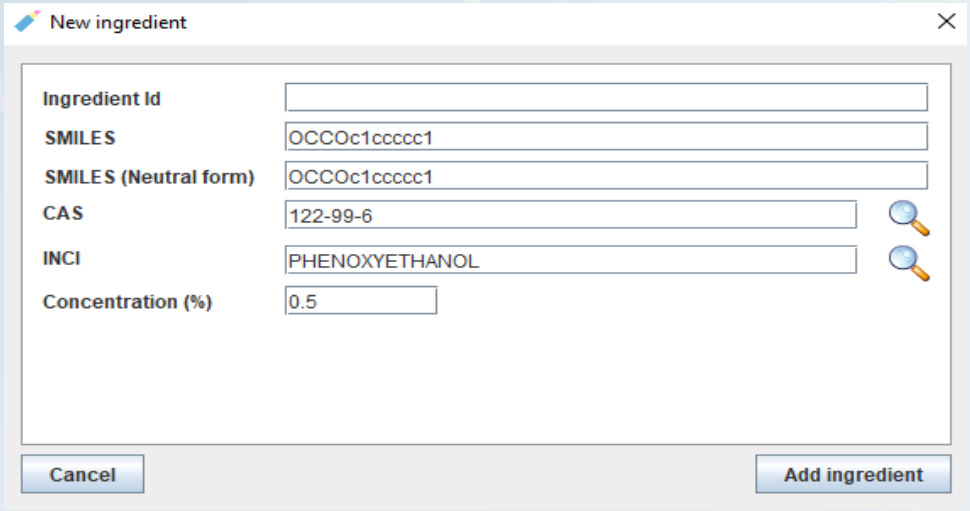
Software Predicting Human and Environmental Risk Assessment

SpheraCosmetics



- The user is asked to provide the information regarding the ingredient, its concentration and the product type

- The software allows to add single or multiple ingredients



SpheraCosmetics

The software provides a preliminary output table with a summary of the hazard and exposure features of the ingredients

Processed product

Product type: **Shower gel**

Ingredients:

	Ingredient Id	CAS	INCI	Conc. %	Annex	Mutagenicity	Dermal abs.	MoS	TTC
Details	DISODIUM EDTA	139-33-3	DISODIUM EDTA	0.05	-	NON-Mutagen (EXPERIMENTAL value)	10%	7168458.78	0.0015 mg/kg bw/day
Details	GLYCERIN	56-81-5	GLYCERIN	5.0	-	NON-Mutagen (EXPERIMENTAL value)	80%	30842.29	0.03 mg/kg bw/day
Details	POTASSIUM BENZOATE	582-25-2	POTASSIUM BENZOATE	2.0	V	NON-Mutagen (EXPERIMENTAL value)	80%	619.62	0.03 mg/kg bw/day
Details	EUGENOL	97-53-0	EUGENOL	0.001	III	NON-Mutagen (EXPERIMENTAL value)	80%	10304659.5	0.03 mg/kg bw/day
Details	GERANIOL	106-24-1	GERANIOL	0.001	III	NON-Mutagen (EXPERIMENTAL value)	40%	6996415.77	0.03 mg/kg bw/day

Question: How to identify safe/risky substances for cosmetics?

- ✓ Libraries of safe substances (SIN, SCIL, CIR)
- ✓ Libraries of substances with threshods
- ✗ Libraries of toxic/excluded compounds

Acceptance depends on regulation

TOXERASER. Future software. The strategy

Identify elements/reasons of risk

Identify lists of safe substances

Identify elements associated to safety

Identify functional use – case studies

Replace substances with safer compounds, if the list of safer substances functional use is available

Identify related compounds with similar phys-chem properties from other safety lists

Design new, safer substances, replacing fragments associated to adverse effect

cC6O4 CAS number: 1190931-41-9
cC6O4 CAS number: 1190931-41-9

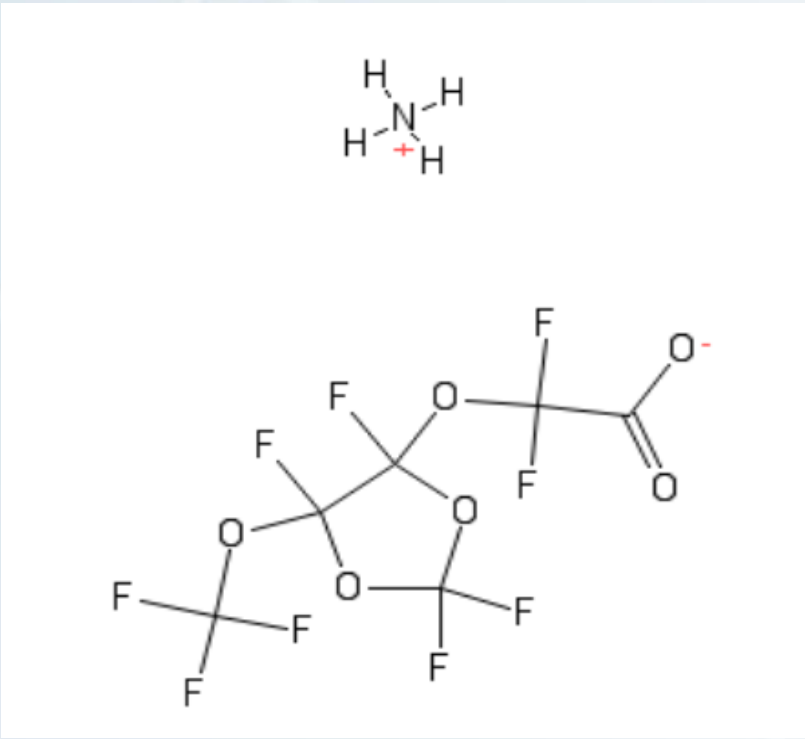
Evaluating a target perfluorinated compound

cC604

CAS: 1190931-41-9

BCF

- *In silico models*
- *Read-across*
- *Reasoning*



Weight-of-evidence

Gather all lines of evidence
Evaluate them
Assemble

- *Relevance*
- *Reliability*
- *Consistency*

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 12 July 2017

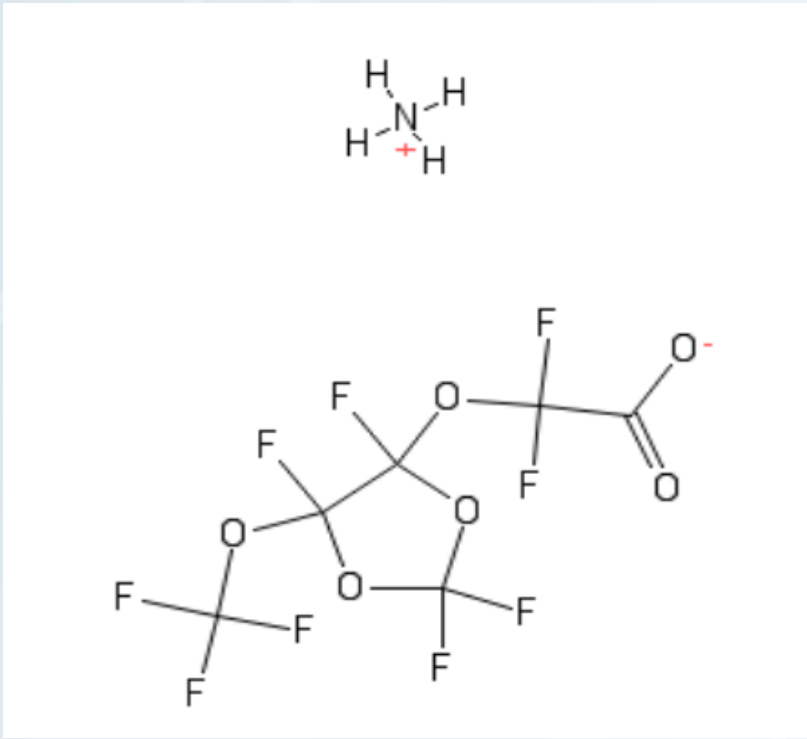
doi: 10.2903/j.efsa.2017.4971

Guidance on the use of the weight of evidence approach in scientific assessments

EFSA Scientific Committee,
Anthony Hardy, Diane Benford, Thorhallur Halldorsson, Michael John Jeger,
Helle Katrine Knutsen, Simon More, Hanspeter Naegeli, Hubert Noteborn, Colin Ockleford,
Antonia Ricci, Guido Rychen, Josef R Schlatter, Vittorio Silano, Roland Solecki,
Dominique Turck, Emilio Benfenati, Qasim Mohammad Chaudhry, Peter Craig

BCF. Multiple in silico models.

- *EPI Suite Meylan* *0.5 (neutral or salt)*
- *OPERA* *0.695*
- *TEST consensus* *1.43 (-1.2 / 3.4)*
- *VEGA CAESAR* *0.06*
- *VEGA Arnot-Gobas* *2.26*



Similar level of reliability: low

Value 0 – 2 - Not bioaccumulative

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.279
Explanation: the predicted compound is outside the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.698
Explanation: no similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 1.301
Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.

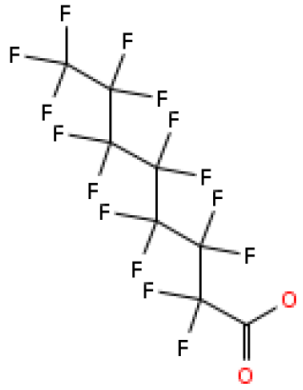
Concordance for similar molecules
Concordance index = 3.301
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

Maximum error of prediction among similar molecules
Max error index = 2.015
Explanation: the maximum error in prediction of similar molecules found in the training set has a high value, considering the experimental variability.

Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

3.1 Applicability Domain:

Similar Compounds, with Predicted and Experimental Values



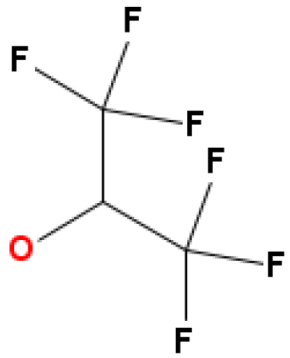
Compound #1

CAS: 335-67-1
Dataset id: 56 (Training set)
SMILES: O=C(O)C(F)(F)C(F)(F)C(F)(F)C(F)(F)C(F)(F)C(F)(F)C(F)(F)C(F)(F)F
Similarity: 0.704

Experimental value [log(L/kg)]: 3.12
Predicted value [log(L/kg)]: 2.534

Alerts (found also in the target): Carbonyl residue (SR 02); COOH group (PG 01)

Alerts (not found in the target): 10 F atoms in the molecule (SO 10)

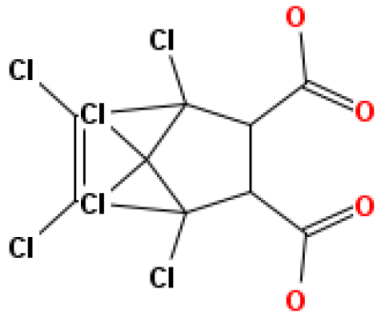


Compound #4

CAS: 920-66-1
Dataset id: 263 (Training set)
SMILES: FC(F)(F)C(O)C(F)(F)F
Similarity: 0.614

Experimental value [log(L/kg)]: 0.3
Predicted value [log(L/kg)]: 0.601

Alerts (not found in the target): OH group (PG 06)



Compound #5

CAS: 115-28-6
Dataset id: 282 (Training set)
SMILES: O=C(O)C1C(C(=O)O)C2(C(=C(C1(C2(Cl)Cl)Cl)Cl)Cl)Cl
Similarity: 0.614

Experimental value [log(L/kg)]: 0.32
Predicted value [log(L/kg)]: 0.261

Alerts (found also in the target): Carbonyl residue (SR 02); COOH group (PG 01)

Read-across. BCF

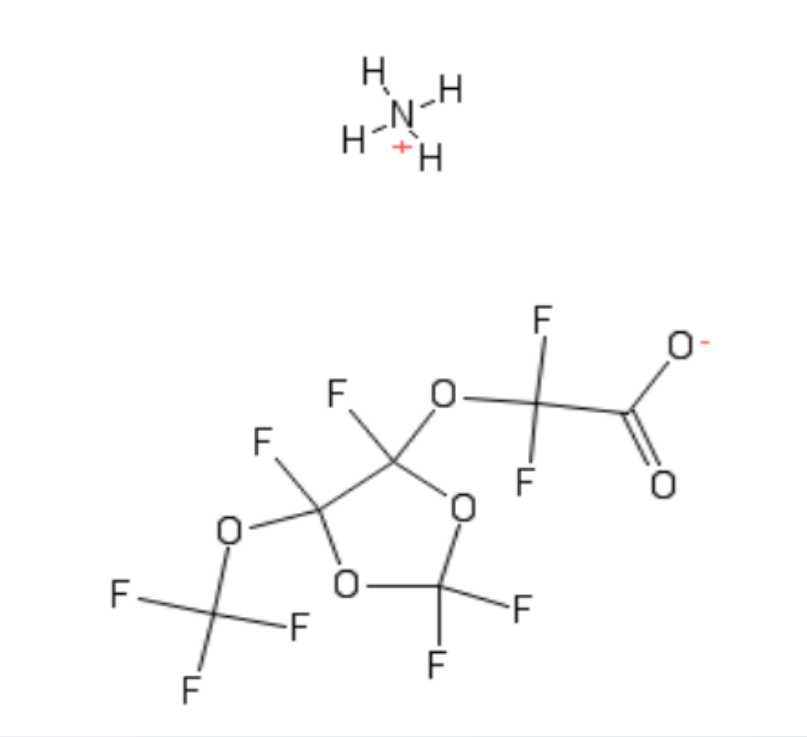
Target:

C 6

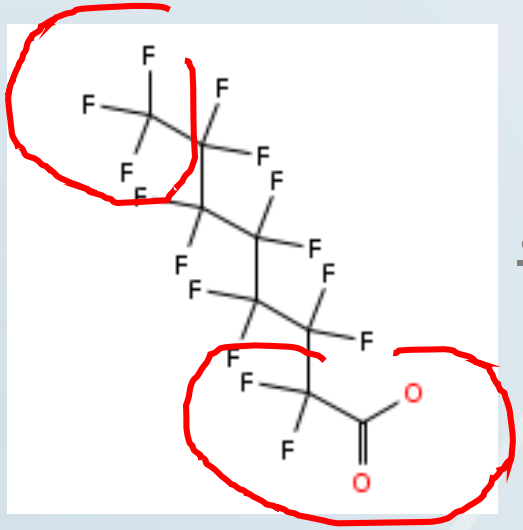
F 9

O 6

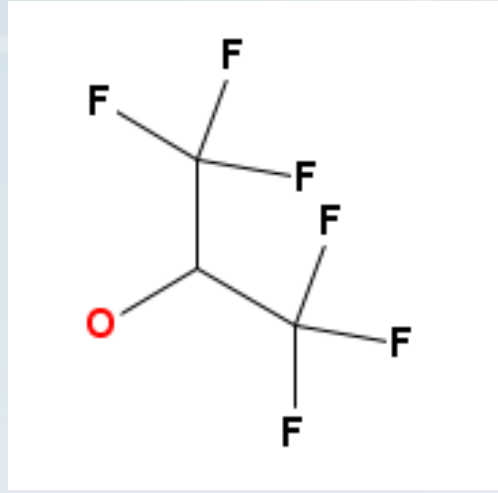
Average 1.7, likely lower



Similar



3.12 (0.977) C8F15O2



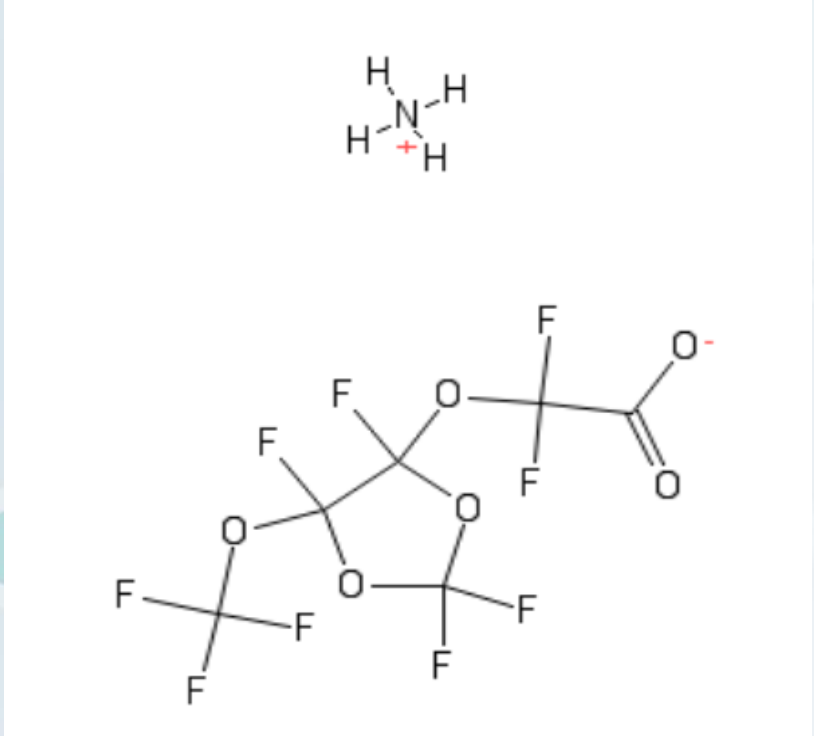
0.3 (-1.3)

C3 F6 0

Weight-of-evidence

Prediction: 0 – 2
Read-across: 0.3, max 1.7 *
Reasoning: COOH, F, chain, oxygen

→ 0.3 – (1.7)



**large experimental variability*

CONCLUSIONS

New software for evaluation of risky substances

Case studies (cosmetics, food, biocides, environmental contaminants, solvents, and generic tool)

Integrated assessment in one single platform.

Risky substances linked to substituents

General tool for substitution

WoE strategy to use in silico and read-across

GRAZIE !