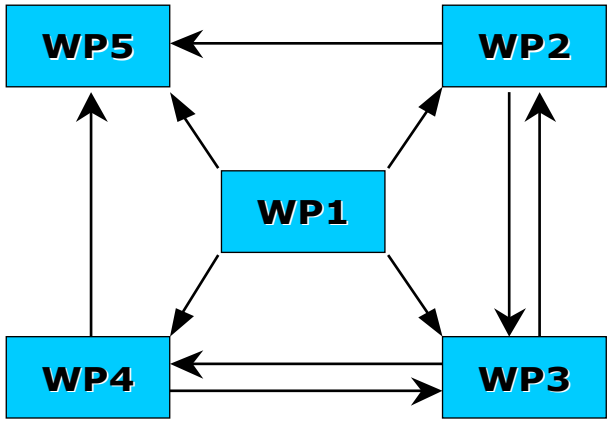

Rijksinstituut voor Volksgezondheid
en Milieu
Ministerie van Volksgezondheid,
Welzijn en Sport

Exemplification of the integration of tools within REACH: the CADASTER project

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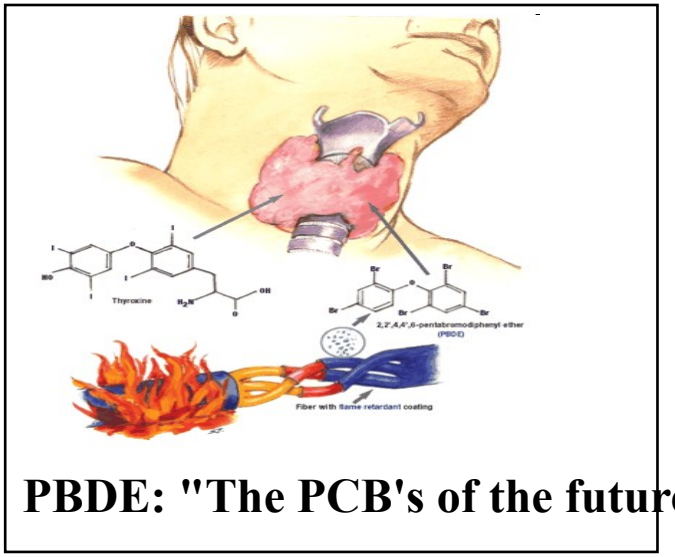
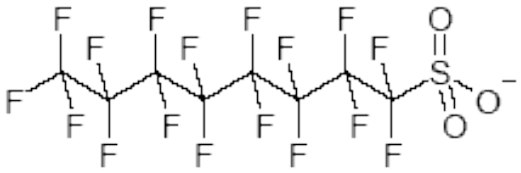
CADASTER: Exemplification of tools within REACH

CADASTER: CAse studies on the Development and Application of *in-Silico* Techniques for Environmental hazard and Risk assessment



PBDE: "The PCB's of the future"



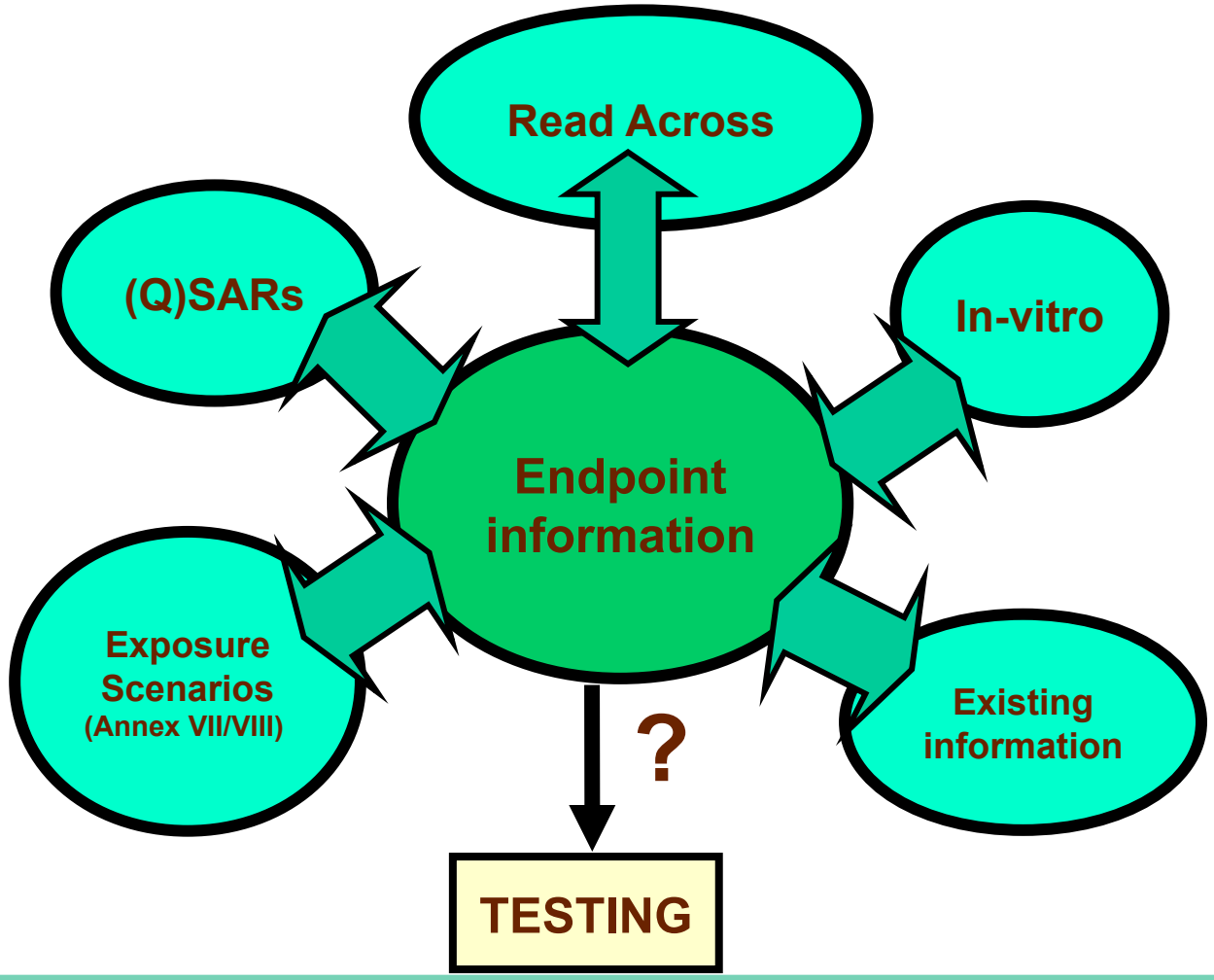
Classification of PFOS-compounds in 22 categories according to OECD

REACH

Registration, Evaluation, Authorisation and Restriction of Chemicals

- REACH requires demonstration of safe manufacture and use of chemicals
- REACH based on precautionary principle, aims at achieving proper balance between social, economic and environmental objectives
- REACH aims to optimise the use of scarce and scattered info on substances
- REACH aims to minimise animal testing by optimal use of info on "related" compounds

Intelligent Testing Strategies (ITS)



CADASTER

Goals:

- Exemplify the integration of information, models, strategies for safety-, hazard-, risk assessment for large numbers of substances
- Carry out "real" risk assessment for large numbers of substances according to the basic philosophy of REACH: < costs, animal testing, time
- Exemplify how to increase non-testing information whilst quantifying and reducing uncertainty

CADASTER

Aim:

Provide full environmental hazard and risk assessment according to the REACH philosophy for chemicals belonging to 4 classes of emerging chemicals:

- 1 – Polybrominated diphenylethers (PBDE), hydrophobic chemicals that pose a threat to man and the environment.
- 2 - Perfluoroalkylated substances and their transformation products, like perfluoroalkylated sulfonamides, alkanoic acids, sulfonates. Persistent hydrophilic compounds that may be toxic for man and environment.
- 3 – Substituted musks/fragrances; a heterogenic group of chemicals of varying composition like substituted benzophenones, polycyclic musks, terpene derivatives. Common emission pattern in the environment.
- 4 - Triazoles/benzotriazoles: increasingly used as pesticides and anti-corrosives.

Outcome:

DSS – regularly updated for new compound classes:

-New testing strategies

-New testing data

-New models

-Actual integrated evaluations, including uncertainty and variability

-On-line and stand-alone tool

Activities

1: **Collection of data and models**

- Experimental data intrinsic hazards – Screening Initial Data Set Dossier (SIDS)
- Models – Screening Initial Data Set Dossier (SIDS)

- Generation new data essential for validation and proper hazard/risk assessment
- Database data/models: dissemination purposes

Activities

2: **Development/validation QSAR models**

- Evaluate performance
- Similarity analysis and multivariate ranking methods for identification of priority chemicals to orient the experimental testing
- Develop new QSARs where gaps are identified due to lack of existing models or due to models of insufficient quality.
- Documentation of the performance of the (final) models selected and developed.

Activities

3: **Integration of QSARs within hazard and risk assessment**

- Integration in probabilistic risk assessment framework: characterize variability/ uncertainty, sensitivity analyses, modeling of variability with regard to application in SSDs
- Evaluate ECETOC TRA screening RA tool
- Evaluate methods and decision points for establishing scientific validity and applicability domains for QSAR models
- Explore possibilities for economic valuation of substitution of chemicals from within chemical classes

Activities

4: **Outreach:** website, newsletters/ workshops, stand-alone tools for dissemination of project results

- Development of on-line, stand-alone DSS: develop, publish, use QSAR/QSPR models for REACH
- Integration of the developed models with the QSAR Application Toolbox developed by OECD: establish the com-patibility of the models with the (Q)SAR Model Reporting Format (QMRF) format
- Provision of a sustainable dissemination of project results by the WWW and as stand-alone tools
- Communication including newsletters and workshop(s).

Some findings

- Lack of sufficient data for relevant endpoints
- Lack of models for relevant endpoints and relevant chemical classes
- Difficult to obtain data from industry

- > 7500 data entries relevant for RA – 4 classes
- Overview of suited (Q)SAR models available
- Identified: need for new/improved models

Toxicity testing of PerFluorinated Compounds

Strategy:

1 – Experimental design: PCA + read across toxicity data other (rodent) species

2 – Selection of ideal set of test compounds

3 – Acquiring test compounds

4 – Design non-ideal set of test compounds

5 – Toxicity assessment

6 - Modelling

Experimental design

Work of University of Insubria

- Inhalation study: 4 descriptors based MLR model
  - Hydrophobicity (M*log*P) → negative
  - Electronegativity (Jhetv, X3v and MATS1e) → positive
- Oral study: 4 descriptors based MLR model
  - Fingerprint descriptors representing frequency of atom pairs like C-C, C-F and C-O are prominent
- 376 extra PFCs predicted including PFCs listed in ECHA
- Prediction and prioritization of toxic PFCs based on rodents toxicity

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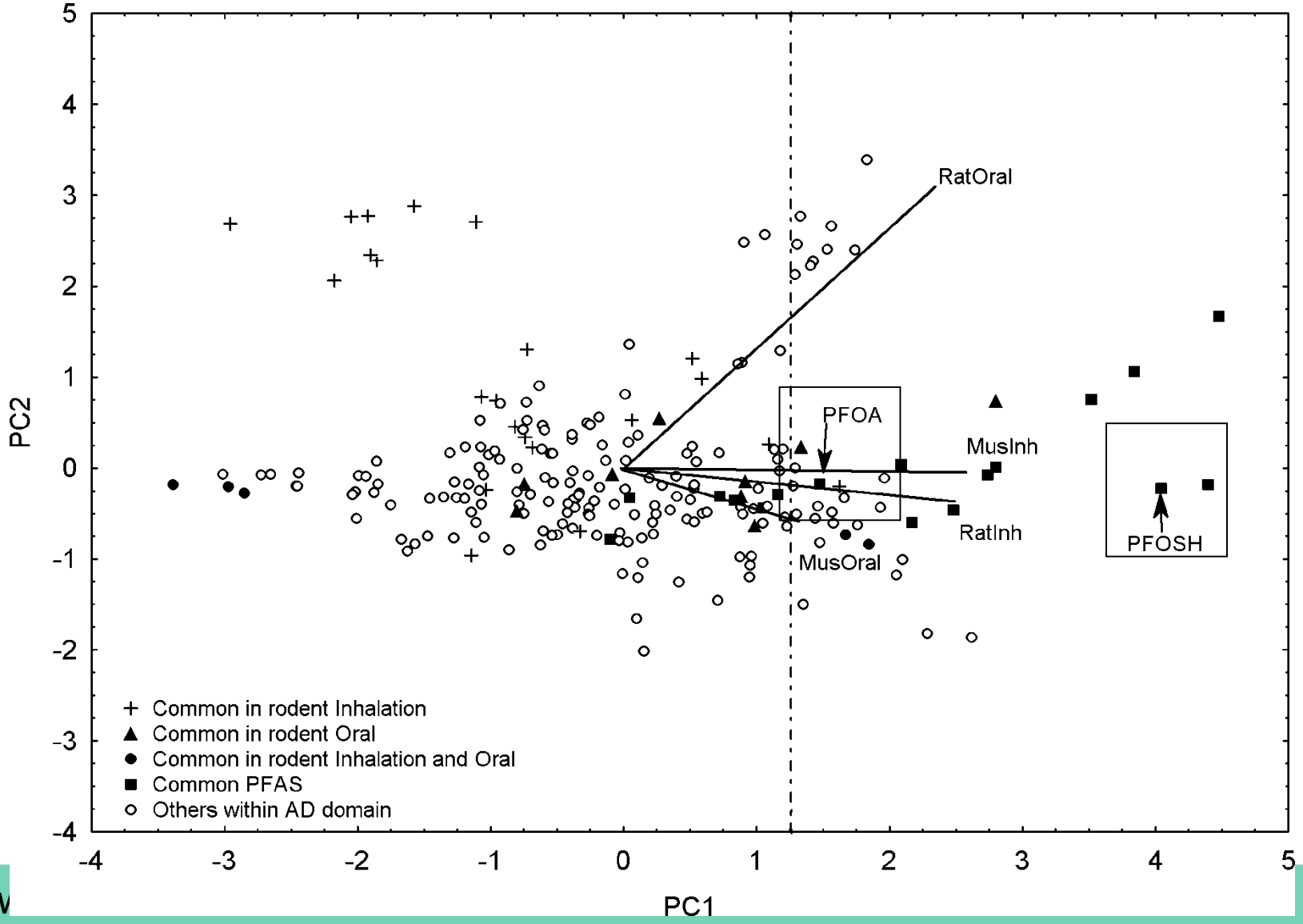
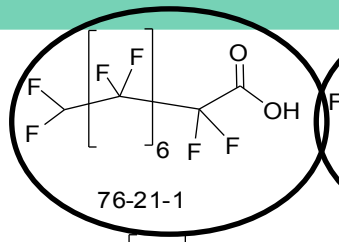

RatOral
PFOA
MusInh
RatInh
MusOral
PFOSH
PC1
PC2
Common in rodent Inhalation
Common in rodent Oral
Common in rodent Inhalation and Oral
Common PFAS
Others within AD domain

CADASTER



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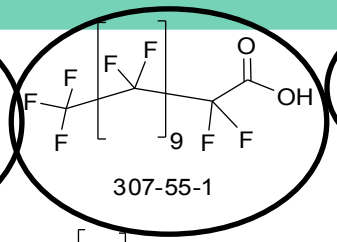

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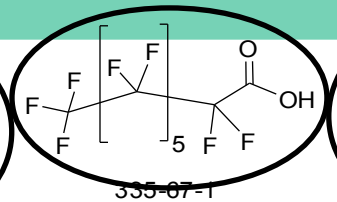

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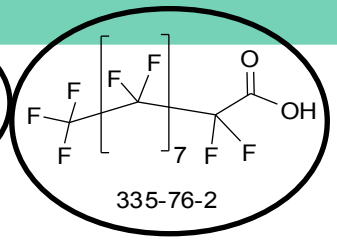

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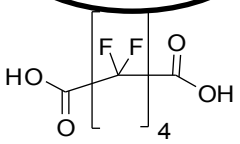
PFOA



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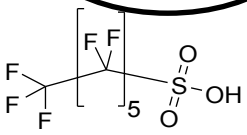

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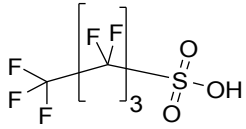

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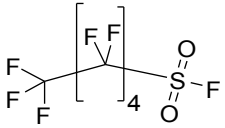

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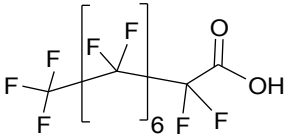

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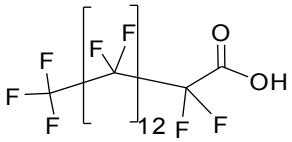

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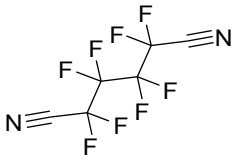

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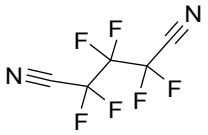

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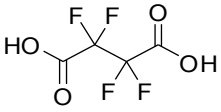

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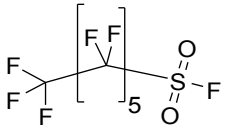

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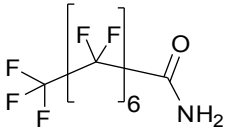

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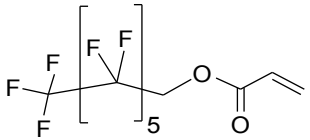

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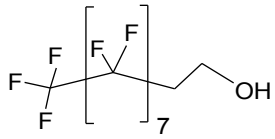

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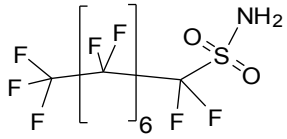

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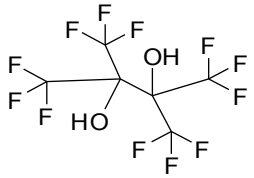

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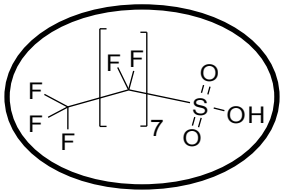
PFOSH



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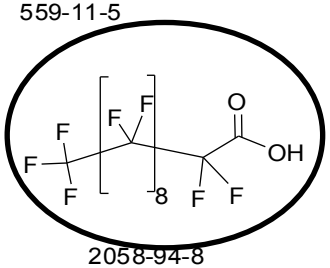

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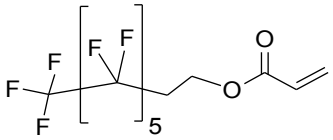

17527-29-6

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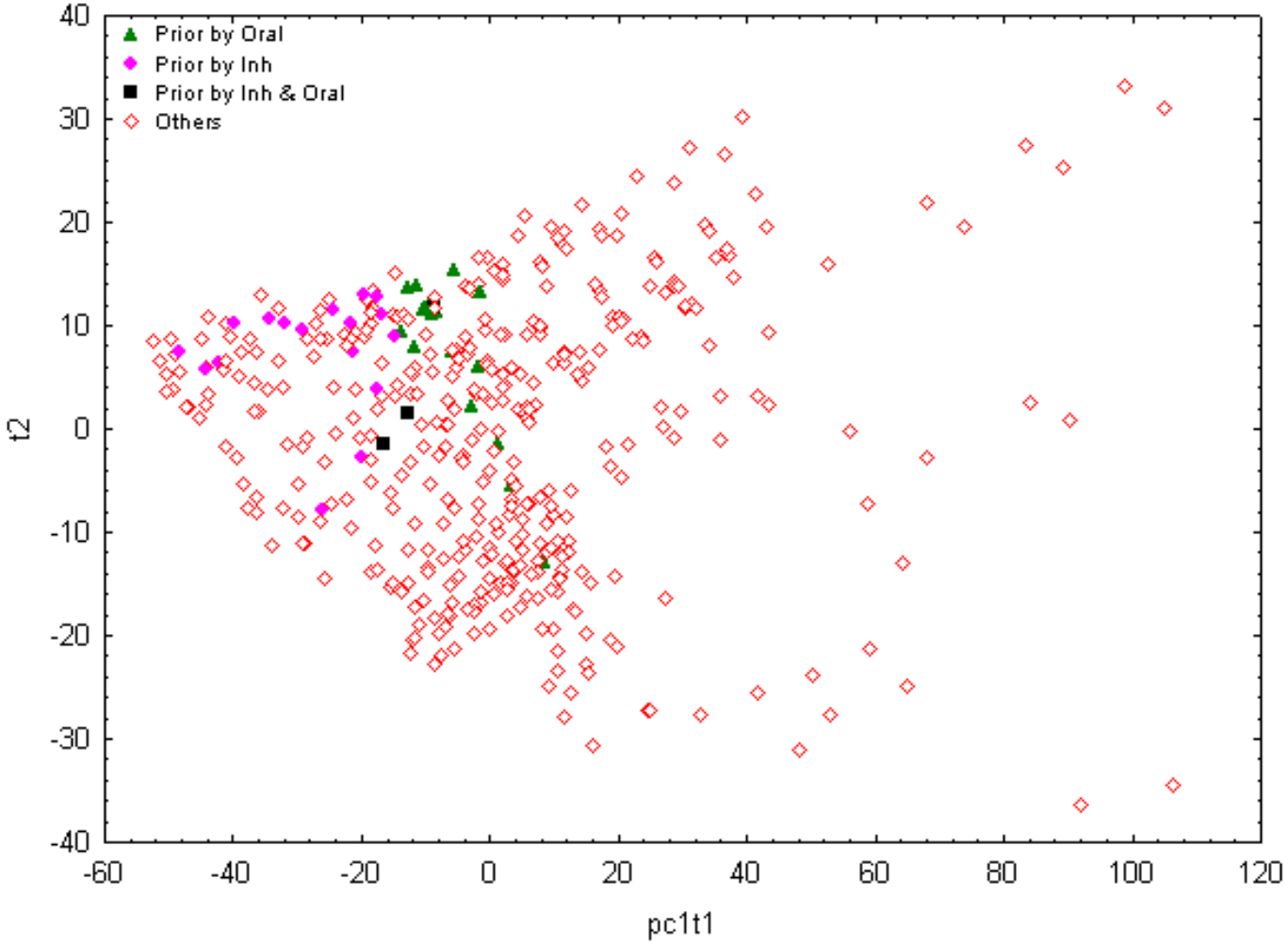
PCA DRAGON descriptors



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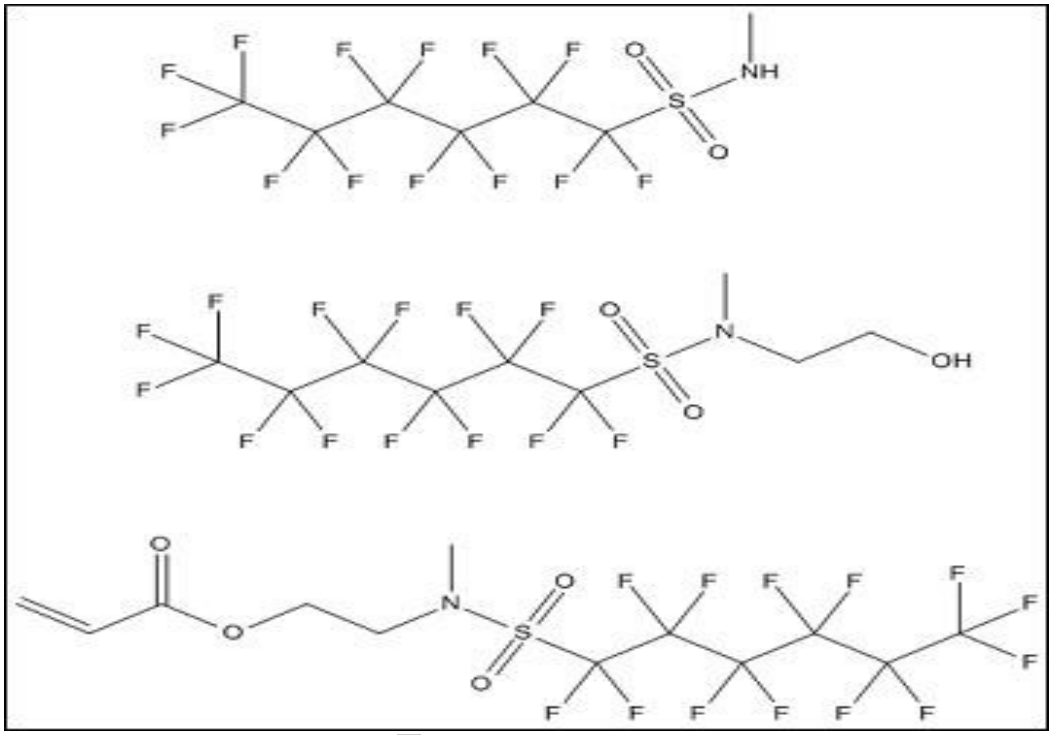
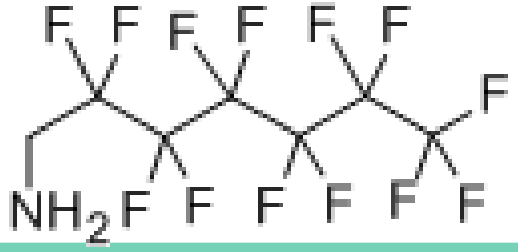
Extended set of compounds





Butanoic acid, heptafluoro-, ethyl ester

Methacrylic acid, 2,2,3,3,4,4,4-heptafluorobutyl ester

3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluoro-1-octanethiol

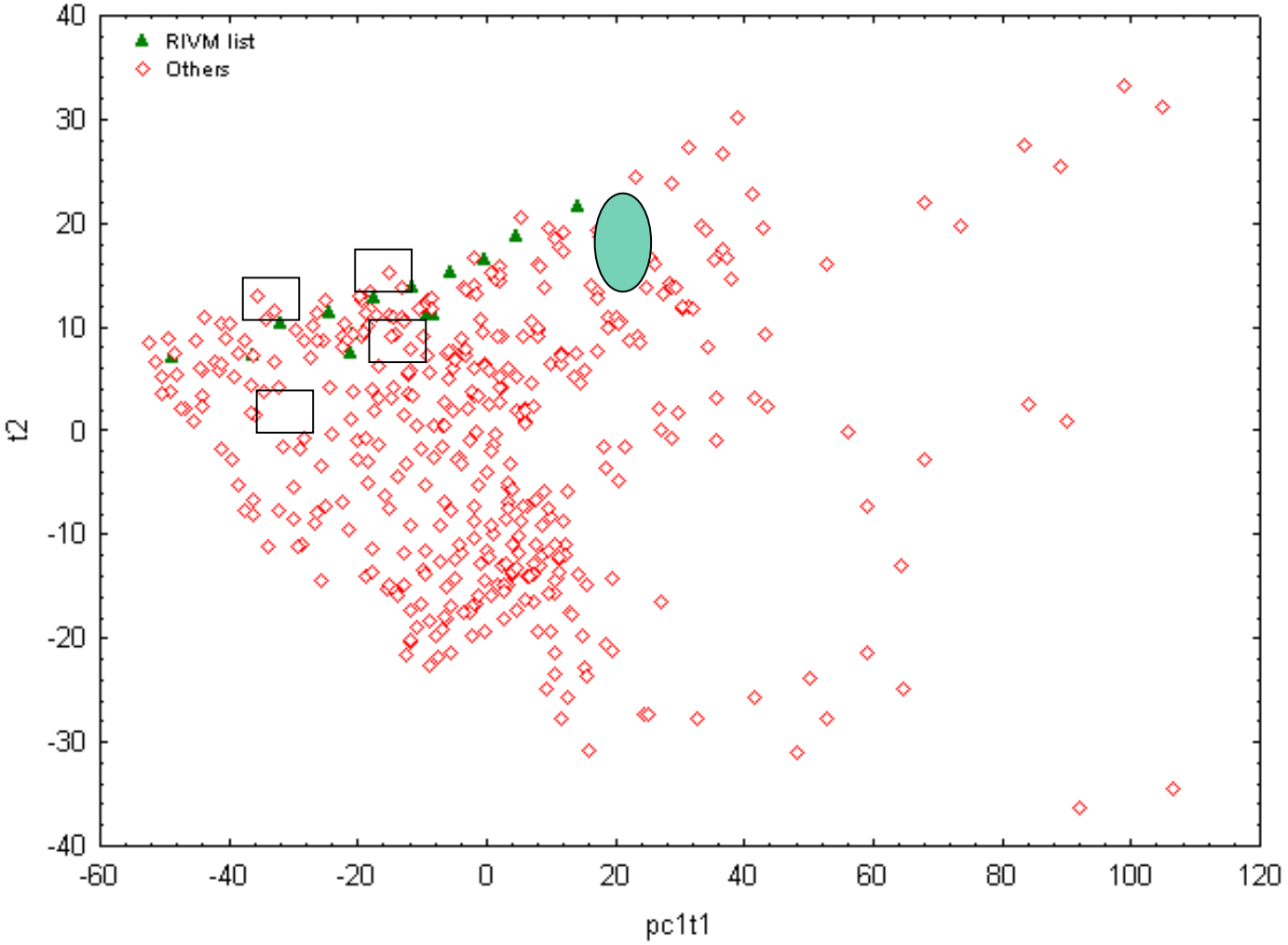
1H,1H,2H,3H,3H-Perfluorononane-1,2-diol; 97%

1H,1H,2H,2H-Perfluorooctyl isobutyrate

2,2,3,3,4,4,5,5,6,6,7,7-Dodecafluoro-1,8-octanediol

CADASTER

Extended set of compounds



Amine

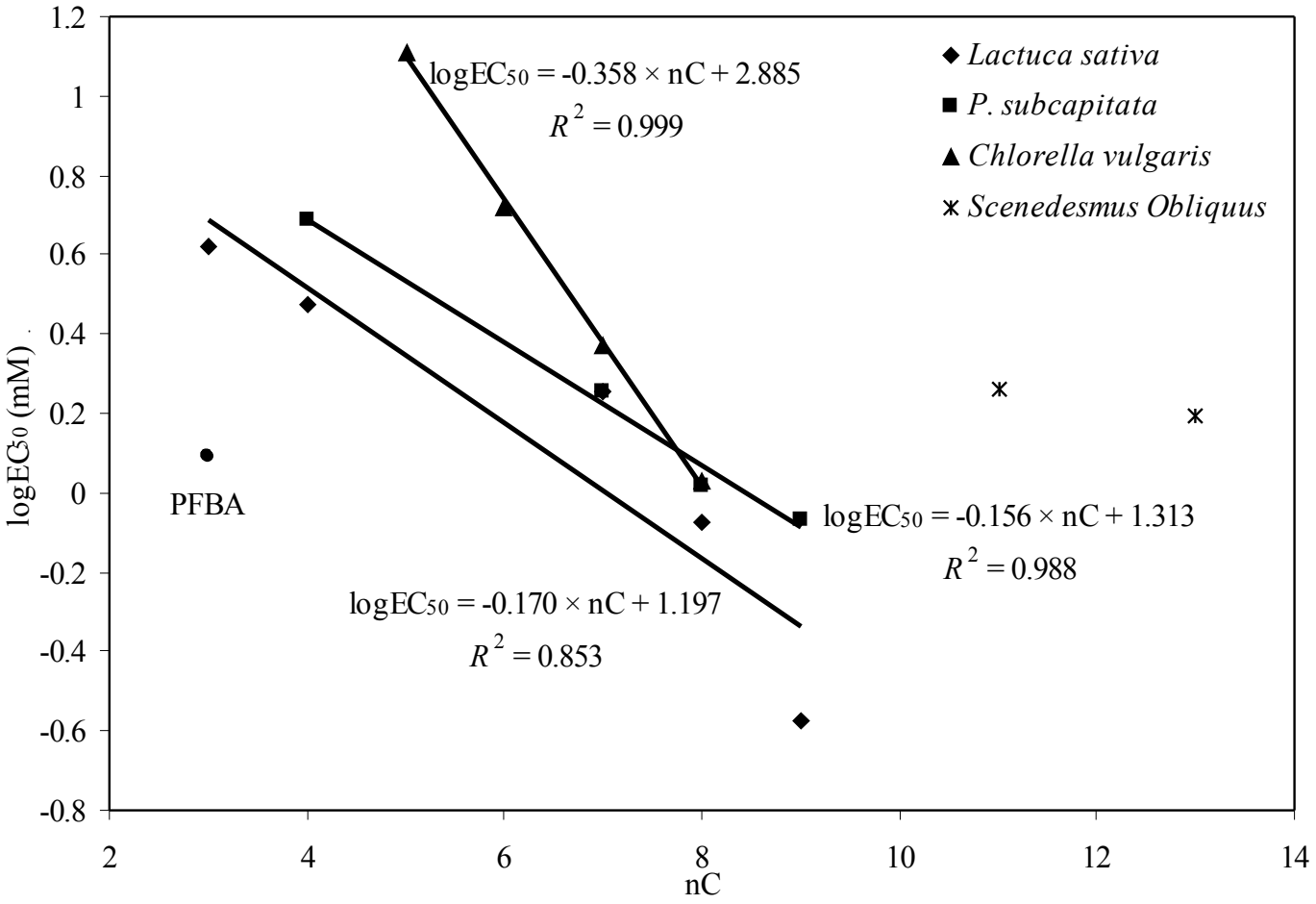
Aquatic Testing

Organism	End point
•Lettuce	root length elongation
•Algae	Photosynthesis inhibition
•Daphnids	Survival
•Zebra fish	Early life stage testing (embryo)

Results - acids

Log EC50, lettuce = – 0.170 × nC + 1.197
***n* = 5, R^2 = 0.853, *p* = 0.0252**

Log EC50, algae = – 0.156 × nC + 1.313
n = 4, R^2 = 0.988, p = 0.006



Interspecies extrapolation read across daphnids

Daphnia magna

Log EC50, 24h = – 0.127 × nC + 0.646
n = 5, R^2 = 0.986, p = 7.090×10-4

Log EC50, 48h = – 0.131 × nC + 0.615
n = 6, R^2 = 0.971, p = 3.265×10-4

Chydorus sphaericus

Log EC50, 24h = – 0.214 × nC + 1.013
n = 7, R^2 = 0.972, p < 0.0001

Log EC50, 48h = – 0.221 × nC + 0.876
n = 7, R^2 = 0.925, p = 5.394×10-4

24h toxicity:

Log EC50, C. sphaericus = 1.560 × log EC50, D. magna – 0.113
n = 5, R^2 = 0.888, p = 0.016

For 48-h toxicity:

Log EC50, C. sphaericus = 1.494 × log EC50, D. magna – 0.277
n = 6, R^2 = 0.846, p = 0.009

CADASTER

CADASTER posters at SETAC 2011

MO-305 (PE01)
Exploring the QSARs for OH Tropospheric Degradation of VOCs using freely available online descriptors.
MO-306 (PE01)
On the agreement of external validation parameters for linear regression QSAR models
TU-112 (ET01)
Stepwise D-Optimal design based on latent variables
TU-337 (RA11)
Study on the toxicity of perfluorinated compounds to aquatic organisms
TU-335 (RA11)
A QSAR-based compound prioritization for lab-testing for chemical safety assessment
TU-342 (RA11)
MOPAC@home – an online database for small organic compounds
TU-346 (RA11)
QSAR and QSPR models for emerging pollutants: WP3 activities within the FP7 European Project CADASTER
TU-347 (RA11)
Physico-chemical property prediction of emerging pollutants: PFC and (B)TAZ for environmental distribution.
TU-348 (RA11)
QSAR prediction of aquatic and mammalian toxicity of triazoles and benzo-triazoles