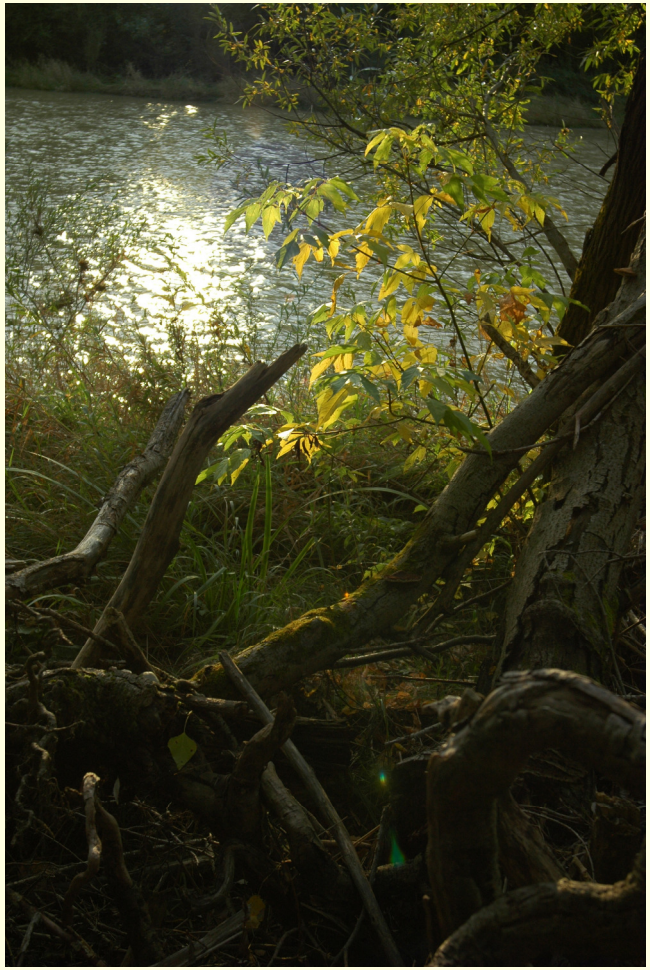
CADASTER Workshop on the use of QSAR models in REACH

Maribor, September 1-2, 2011

CADASTER achievements

WP2: Collection of Data and Models

Public Health Institute Maribor, Slovenia
RIVM, The Netherlands
University of Insubria, Italy
Linnaeus University, Sweden
Helmholtz Zentrum München, Germany
IVL, Sweden
MCC, Belgium



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WP2: Collection of Data and Models

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WP2: Collection of Data and Models

1. Collection of existing experimental data 1-12
Development of new QSARs in WP3

2.1 Overview of QSAR models 1-12
Evaluation of existing QSARs in WP3
2.2 Overview of non-testing approaches 6-18

3. Generation of new data 6-38

Selection of chemicals	– Prioritization WP3
	– Applicability domain WP5
New experimental data	– Development of new QSARs in WP3
	– Validation of new QSARs in WP3

4. Establishment of a database on experimental data 4-36
Development of a prototype of the www site – experimental database and models in WP5

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WP2: Collection of data and models

1. *Collection of experimental data*

Existing testing information were collected

ON: Physico-chemical properties,
Environmental fate parameters and
Ecotoxicity data, toxicity data.

FROM: Literature, EU RAR, Dossiers for Active Substances (PPP),
Databases,
Industry sources: RIFM (Fragrances), Dupont (PBDEs, PFCs).

FOR: 1 - Heterogeneous Brominated Compounds (Flame Retardants)
2 - Perfluoroalkylated substances
3 - Substituted musks/fragrances
4 - Triazoles/benzotriazoles

SIDS endpoints

OECD Screening Information Data Set used in assessing existing chemicals includes endpoints from a wide variety of OECD Test Guidelines

Other endpoints

Biological activities

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WP2: Collection of data and models

1. *Collection of experimental data*

Cadaster Database includes 11918 (1911) experimental data for:

- *BFR including 209 PBDEs; 2329/243*
- *Perfluoroalkylated substances; 3279/690*
- *Substituted musks/fragrances; 2191/532*
- *Triazoles and Benzotriazoles; 4020/446*

Number of experimental data is quite large and is still expanding
Only limited data are available for the SIDS endpoints.

http://www.cadaster.eu/database/

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2.1 *Overview of (Q)SAR models*

University of Insubria, Dr. Paola Gramatica

A survey of the existing QSAR/QSPR models

A few QSAR models specifically developed have been published.

Publicly available EPI Suite models.

BFR

QSPR models for some SIDS physico-chemical properties

PFC, Fragrances, (B)TAZ

EPI suite models

QSAR models are predominantly developed for non-SIDS endpoints.

ECOSAR estimation program (EPI suite) - predict acute and chronic toxicity to fish, aquatic invertebrates and algae.

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2.2 ***Overview of* non-testing *approaches*** *available for implementation in REACH*

RIVM, Dr. Willie Peijnenburg, Dr. Emil Rorije

The purpose:

- To replace experimental testing.
- To strengthen confidence in experimental results.

The non-testing options available under REACH:

- QSARs →Overview of (Q)SAR models
- Read-across → Selection of chemicals
- Category approaches → Selection of chemicals
- Exposure based waiving

WP2 Collection of data and models

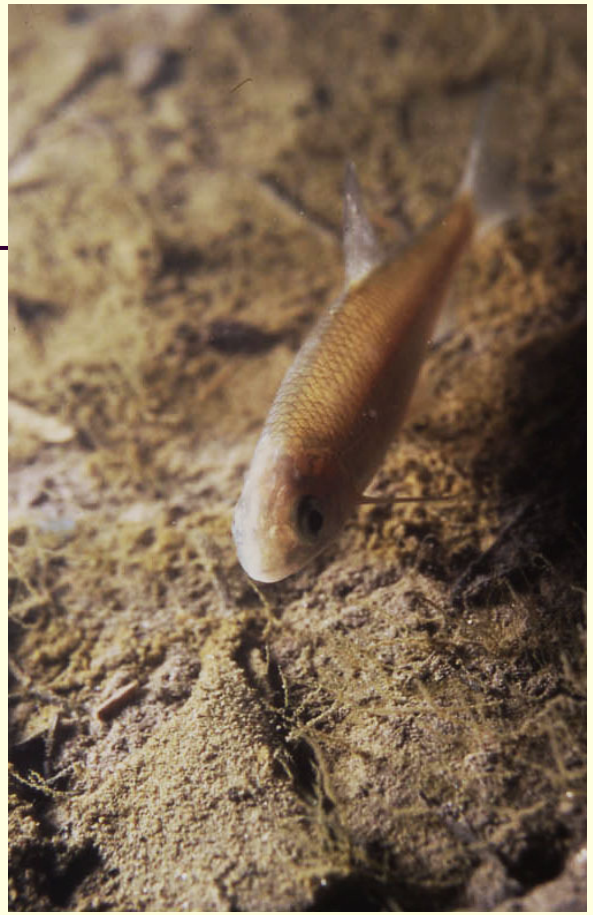
*3. **Generation of new data** for which insufficient data are available for model validation and proper hazard/risk assessment*

1 - Polybrominated diphenylethers (PHI)

2 - Perfluoroalkylated substances (RIVM)

3 - Substituted musks/fragrances (PHI)

4 - Triazoles/benzotriazoles (RIVM, PHI)



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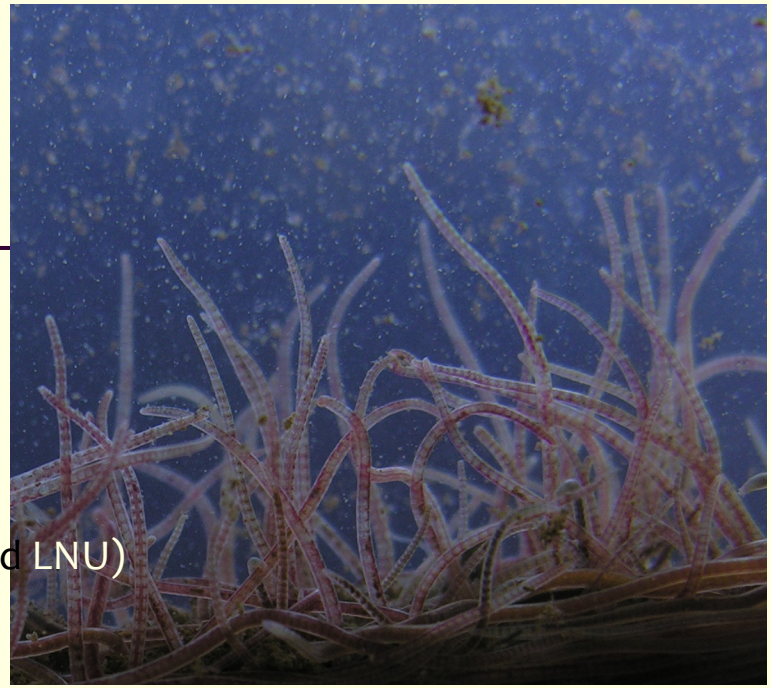
3. *Generation of new data*

Polybrominated diphenylethers (PHI)



Strategy:

- Selection of ideal set of test compounds (UI and LNU)
- Aquiring test compounds
- Development of experimental test design

28-day sediment test with Tubifex tubifex:
OECD 315: Bioaccumulation in Sediment-dwelling Benthic Oligochaetes

3 PBDE commercial mixtures TBDE-71, TBDE-79 and TBDE-83R
5 BDE individual congeners PBDE-002, PBDE-077, PBDE-126, PBDE-198 and PBDE-204

1 draft manuscript finished
1 draft manuscript in preparation

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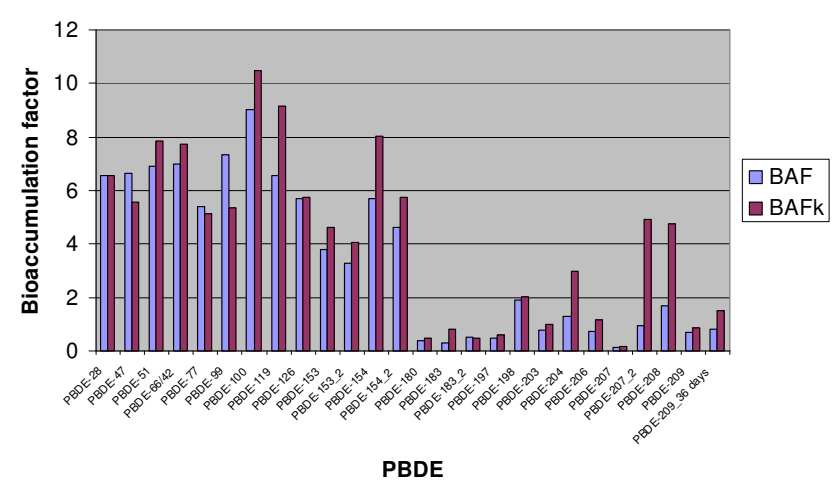
3. *Generation of new data*

Polybrominated diphenylethers (PHI)

Bioaccumulation of different PBDEs by *Tubifex tubifex*



The method appeared practicable and gave reproducible results that can be used for the calculation of new QSAR models (21 compounds tested).

The BCF values can also be used to calculate toxicity endpoints:

- using experimentally obtained critical body burdens (CBBs) for the various PBDE's or
- using QSAR approaches for predicting CBBs.

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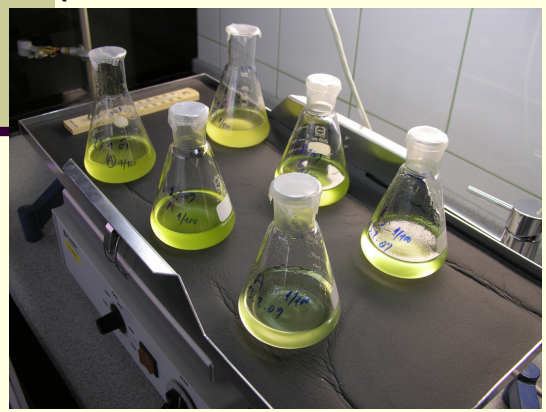
3. *Generation of new data*

Substituted musks/fragrances (PHI)

Strategy:

- Selection of ideal set of test compounds (UI and LNU)
- Aquiring test compounds
- Development of experimental test design

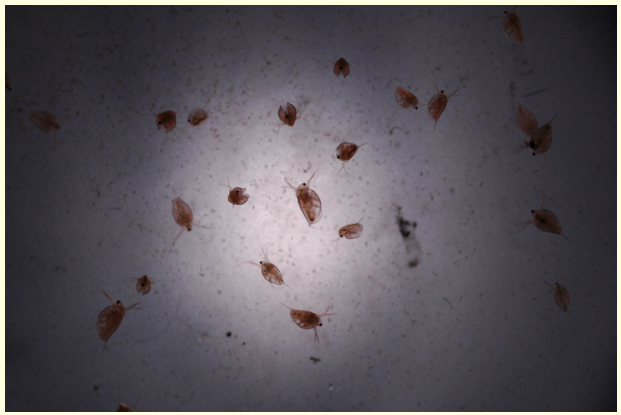
Algae, Growth Inhibition Test
OECD 201, Acute and longterm, ErC50, NOEC
72 hours test



PHI has tested 11 fragrances:

1. Acethyl cedrene
2. Benzyl cinnamate
3. Hexyl salycilate
4. Hexylcinnamaldeyde
5. HHCB (Galaxolide)
6. Methyl dihydrojasmonate
7. Quinidine
8. α-amylcinnamyl alcohol
9. Musk ambrette
10. Cyclopentadecanolide
11. Benzyl Benzoate

Daphnia sp., Acute Immobilisation Test
OECD 202, Acute, EC50
48 hours test



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WP2 Collection of data and models

3. *Generation of new data*

Perfluoroalkylated substances (RIVM)

Strategy:

- Selection of ideal set of test compounds (UI and LNU)
- Aquiring test compounds
- Development of experimental design

2 draft manuscripts finished
1 review paper

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

Effects of seven PFCs (EC50 – mM)

Chemical	CAS number	nCa	Lettuce (Lactuca sativa)	Green algae (P. subcapitata)
PFBA	375-22-4	3	4.186 (3.937-4.450)	1.225 (1.002-1.497)
5H 4:1 FTOH	355-80-6	4	2.976 (2.539-3.489)	4.853 (4.058-5.804)
PFOA	335-67-1	7	1.801 (1.635-1.984)	1.807 (1.757-1.859)
PFNA	375-95-1	8	0.846 (0.558-1.281)	1.038 (0.975-1.104)
PFDA	335-76-2	9	0.266 (0.188-0.375)	0.851 (0.644-1.124)
PFUnA	2058-94-8	10	0.210*	0.565*
PFDoA	307-55-1	11	0.142*	0.394*

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* = above solubility – calculated values

WP2 Collection of data and models

4. Development of a database on experimental data and (Q)SAR models

HMGU, Dr. Igor Tetko

- Allows to introduce properties, conditions, units (automatic conversion)
- Private/hidden data
- Group of CADASTER users – same space to work with hidden data
- Tracking of changes; user rights
- Automatic verification of names using PubChem
- Batch upload; batch editing
- Upload of models

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WP2 Collection of data and models

BFR including 209 PBDEs
Perfluoroalkylated substances (PFC)
Substituted musks/fragrances
Triazoles and Benzotriazoles (TAZ/BTAZ)

1. *Collection of existing experimental data* → Development of new QSARs

2.1 Overview of QSAR models → Evaluation of existing QSARs
2.2 Overview of non-testing approaches

3. *Generation of new data* → Development of new QSARs
   → Validation of new QSARs

4. *Database on experimental data*

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