Ranking REACH registered chemicals for Persistency and Mobility: Neutral, Ionizable and Ionic Compounds

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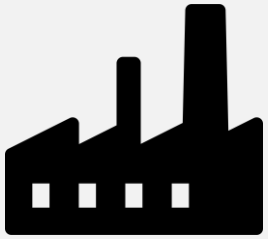
ICCE

Two properties of a drinking water contaminant

Persistency and Mobility



Chemical Synthesis

Uses / Products

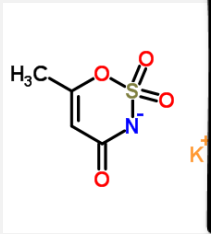
Transport through the environment or infrastructure

Water treatment and production

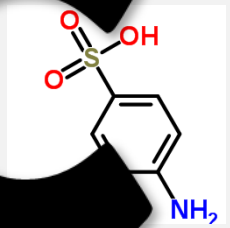
Consumption

Mind the GAP

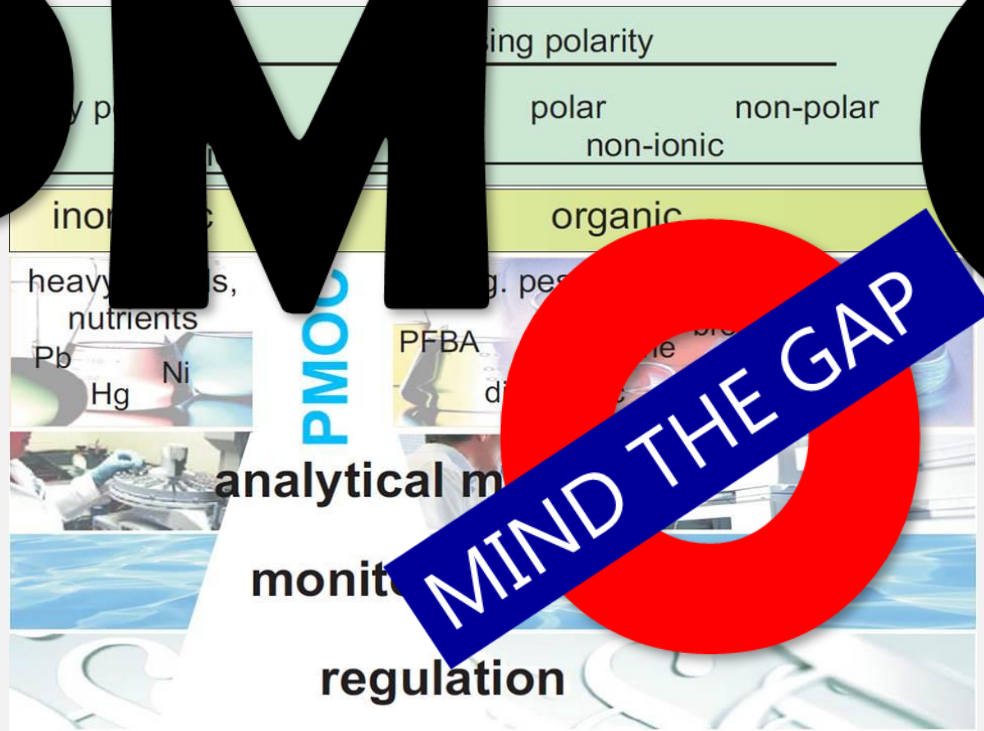
Acesulfame



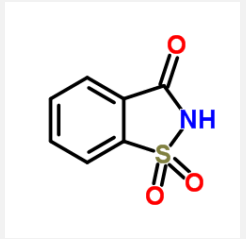
Sulfanilic acid



PMOC



Melamine



Saccharin

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Goals of this Study

- **Develop:**
  - a ranking system based on Persistency (P) and Mobility (M) in a REACH-relevant manner
- **Rank:**
  - REACH registered compounds using best available data
- **Be Sensitive:**
  - conduct a sensitivity analysis to find most sensitive parameters
- **Compare:**
  - Identified PMOCs with groups of prioritized chemicals

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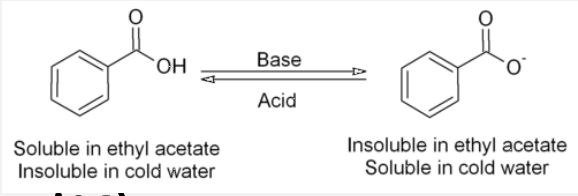
DEVELOP

REACH substances considered



- **REACH substances with a CAS RN – 7313 compounds (Dec ’14)**
  - Excluded metals, metal salts, minerals, mixtures and natural products)
  - 5530 substances included, covering organics, pseudoorganics, organometallics, organoborates and organosilicates included
  - 5155 unique stuctures (due to repeating substances/fragments)
- **Neutral Organic Compounds (between pH 4 – 10) – 2673 compounds**
- **Ionizable OC (between pH 4-10) – 2283 compounds**
  - Includes acids (760), bases (742), amphoprotic/other compounds (599)
- **Permanently Charged OC – 574 compounds**
  - includes permanent cations (128), permanent anions (405)
  - permanent zwitterions (41)

PERSISTENCE in REACH

- Annex XIII of REACH defines Persistence in fresh water as follows:
  - **Persistence (P)** = the half-life in fresh- or estuarine water is higher than 40 days at 12 °C
  - **Very Persistent (vP)** = the half-life in marine, fresh- or estuarine water is higher than 60 days at 12 °C
- The criteria of 12 °C is based on the new PBT guidance in REACH; most data is available at Room Temperature
- Readily Biodegradable: As defined by OECD 301+310 (common test used in REACH)

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MOBILITY in REACH

- **REACH is not clear what this means**
  - Annex II. 12.2. MOBILITY: The potential of the substance or the appropriate constituents of a preparation, if released to the environment, to transport to groundwater or far from the site of release."

- For Neutral compounds, UFOPLAN Project FKZ 371265416 (2015) Kalberlah, Oltmanns, Markus (FoBiG GmbH) & Baumeister, Striffler (denkbares GmbH)
  - Recommended water solubility (S_L) = 150 µg/L and log K_{oc} = 4.5 as the cutoff mobility of *persistent chemicals*.

- pH needs to be considered for ionizable compounds

$$D_{oc} = K_{oc} / (1 + 10^{pH - pKa}) \quad \text{- monoprotic acids}$$

- Log K_{oc} data is problematic for ionic and permanently charged compounds (few data, dependent on ion exchange sites)

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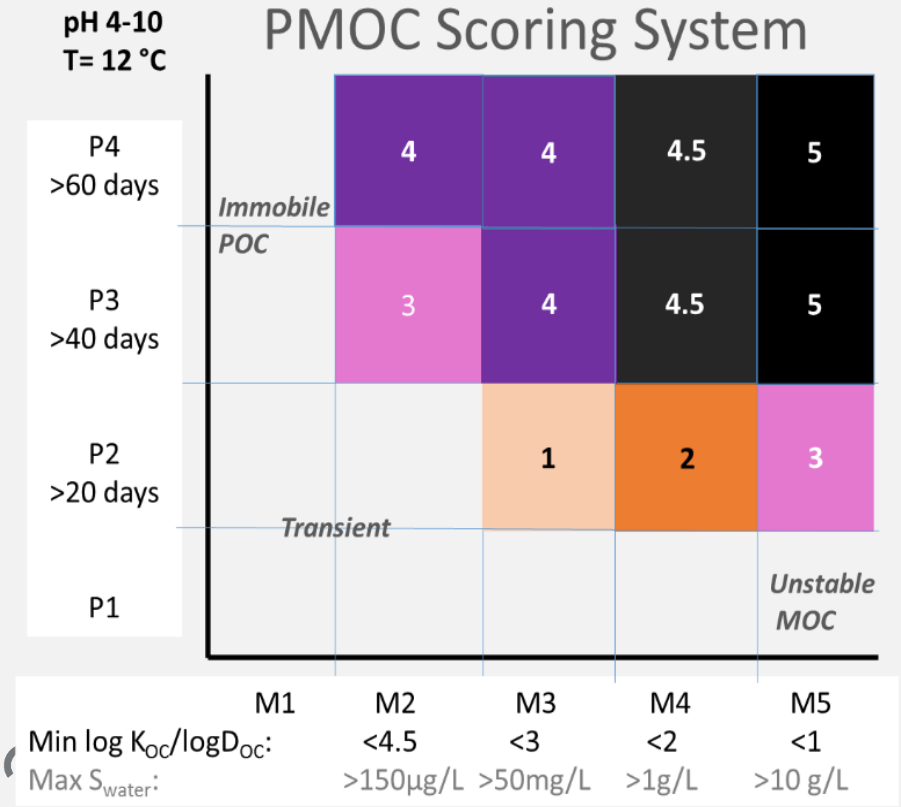
PMOC scoring system



- PMOC «classes» of 1 to 5, with 5 being the compound most likely to be PMOC

- Non-PMOCs sorted as
  - Unstable MOC
  - Immobile POC
  - Transient

Data Prioritization

Priority	Source	% of substances
1st	REACH dossier experimental data	~ 20% (P,M)
2nd	Peer-reviewed experimental databases PP-LFERs (using experimental input data)	
3rd	EPI Suite experimental database	
4th	QSARs: P – EPISuite (Biowin, Hydrowin), QSARToolbox M - SPARC, EPISuite, Chemaxon, Insight for Excel, ADMET	~75% (P) ~80% (M)
5th	Original IFS PMOC QSAR (if nothing else worked)	426 substances (P, mainly ionic) 13 substances (M, mainly organometallics)

Accuracy of QSARs compared to experimental data

- **pK_a** (exp. n = 380) – one order of magnitude***.
  - SPARC and ADMET best performing
- **K_{ow}** (n= 745) /**Solubility** (exp. n = 949) – one order of magnitude.***
  - ADMET best performing
- **Biodegradation half-lives** (exp. n= 29) – one order of magnitude***
- **Biodegration «readily biodegradable»** (exp. n=1714) – correctly predicted 72% of the time
- **Hydrolysis** (exp. n = 253) very poor predicitons (2 – 3 orders of magnitude)
- *** A minority of substances (ca 5%) were extreme outliers (off by 2 – 8 orders of magnitude), these were driving the statistics

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Original Iterated Fragment Selection QSAR

P > 40 days (y/n) based on a_1Fragment 1 + a_2Fragment 2 + ...+ a_nFragment n

	Training Dataset (n = 396)	Validation Dataset (n = 498)
% Total Correct	78.3	69.2

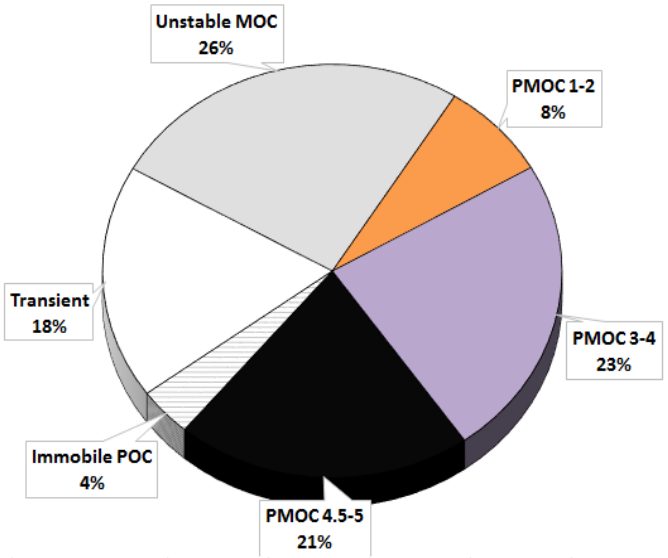
M score = a_1Fragment 1 + a_2Fragment 2 + ...+ a_nFragment n

	Training Dataset (n = 663)	Validation Dataset (n =657)
% Total M-Score Correctly Predicted	78.6	71.7

RANK

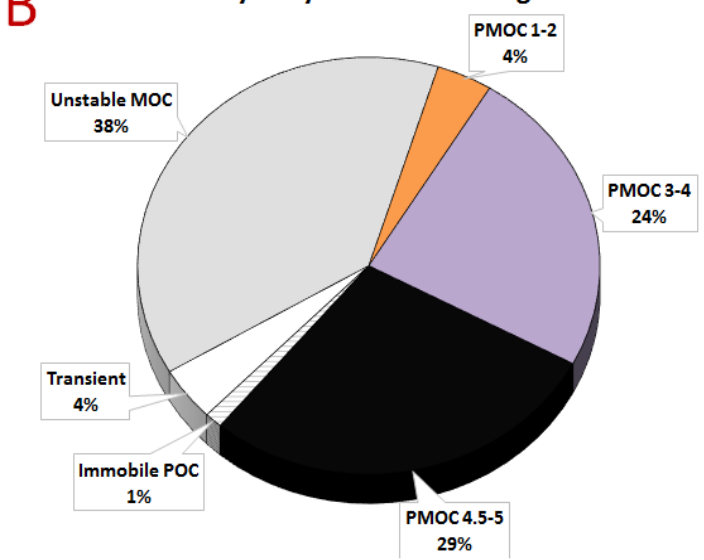
PMOC distribution: Parents v Hydrolysis

A



Sum	0%	9%	16%	16%	15%	45%	%
4	0%	3%	6%	5%	4%	8%	27%
3	0%	0%	1%	1%	1%	3%	7%
2	0%	1%	2%	3%	3%	8%	17%
1	0%	3%	6%	6%	6%	19%	41%
no P data	0%	0%	1%	1%	1%	6%	8%
P vs M	no M data	1	2	3	4	5	Sum

B



Sum	0%	1%	5%	6%	9%	76%	%
4	0%	1%	3%	2%	3%	19%	28%
3	0%	0%	0%	1%	1%	5%	7%
2	0%	0%	1%	1%	2%	17%	22%
1	0%	0%	1%	2%	3%	35%	41%
no P data	0%	0%	0%	0%	0%	0%	1%
P vs M	no M data	1	2	3	4	5	Sum

Ionic substances most likely to be PMOCs

- Only 9% of neutral compounds received PMOC-score 4.5-5, compared to 30% of the ionizable compounds and 47% of the ionic ones.

- BUT!
  - Fewest experimental data were for ionics
  - QSARs very uncertain for all parameters (except solubility)
  - Mobility score does not account for ion-exchange interactions and percipitation processes, which would reduce mobility

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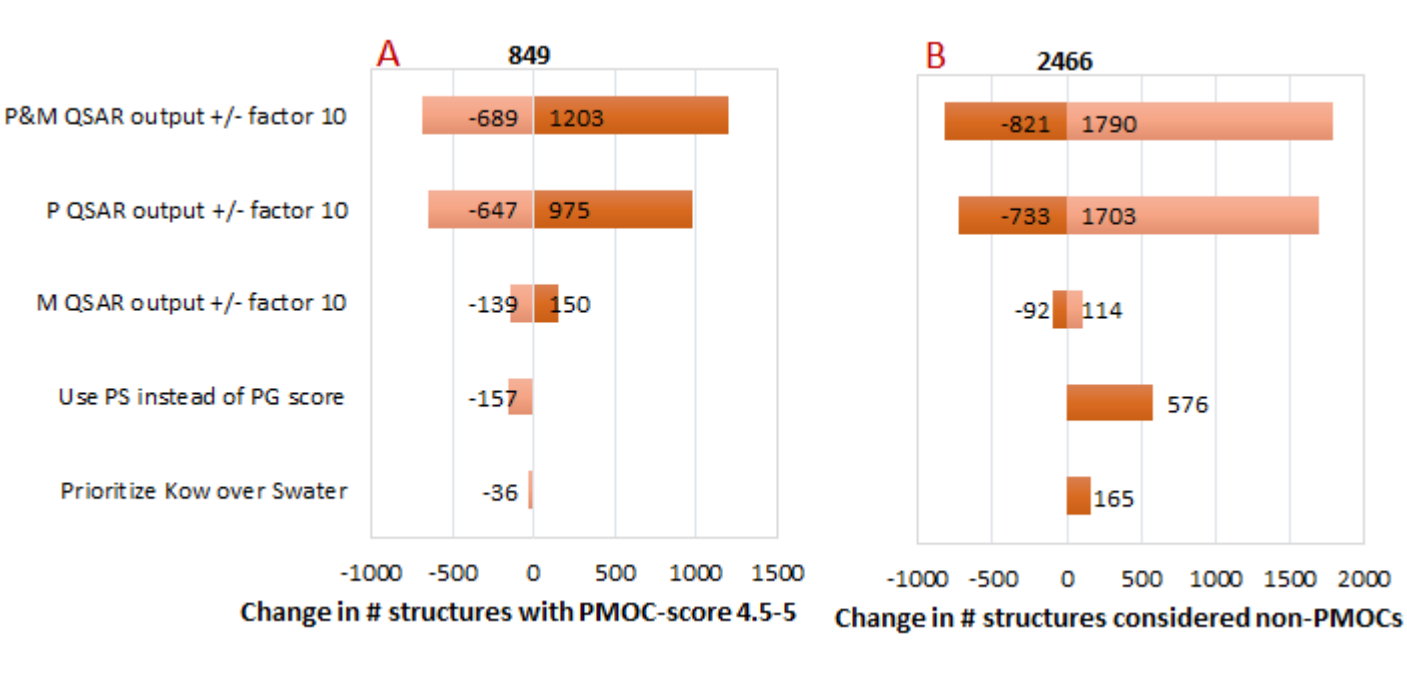
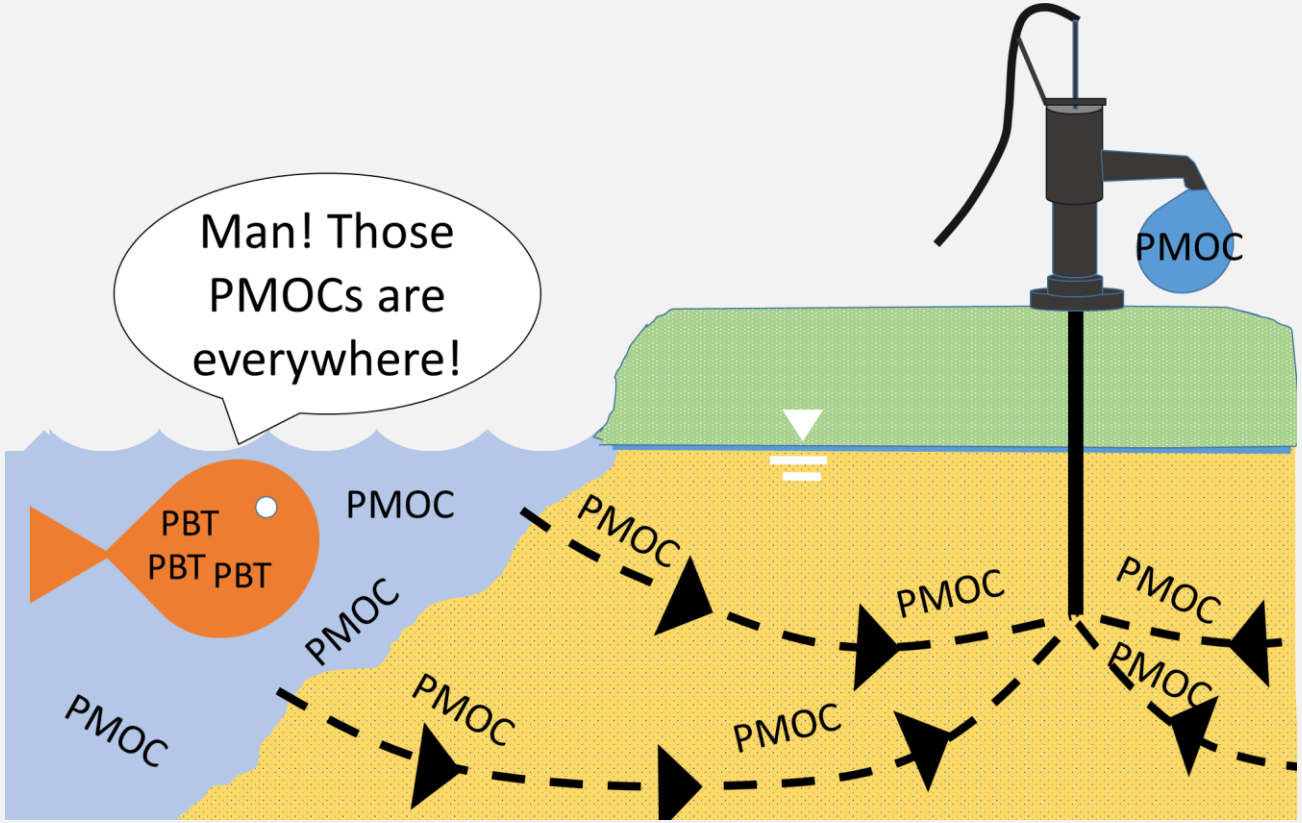
BE SENSITIVE

Sensitivity Analysis



COMPARE


Man! Those PMOCs are everywhere!
PMOC
PBT
PBT PBT
PMOC
PMOC
PMOC
PMOC
PMOC
PMOC
PMOC
PMOC
PMOC

PMOCs are everywhere

Category	Number evaluated in this study	PMOC (score 4-5)
SVHC	62	23 (17)
PB and LRTP (Zarfl & Mathis, 2013)	268	104 (57)
US drinking water contaminants	71	46 (27)
Normal list of emerging substances	213	104 (66)

- Contaminants that are PMOC, PBT and LRTP are particularly worrisome, as they can present multiple exposure routes to humans and the environment.

Conclusions

- We have tools to rank neutral, ionizable and ionic compounds for being PMOCs, but ionic compounds are most uncertain
- More experimental persistency data is needed for better accuracy, not just for PMOCs but for PBT and green alternative assessments.
- Tools to identify PMOCs in drinking water need to be presented.

More information

From the journal:
Environmental Science: Processes & Impacts

Ranking REACH registered neutral, ionizable and ionic organic chemicals based on their aquatic persistency and mobility

Check for updates

Hans Peter Heinrich Arp, Trevor N. Brown, Urs Berger and Sarah Hale

Abstract

The contaminants that have the greatest chances of appearing in drinking water are those that are mobile enough in the aquatic environment to enter drinking water sources and persistent enough to survive treatment processes. Herein a screening procedure to rank neutral, ionizable and ionic organic compounds for being persistent and mobile organic compounds (PMOCs) was developed and applied to the list of industrial substances registered under the EU REACH legislation as of December 2014. This comprised 5155 identifiable, unique organic structures. The minimum cut-off criteria considered for PMOC classification herein are a freshwaterhalf-life > 40 days, which is consistent with the REACH definition of freshwater persistency, and a log DOC < 4.5 between pH 4-10 (where DOC is the organic carbon-water distribution coefficient). Experimental data were given the highest priority, followed by data from an array of available quantitative structure-activity relationships (QSARs), and as a third resort, an original Iterative Fragment Selection (IFS) QSAR. In total, 52% of

Water JPI PROMOTE

http://www.ufz.de/promote/

REGISTRIERUNG EVALUIERUNG UND AUTORISIERUNG VON CHEMIKALIEN

https://www.umweltbundesamt.de/mobile-chemikalien

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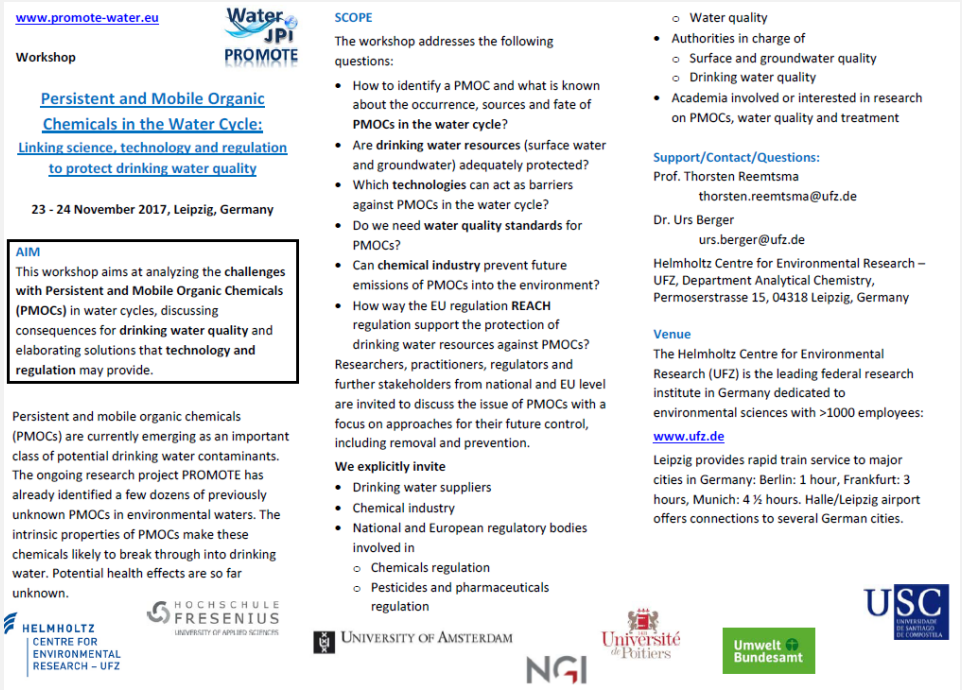
Workshop Announcement

- Persistent and Mobile Organic Chemicals in the Water Cycle: Linking science, technology and regulation to protect drinking water quality
- 23 - 24 November 2017, Leipzig, Germany



www.promote-water.eu

Water JPI PROMOTE

Workshop

Persistent and Mobile Organic Chemicals in the Water Cycle: Linking science, technology and regulation to protect drinking water quality

23 - 24 November 2017, Leipzig, Germany

AIM

This workshop aims at analyzing the **challenges with Persistent and Mobile Organic Chemicals (PMOCs)** in water cycles, discussing consequences for **drinking water quality** and elaborating solutions that **technology and regulation** may provide.

Persistent and mobile organic chemicals (PMOCs) are currently emerging as an important class of potential drinking water contaminants. The ongoing research project PROMOTE has already identified a few dozens of previously unknown PMOCs in environmental waters. The intrinsic properties of PMOCs make these chemicals likely to break through into drinking water. Potential health effects are so far unknown.

HELMHOLTZ CENTRE FOR ENVIRONMENTAL RESEARCH – UFZ

HOCHSCHULE FRESENIUS UNIVERSITY OF APPLIED SCIENCES

SCOPE

The workshop addresses the following questions:

- How to identify a PMOC and what is known about the occurrence, sources and fate of **PMOCs in the water cycle**?
- Are **drinking water resources** (surface water and groundwater) adequately protected?
- Which **technologies** can act as barriers against PMOCs in the water cycle?
- Do we need **water quality standards** for PMOCs?
- Can **chemical industry** prevent future emissions of PMOCs into the environment?
- How way the EU regulation **REACH** regulation support the protection of drinking water resources against PMOCs?

Researchers, practitioners, regulators and further stakeholders from national and EU level are invited to discuss the issue of PMOCs with a focus on approaches for their future control, including removal and prevention.

We explicitly invite

- Drinking water suppliers
- Chemical industry
- National and European regulatory bodies involved in
  - Chemicals regulation
  - Pesticides and pharmaceuticals regulation
  - Water quality
- Authorities in charge of
  - Surface and groundwater quality
  - Drinking water quality
- Academia involved or interested in research on PMOCs, water quality and treatment

Support/Contact/Questions:

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Dr. Urs Berger
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Helmholtz Centre for Environmental Research – UFZ, Department Analytical Chemistry, Permoserstrasse 15, 04318 Leipzig, Germany

Venue

The Helmholtz Centre for Environmental Research (UFZ) is the leading federal research institute in Germany dedicated to environmental sciences with >1000 employees:

www.ufz.de

Leipzig provides rapid train service to major cities in Germany: Berlin: 1 hour, Frankfurt: 3 hours, Munich: 4 ½ hours. Halle/Leipzig airport offers connections to several German cities.

UNIVERSITY OF AMSTERDAM

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Université de Poitiers

Umwelt Bundesamt

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

Acknowledgements

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- JPI Water PROMOTE project (http://www.ufz.de/promote/)
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  - Urs Berger, Stefanie Schulze, Thorsten Reemstma (UFZ Leipzig)
  - José Quintana and Rosa Montes Goyanes (USC)

Any persistent or mobile questions?

Contact: hpa@ngi.no

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Thank-you!

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Representing OC as SMILES! ☺

- SMILES = simplified molecular-input line-entry system
- E.g. formaldeyde: C=O, aspirin; CC(=O)Oc1ccccc1C(=O)O
- Needed for QSARs
- Publically available REACH dossiers do not provide SMILES ☹
- We complied and compared SMILES from the following:
  - Chemaxon (https://www.chemaxon.com/)
  - QSARToolbox (http://echa.europa.eu/support/oecd-qsar-toolbox)
  - PubChem (https://pubchem.ncbi.nlm.nih.gov/)
  - ChemSpider (www.chemspider.com/)
  - Manual sketching and converting to SMILES in software

Quality Assurance of SMILES

- Dative bond notation to avoid confusing resonance charges with permenant and ionizable charges
  - E.g. Represent Nitrate as O=N=O, not [O-][N+]=O (otherwise some algorithms may think it is a zwitterion)

- Net charge must always be zero, counterion must be present!
  - E.g. Magnesium acetate, some sources gave
    - CC(=O)[O-] : WRONG! where is Mg?
    - CC(=O)O : WRONG! Where did the charge go, and where is Mg?
    - CC(=O)[O-].CC(=O)[O-].[Mg+2] : Correct! That's a BINGO!

- Compare SMILES between different sources, and manually pick the correct one if they differ.