Cefic LRI Eco38 - Cross-validation for improving determinations of water solubility for difficult to test substances

Brussels, 21 November 2019

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Technical University of Denmark,

Aaron Redman & Daniel Letinski
ExxonMobil Biomedical Sciences, Inc,

Water solubility

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- A fundamental parameter for environmental risk assessment
- Important input parameter in exposure and fate models
- Sets upper concentration limit in aqueous toxicity testing
- Sets upper limit for concentration gradients driving diffusion and bioconcentration

105
Adopted:
27.07.95

OECD GUIDELINE FOR THE TESTING OF CHEMICALS

Adopted by the Council on 27th July 1995

Water Solubility

INTRODUCTION

1. This guideline is a revised version of the original Guideline 105 which was adopted in 1981. There are no differences of substance between the current version and that from 1981. Mainly the format has been changed. The revision was based on the EC method "Water Solubility" (1).

Objectives

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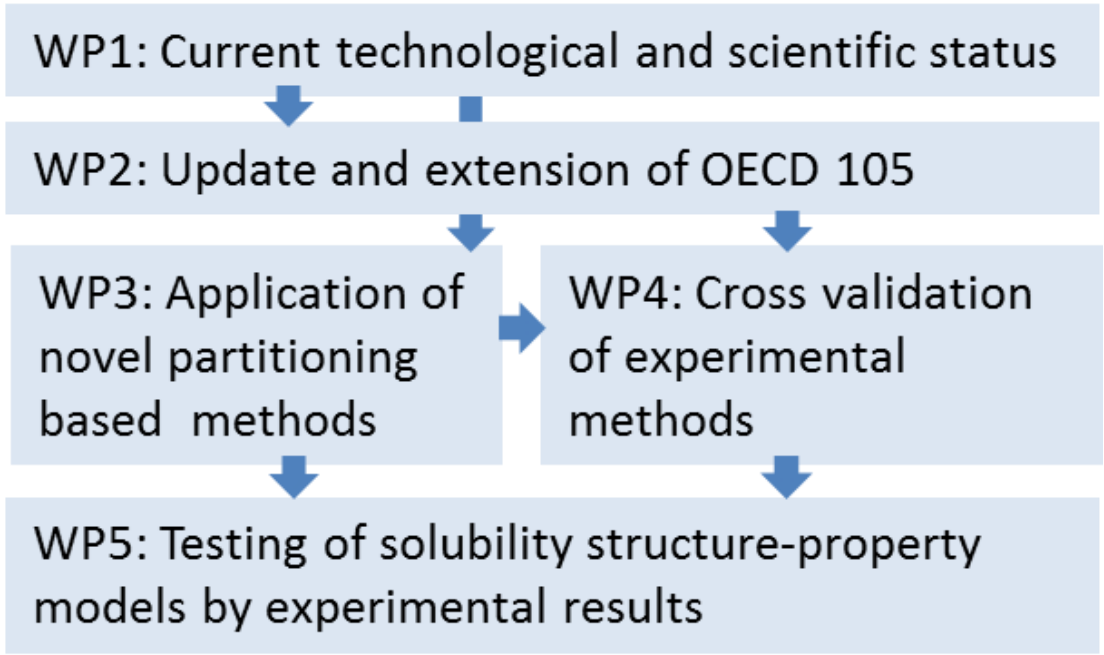
- to bundle existing expertise on determinations of aqueous solubility for difficult to test substances
- to improve, apply and compare the best methods for single compounds and UVCBs
- to facilitate progress in this area on the technical, analytical and scientific level

Project outline



Current technological and scientific status

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Analytica Chimica Acta 1086 (2019) 16–28

Contents lists available at ScienceDirect

Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

Tutorial

Determining the water solubility of difficult-to-test substances: A tutorial review

Heidi Birch [a, *], Aaron D. Redman [b], Daniel J. Letinski [c], Delina Y. Lyon [d], Philipp Mayer [a]

Water solubility challenges

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Technical challenges

- Establish and maintain concentrations exactly at solubility
- Ensure absence of pure substance (liquid or crystal)
- Ensure absence of substance bound to a third phase

Analytical challenges

- Measure low concentrations in small water volumes
  - Volatile chemicals
  - Highly hydrophobic chemicals
- Good alignment of solubility experiments and analytical measurements

Scientific challenges

- Surfactants?
- Multi-constituent substances?
- UVCBs?

Main solubility methods

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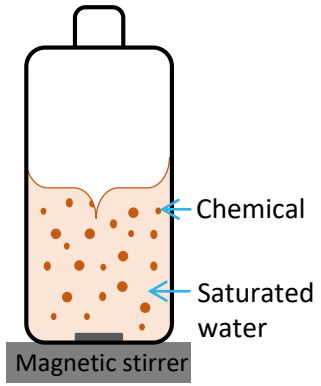
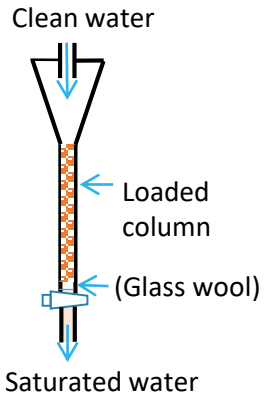
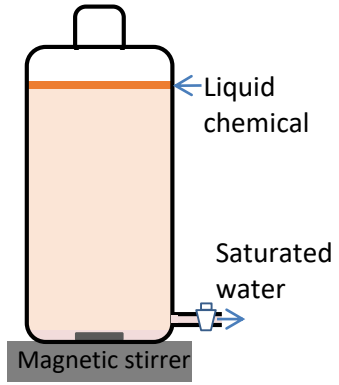
Shake Flask



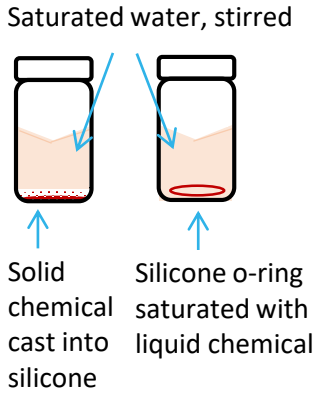
Column Elution



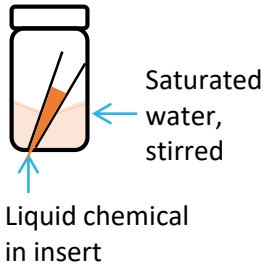
Slow Stir



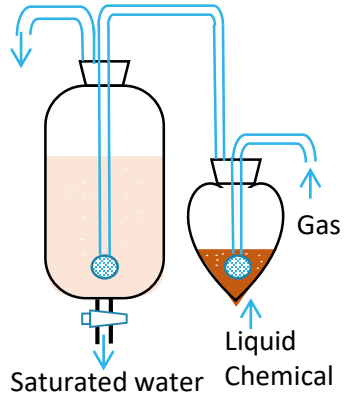
Passive Dosing



Headspace Passive Dosing

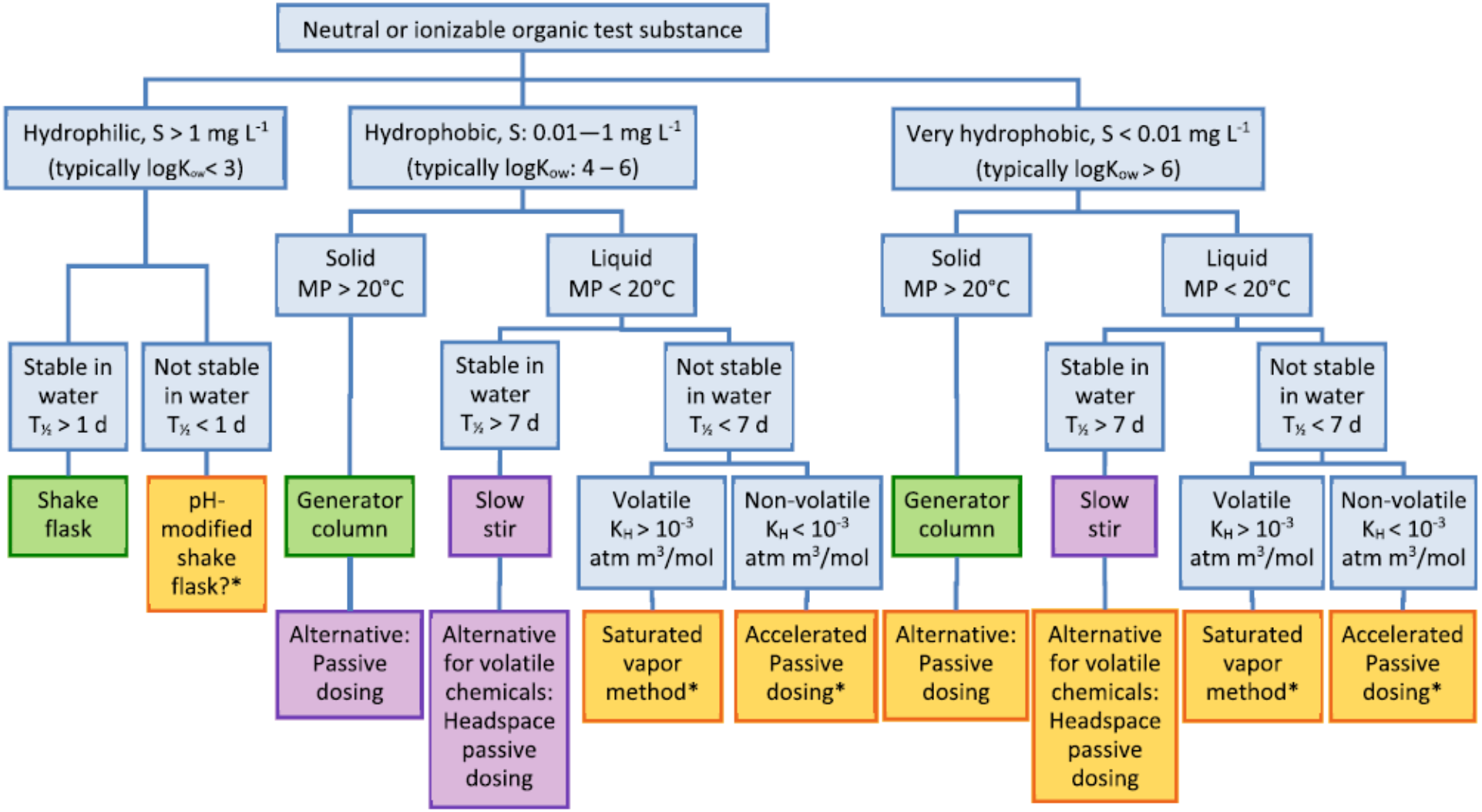


Saturated Vapor

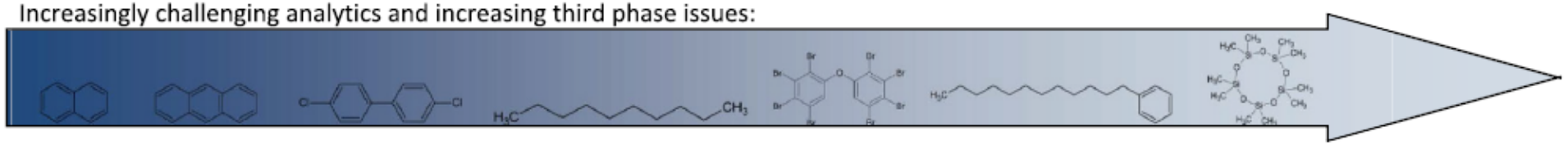


Target chemicals:

Hydrophilics	Solids	Liquids	Hydrophobics	Liquid volatiles	Liquid volatiles



Increasingly challenging analytics and increasing third phase issues:



Main solubility methods

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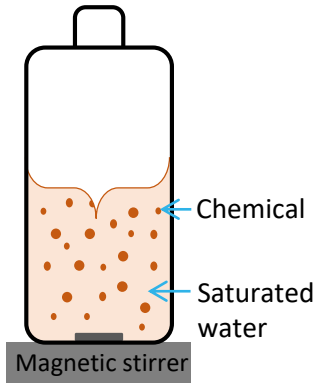
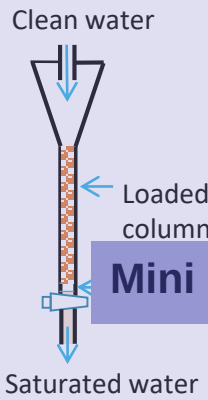
Shake Flask

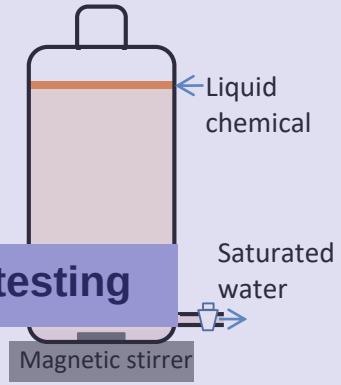


Target chemicals:
Hydrophilics

Column Elution



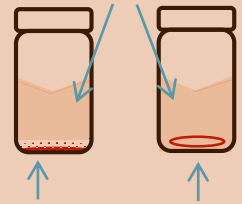
Slow Stir



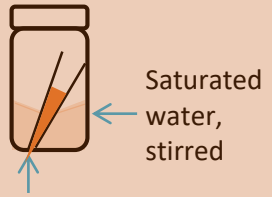
Mini ring-testing

Solids Liquids

Passive Dosing



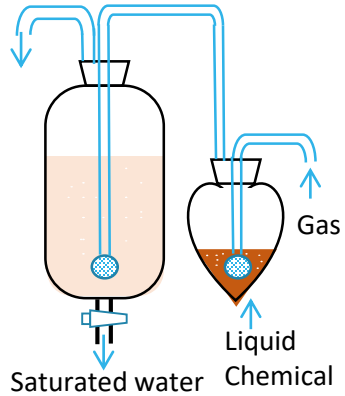
Headspace Passive Dosing



Explorative research

Hydrophobics Liquid volatiles

Saturated Vapor



Liquid volatiles

Ring testing of 2 methods with 5 participating labs

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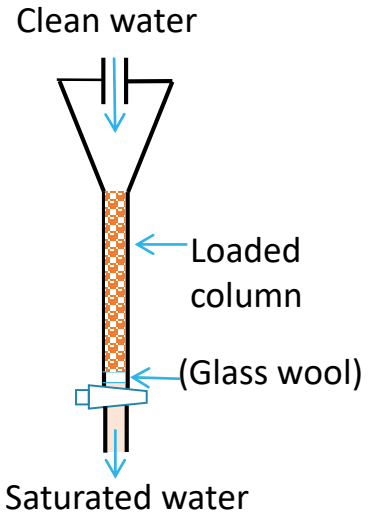
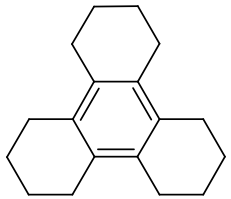
Column Elution / Generator Column Method



Dodecahydrotriphenylene

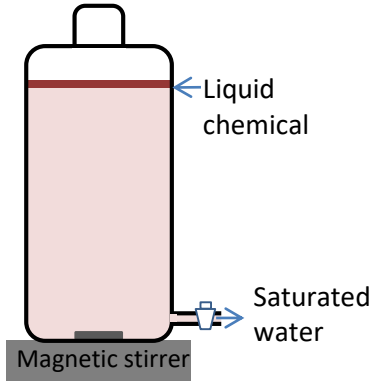
(CAS 1610-39-5)



solid chemical

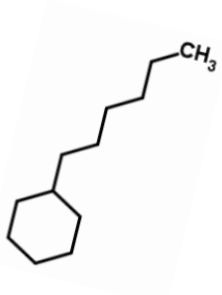
$K_{air/water} < 1$

Slow Stir method



Hexylcyclohexane

(CAS 4292-75-5)



liquid volatile chemical

$K_{air/water} > 1$

Ring testing results

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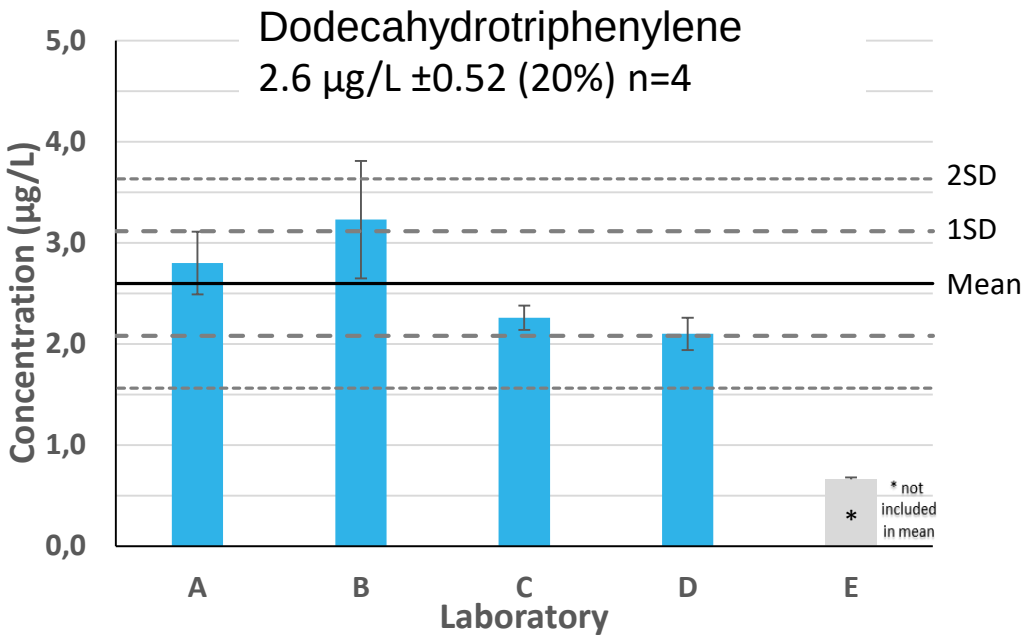
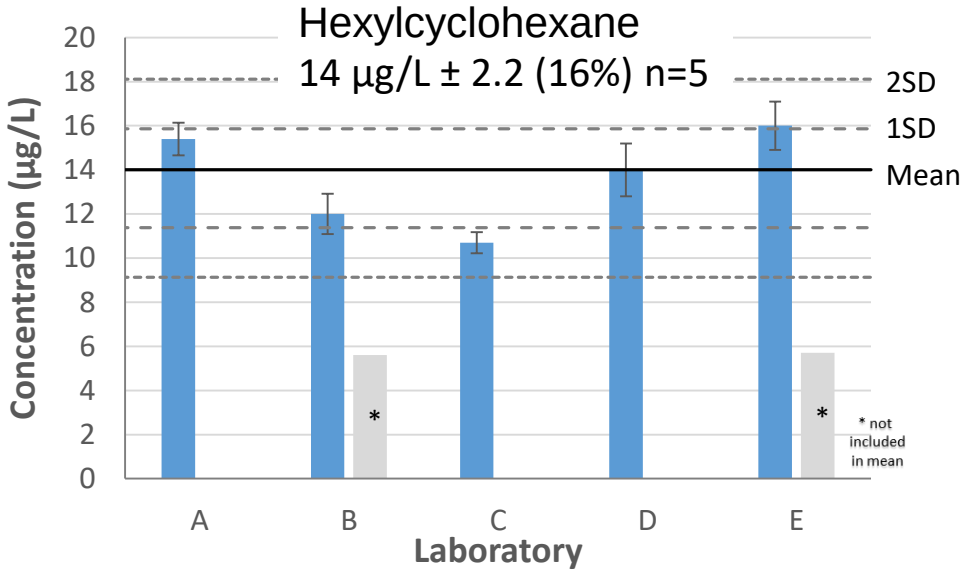
Generator column



Slow Stir



Additional guidance:

- mixing speed (80-250 rpm)
- vessel size (2L minimum)
- vessel headspace (<10% of vessel volume)

Headspace Passive Dosing of volatile hydrophobic chemicals – toxicity testing at and below the saturation level

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Chemosphere 211 (2018) 694–700

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

Headspace passive dosing of volatile hydrophobic chemicals – Aquatic toxicity testing exactly at the saturation level

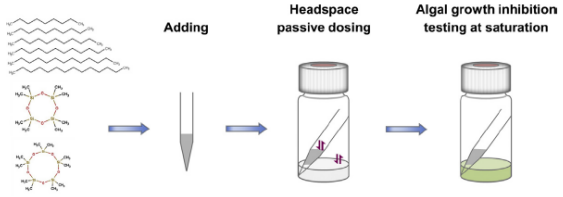
Lam Ngoc Trac*, Stine Nørgaard Schmidt, Philipp Mayer

Department of Environmental Engineering, Technical University of Denmark, DK-2800 Kgs. Lyngby, Denmark

HIGHLIGHTS

- Passive dosing via the headspace established and maintained constant exposure.
- Headspace passive dosing was cross validated by silicone rod passive dosing.
- Aquatic toxicity testing of volatile hydrophobic chemicals exactly at saturation.
- Algal growth inhibition limit tests showed toxicity of alkanes and D4, but not D5.

GRAPHICAL ABSTRACT



Environmental Science & Technology

Article

Cite This: *Environ. Sci. Technol.* XXXX, XXX, XXX–XXX

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Headspace Passive Dosing of Volatile Hydrophobic Organic Chemicals from a Lipid Donor—Linking Their Toxicity to Well-Defined Exposure for an Improved Risk Assessment

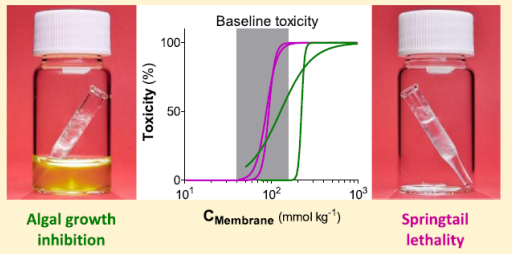
Lam Ngoc Trac,[†] Stine Nørgaard Schmidt,[†,§] Martin Holmstrup,[‡] and Philipp Mayer*[,†]

[†]Department of Environmental Engineering, Technical University of Denmark, DK-2800 Kgs Lyngby, Denmark

[‡]Department of Bioscience, Aarhus University, DK-8600 Silkeborg, Denmark

Supporting Information

ABSTRACT: High hydrophobicity and volatility of chemicals often lead to substantial experimental challenges but were here utilized in headspace passive dosing (HS-PD) to establish and maintain exposure: the pure chemical served as a passive dosing donor for controlling exposure at saturation, whereas triglyceride oil containing the chemical was used to control lower exposure levels. These donor solutions were added to glass inserts placed in the closed test systems. Mass balance calculations confirmed a dominant donor capacity for all chemicals except isooctane. This HS-PD method was applied to algal growth inhibition and springtail lethality tests with



Establish and validate new approaches for liquid hydrophobic chemicals

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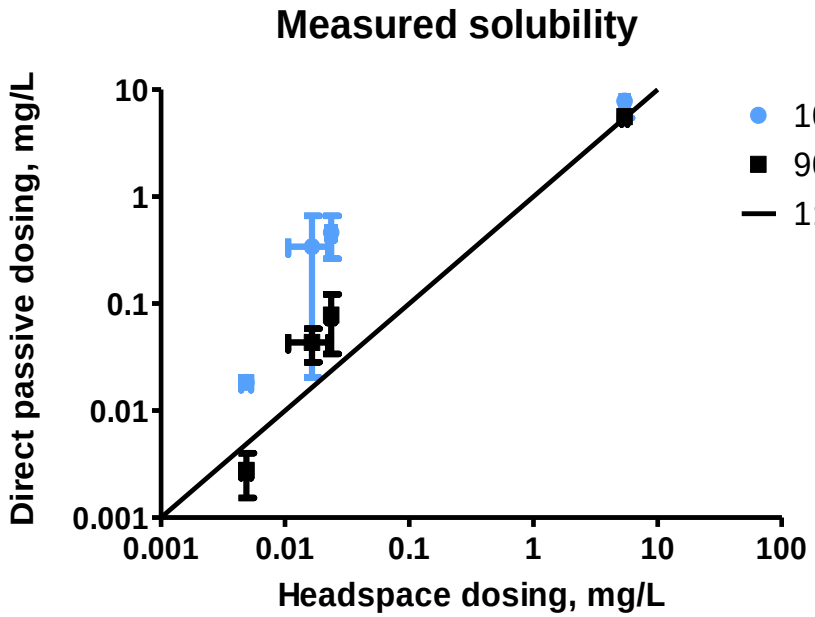
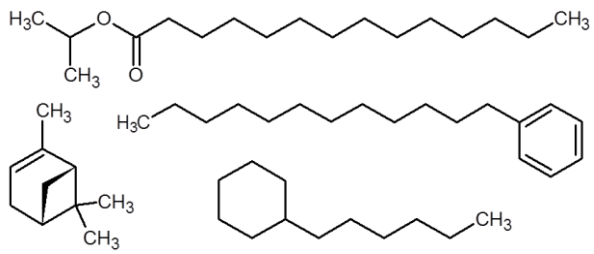
Passive Dosing



Headspace Passive Dosing



Validation and cross-validation – testing close to saturation

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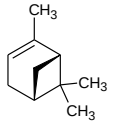
HPD

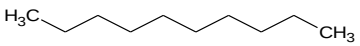
DPD

(+)-α-Pinene

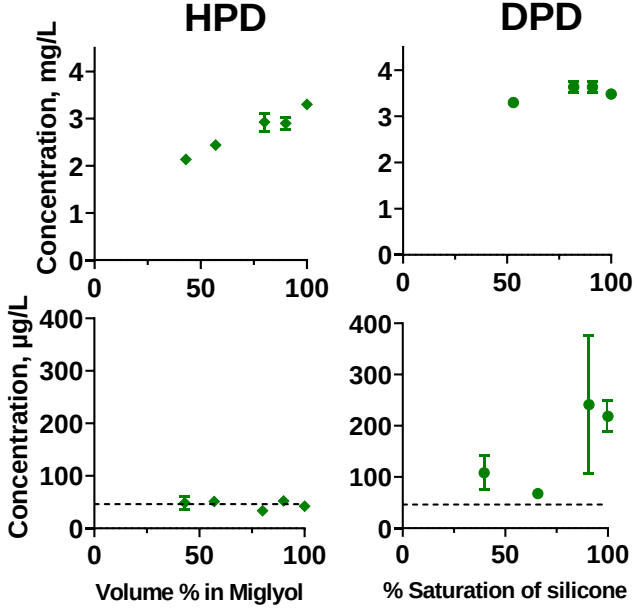


$logK_{ow}$: 4.44

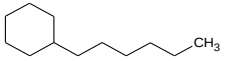
_n_-Decane



$logK_{ow}$: 5.01

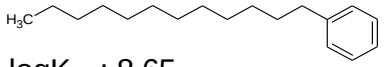


Hexylcyclohexane

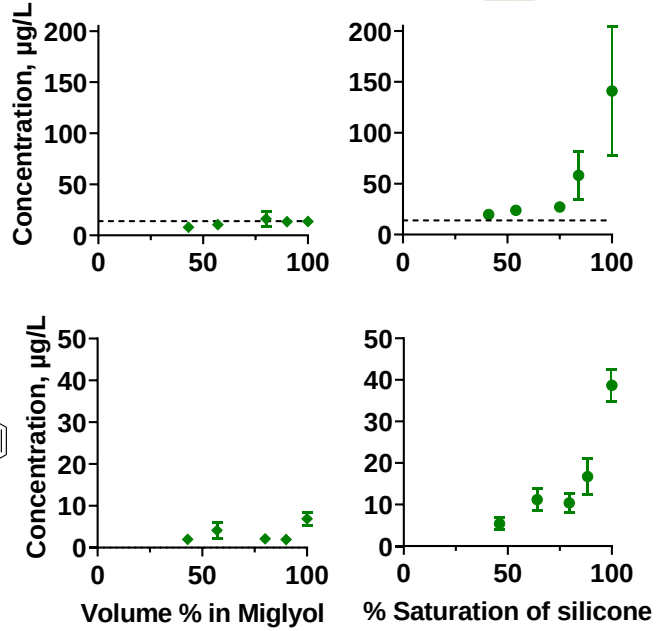


$logK_{ow}$: 6.05

Dodecylbenzene



$logK_{ow}$: 8.65



Partitioning based methods for solubility determinations

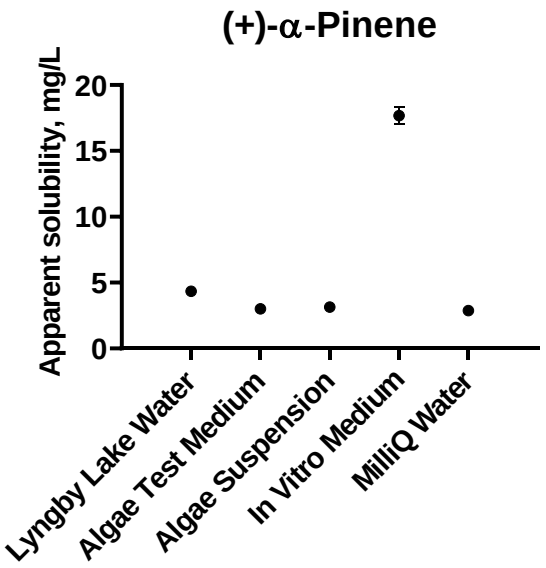
Headspace passive dosing

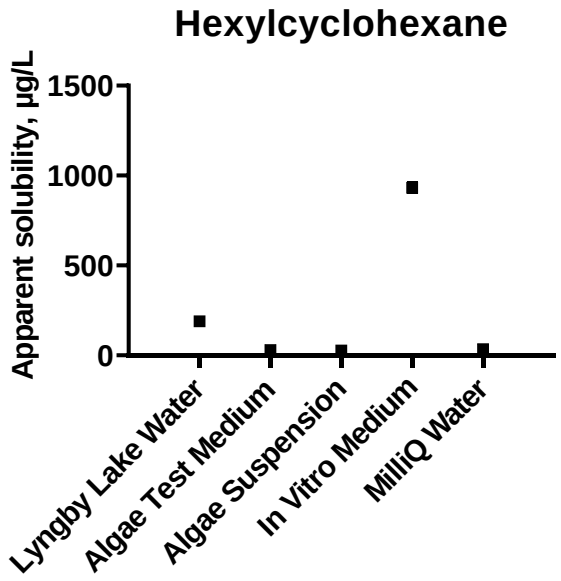
- Careful temperature equilibration of all materials is important to avoid condensation of test chemical during equilibration
- Precision was confirmed by measurements at and slightly below saturation and ring test results
- Headspace passive dosing was a fast solubility method, and accuracy was confirmed by the more established slow stir method
- Binary mixtures in miglyol can be used to check for pure phase droplet artefacts and for validation

Direct passive dosing from silicone

- Worked up to log K_{ow} of 4.4, but not for highly hydrophobic liquids at saturation

Medium effects on ‘apparent’ solubility





	TSS, mg/L	DOC (non-volatile), mg/L
Lyngby Lake Water	16.0	10.3
Algae Test Medium	< 2	0.23
Algae Suspension	< 2	0.20
In Vitro Medium	< 2	1790

Comparison of experimental results with predictions from established methods

Compound	Technique	Measured WS (µg/L)	Letinski et al (2015) slow stir	Tolls et al (2002) slow-stir	SPARC	EPIWIN WATER NT (v1.01)	EPIWIN WSKOW (v1.42)	ACD/Labs (v11.02)
Hexylcyclohexane	Slow-stir	14*			8.8	124	61	19
Dodecahydro triphenylene	Column elution	2.6*			0.37	26	4.9	55
α-Pinene	Headspace PD	3300			3080	3483	4071	8900
n-Decane	Headspace PD	42	49	46	83	92	1252	65
Dodecylbenzene	Headspace PD	6.9			0.32	1	1	16

*mean from ECO38 ring test

Establish and validate new approach for UVCBs – Hammershøj et al., Accelerated passive dosing of hydrophobic complex mixtures …

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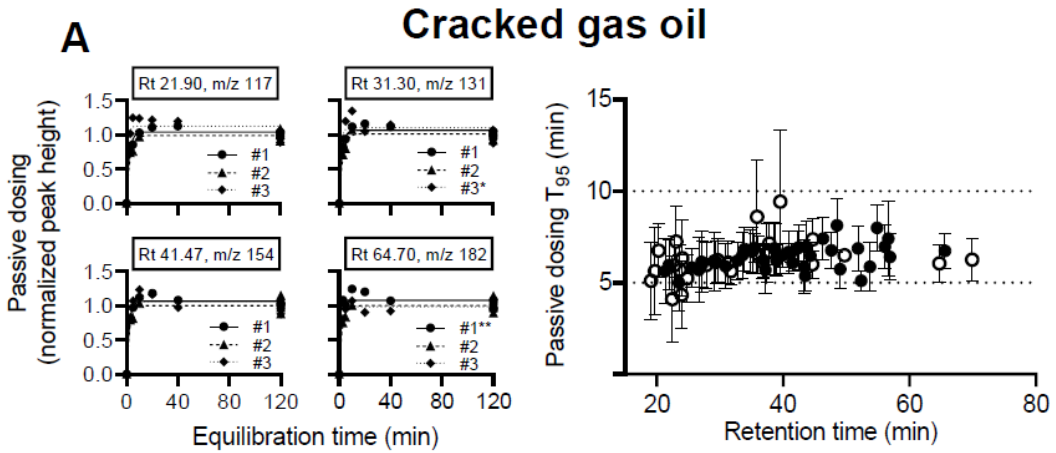

Submitted manuscript.
Co-funded by Concawe, RIFM and CEFIC-LRI

Finalizing the project and next steps

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- Feed ring testing results into the next OECD guideline on solubility testing, which needs to include slow stirring for hydrophobic liquids
- Develop and apply analytical approach to characterize and quantify UVCBs in saturated aqueous solution
- Aquatic toxicity testing of UVCBs at the solubility limit
- Aqueous solubility instead of K_{ow} to investigate and determine hydrophobicity cut-offs in aquatic toxicity

Presentations

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- Heidi Birch, Ngoc Lam Trac, Aaron Redman, Daniel Letinski, Philipp Mayer. Cross-validation for improving determination of water solubility for difficult-to-test substances. Poster at Cefic-LRI 19th Annual Workshop, November 2017, Brussels, Belgium.

- Heidi Birch, Lam Ngoc Trac and Philipp Mayer. New approaches for determining solubility of volatile liquid chemicals. SETAC Europe 28th Annual Meeting, May 2018, Rome, Italy.

- Heidi Birch, Lam Ngoc Trac, Philipp Mayer. Partitioning based determinations of water solubility for volatile hydrophobic liquid chemicals. SETAC Europe 29th Annual Meeting, May 2019, Helsinki, Finland.

- Philipp Mayer, Heidi Birch, Aaron Redman, Daniel Letinski. ECO 38 Cross-validation for improving determinations of water solubility for difficult to test substances. Cefic-LRI Cefic-LRI 21th Annual Workshop, November 2019, Brussels, Belgium.

Publications

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Published

Heidi Birch, Aaron D. Redman, Daniel J. Letinski, Delina Y. Lyon, Philipp Mayer. Determining the water solubility of difficult-to-test substances: A tutorial review. Analytica Chimica Acta 2019; 1086: 16-28. https://doi.org/10.1016/j.aca.2019.07.034

Submitted

Rikke Hammershøj, Heidi Birch, Karina K. Sjøholm, Philipp Mayer. Accelerated passive dosing of hydrophobic complex mixtures – controlling level and composition in aquatic tests. Submitted manuscript. (main funding CONCAWE/RIFM, co-funded by ECO-38)

Planned

”Ring testing and cross-validations for determining water solubility of highly hydrophobic chemicals” – Joint paper including data from ring-test (EXXON) and headspace dosing work (DTU).

We'd like to thank

Hanne Bøggild for laboratory assistance

CEFIC-LRI for the funding of the ECO 38 project

ECETOC and the project liaison team:

- Delina Lyon (Shell)
- John Parsons (University of Amsterdam)
- Chris Sparham (Unilever)
- Lucy Wilmot (ECETOC)

Thank you for your attention!

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