Experimentally determined permeability ratios (aq. dilution/neat) for 30 organic solvents suggest highly variable influence of water on percutaneos absorption

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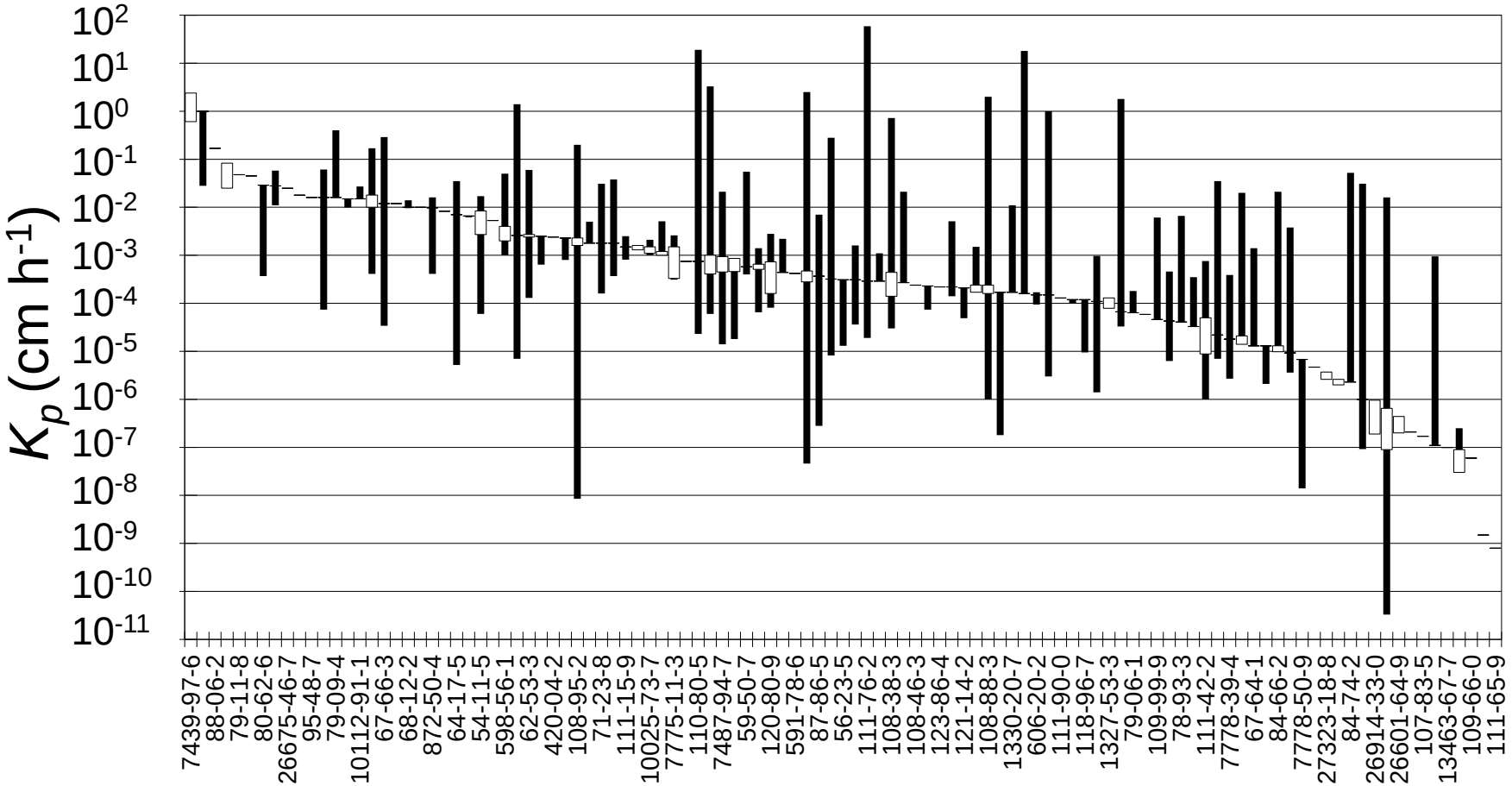
Background

Large variability between and within chemicals:



Johanson & Rauma, 2008

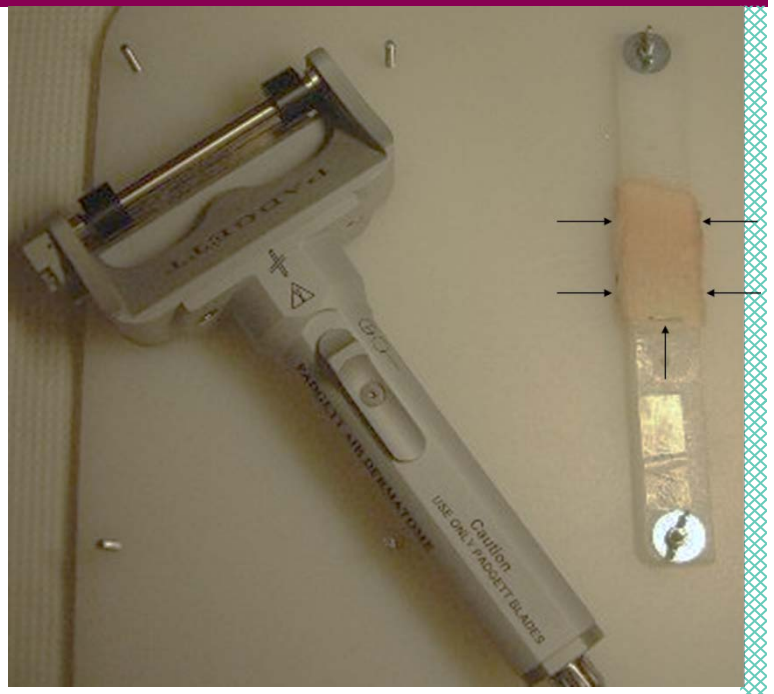
Aim

Investigate a larger number of substances in neat and diluted in water, using the same experimental conditions.

10%		1%	0.1%
Acetone	n-Butanol	1,2-Dichloroethane	n-Butyl acetate
Acetonitrile	2-Propanol	2-Hexanone	Butyl acrylate
2-Butanone	2-Propen-1-ol	3-Methyl-1-butanol	Cyclohexane*
1-Butoxy-2-propanol	1-Propoxy-2-propanol	4-Metyl-2-pentanol	
2-Butoxyethanol	2-Propoxyethanol	Dichloromethane	
Ethanol		Ethyl acetate	
2-Ethoxyethanol		Ethyl acrylate	
2-Furanmethanol		Methyl acrylate	
2-Isopropoxyethanol		Methyl methacrylate	
Methanol		Methyl tertiary butyl ether	
1-Methoxy-2-propanol		m-Xylene*	**PBS+PEG-20 donor*

Methods: Skin preparation

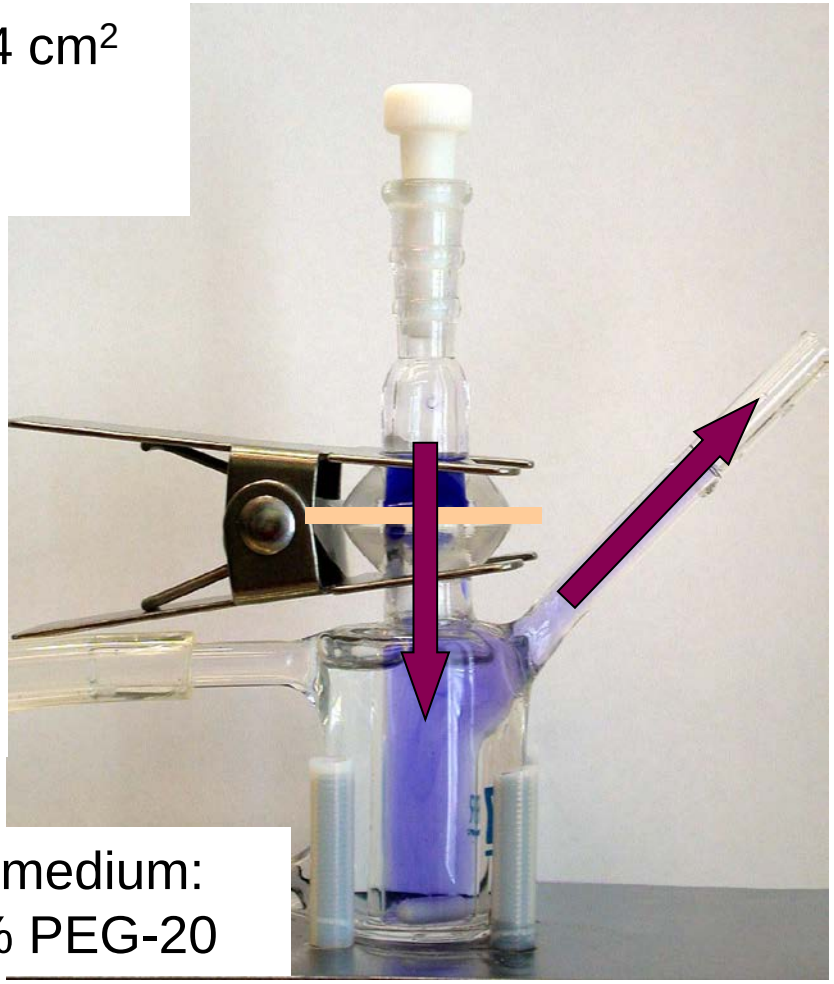
- **Skin from Duroc piglets**
  - Obtained from local commercial breeders
  - Back and flank
  - Frozen (-20°C)
  - Dermatomed (400-500 µm)



  - Skin integrity measured 24h before exposure
    - Discarded if <50kΩ
  - Stored in PBS overnight (+8°C)

Methods: Franz diffusion cells

Exposure area: 0.64 cm^2
Volume: 5 ml
32°C



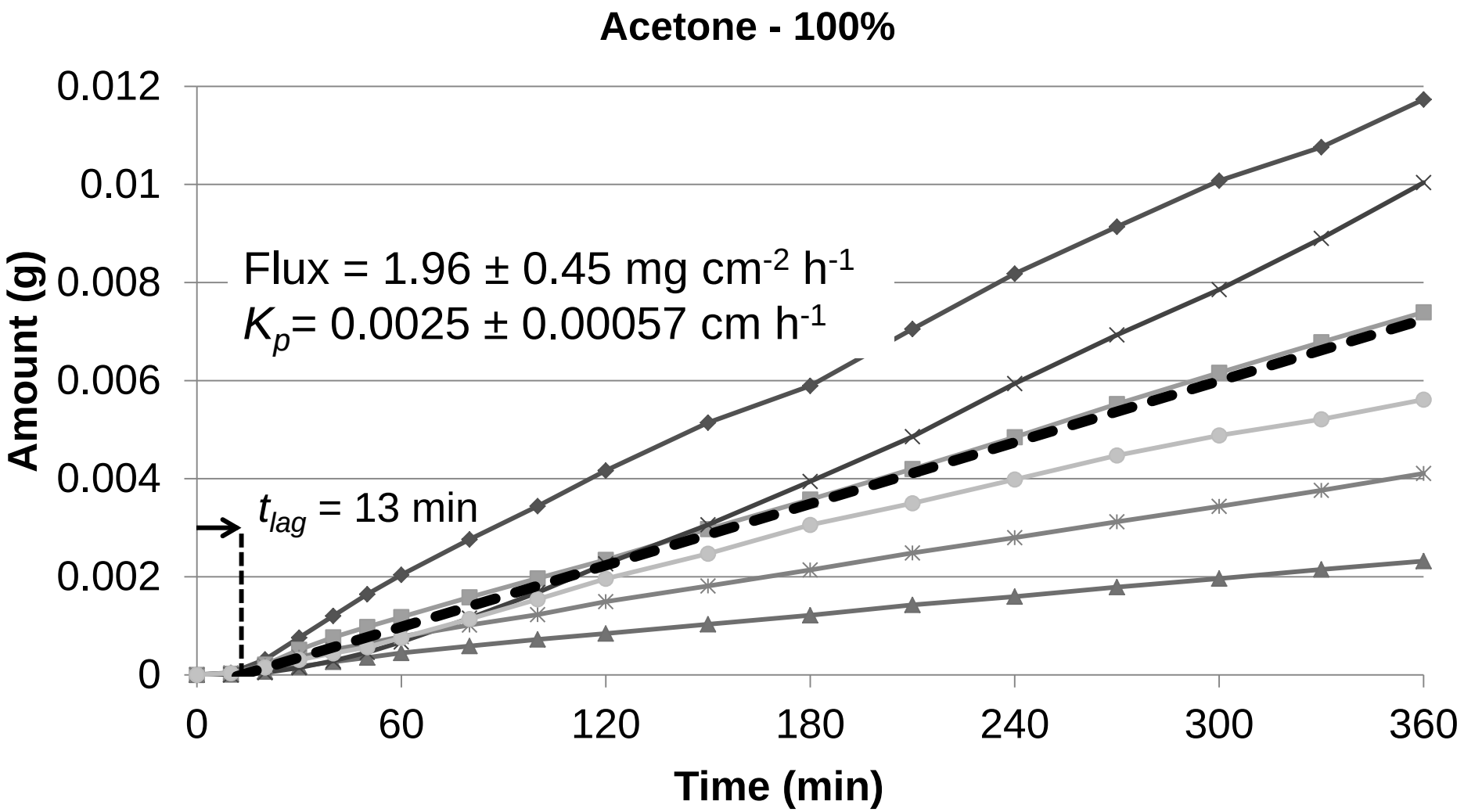
Sampling 50 µl
Every 10-30 min

gas chromatograph

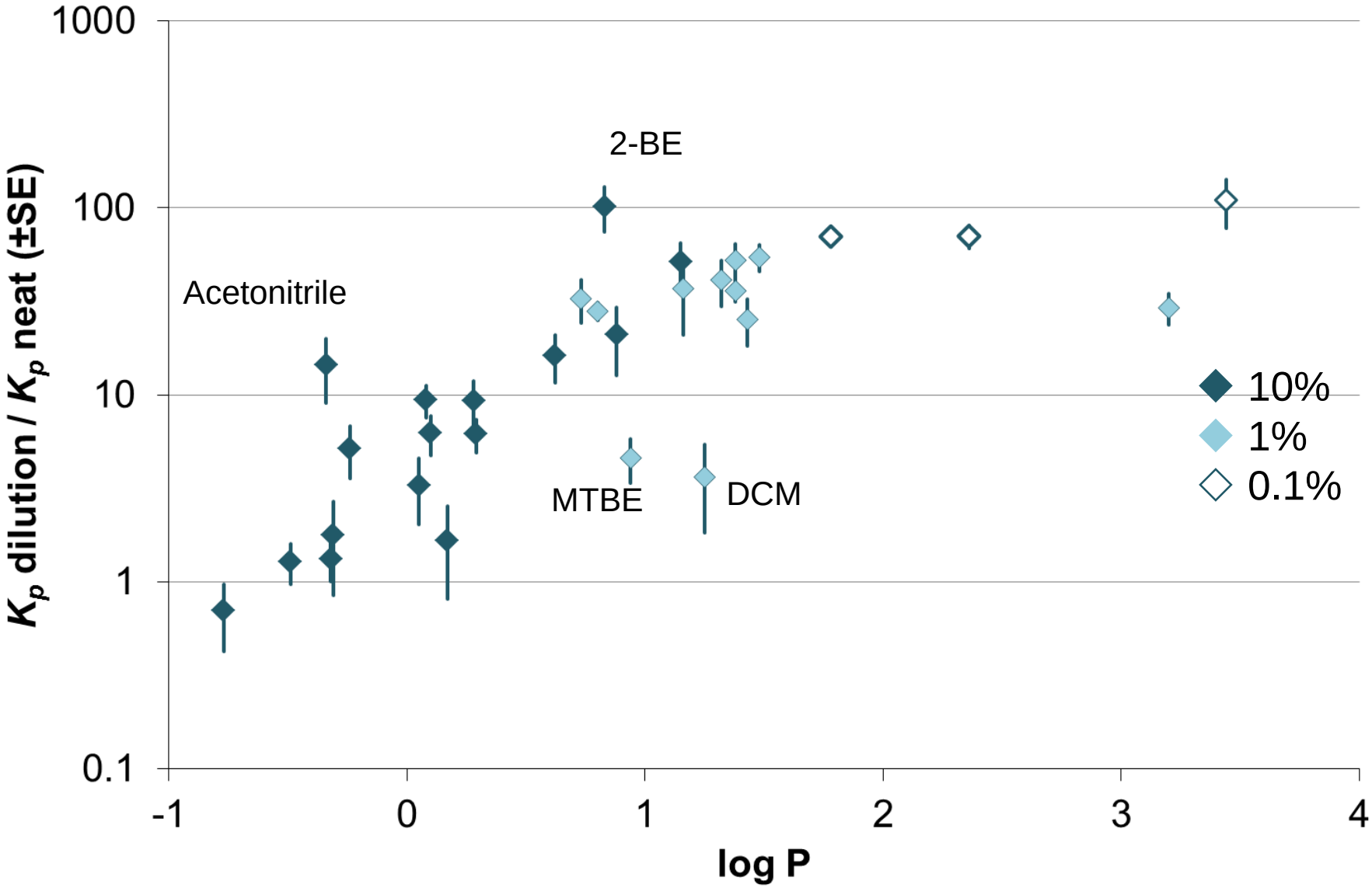
6 replicates
different individuals

Receptor medium:
PBS + 6% PEG-20

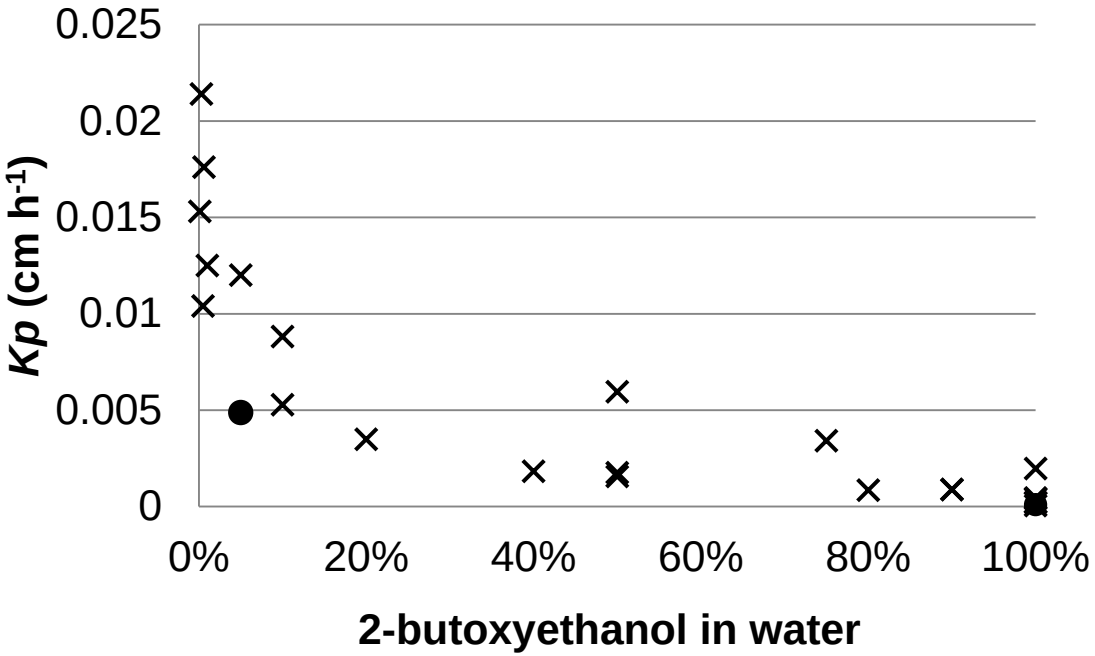
Results


Acetone - 100%
Amount (g)
0.012
0.01
0.008
0.006
0.004
0.002
0
Flux = 1.96 ± 0.45 mg cm-2 h-1
Kp= 0.0025 ± 0.00057 cm h-1
tlag = 13 min
0
60
120
180
240
300
360
Time (min)

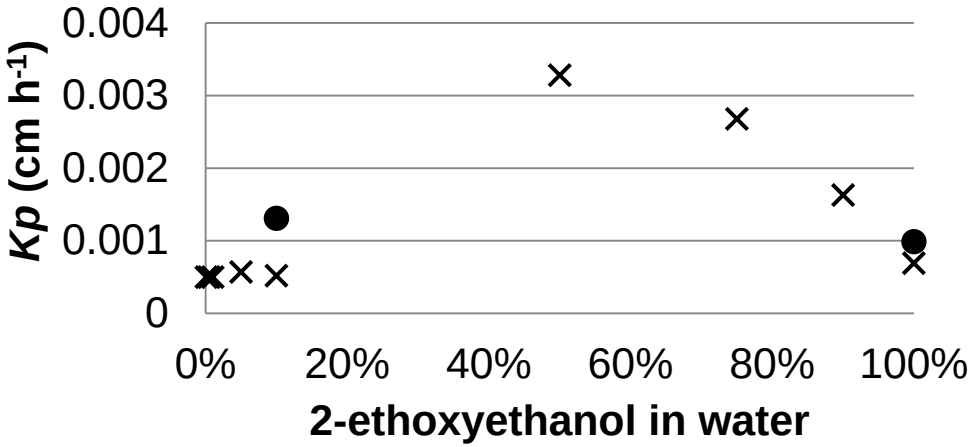
Results


1000
100
10
1
0.1
K_p dilution / K_p neat (±SE)
-1
0
1
2
3
4
log P
2-BE
Acetonitrile
MTBE
DCM
10%
1%
0.1%

Discussion

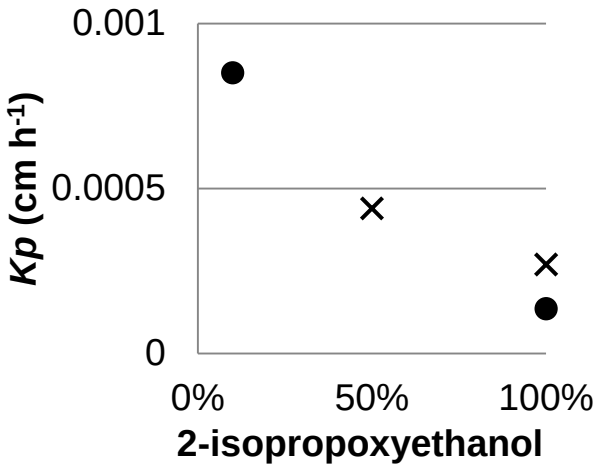


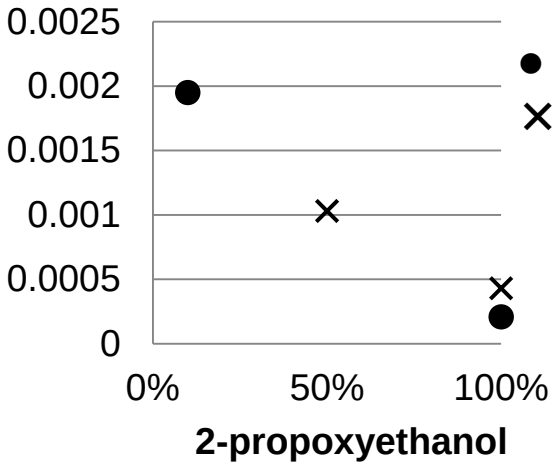
● Our data
× Previous studies



Data from: Dugard et al 1984; Johanson et al. 1998; Johansson & Fernström 1986; Johansson & Fernström 1988; Wilkinson & Williams 2002; Jakasa et al. 2004; Traynor et al. 2007; Korinth et al. 2012.

Discussion





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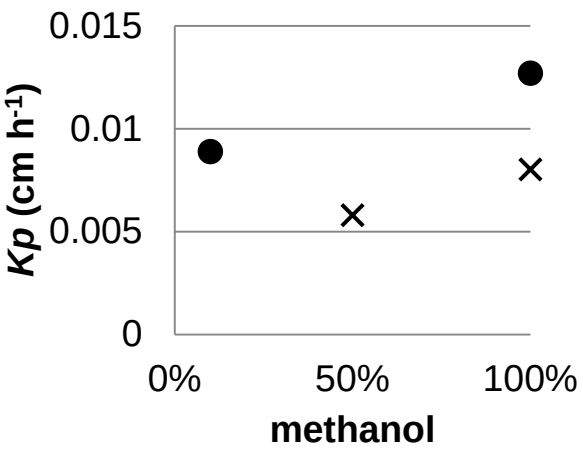

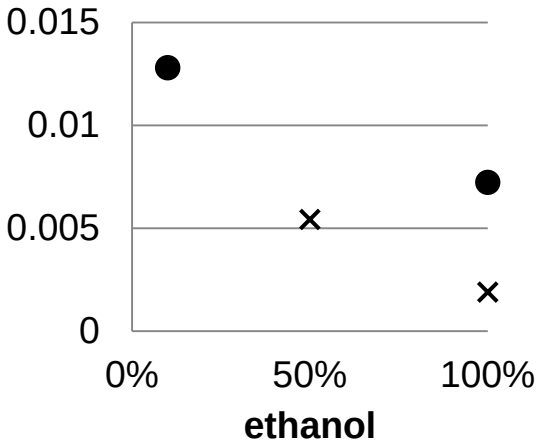

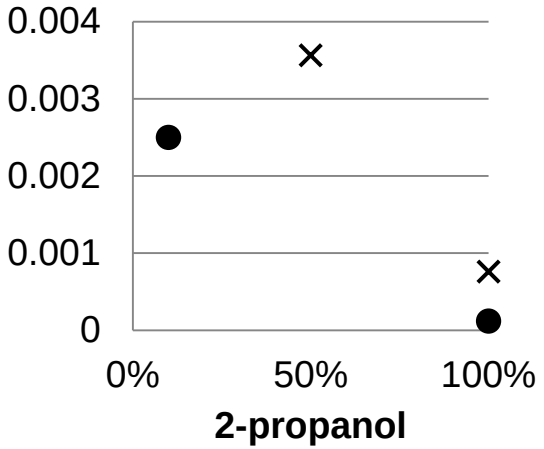

Data from Venier et al., 2004; Korinth et al., 2012

Discussion

Complicating factors

- Only neat + one dilution tested
- Diffusion, and hence true *Kp*, is proportional to activity – not concentration
- Hydration/dehydration of the skin

Conclusions

- The *Kp* ratio (diluted/neat) varies widely:

  10%: **0.7**-102 1%: 4-55 0.1%: 70-**110**

- For hydrophilic solvents (log P < 1) the *Kp* ratio seems proportional to log P.
- Ratio seems unaffected by log *P* for more lipophilic solvents.
  - However, both % dilution and log P are inversely dependent on water solubility.
- Previously published data also suggest variable influence from water dilution on *Kp* for different substances.
- For better understanding, solvents with different log P should be tested neat and at several dilutions.

Thank you for your attention!