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9-23-2018

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Recommended Citation

Samuel Dorey, Armin Hauk, Roberto Menzel, Thomas Loewe, and Ina Pahl, "The proper use of extractables data - aspects beyond extractables-measurment" in "Single-Use Technologies III: Scientific and Technological Advancements", Weibing Ding, Amgen Martina Micheletti, University College London Robert Repetto, Pfizer Eds, ECI Symposium Series, (2018).
http://dc.engconfintl.org/sut_iii/32

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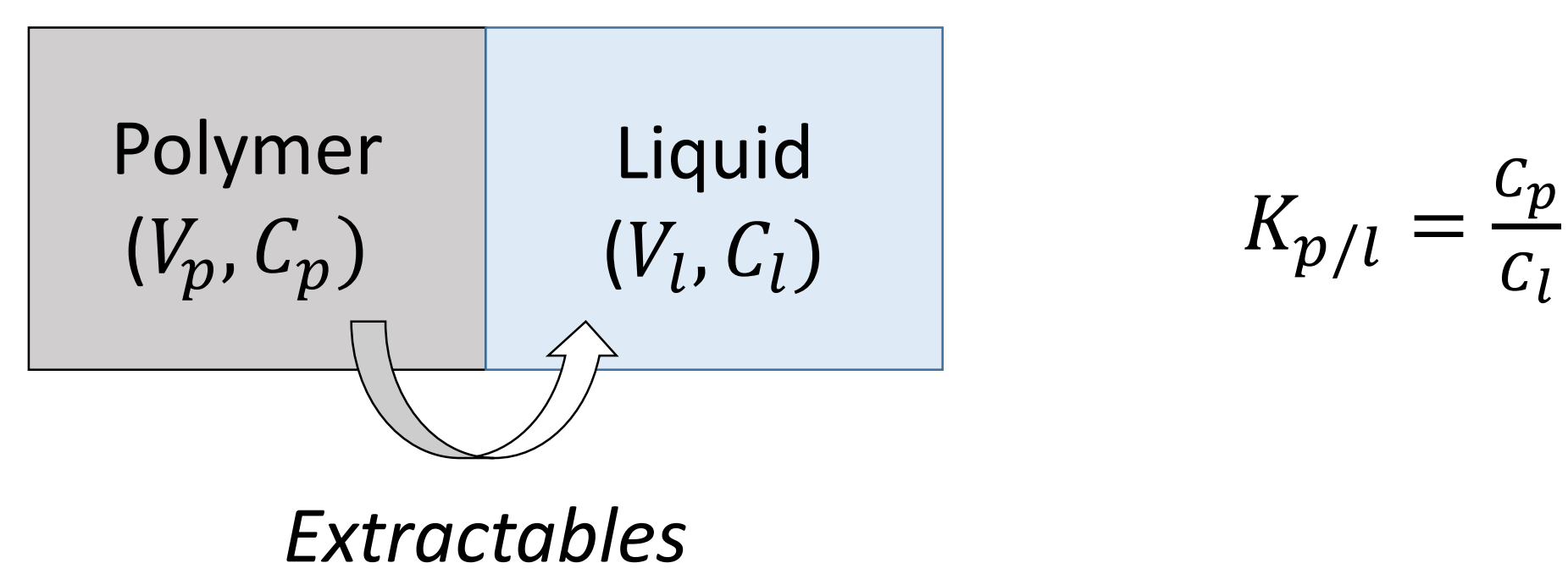
The proper use of extractables data – Aspects beyond extractables measurement: extractables estimation in complex single use systems by the use of equilibrium calculation

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The single-use systems used in the biopharmaceutical industry can release extractables. The extractable concentrations can be determined using different extraction matrices, which can mean different solvents. The purpose of this study was to show the possibility to calculate the extractable concentration in different solvent systems, in combination of systems of different sizes and assembled with different components.

Theoretical background

When single-use systems are in contact with a fluid, extractables can be distributed between the two phases. At long contact times an equilibrium can be reached, which is described by the partition constant $K_{p/l}$ which is the ratio of extractables concentration in the polymer versus the liquid phase:



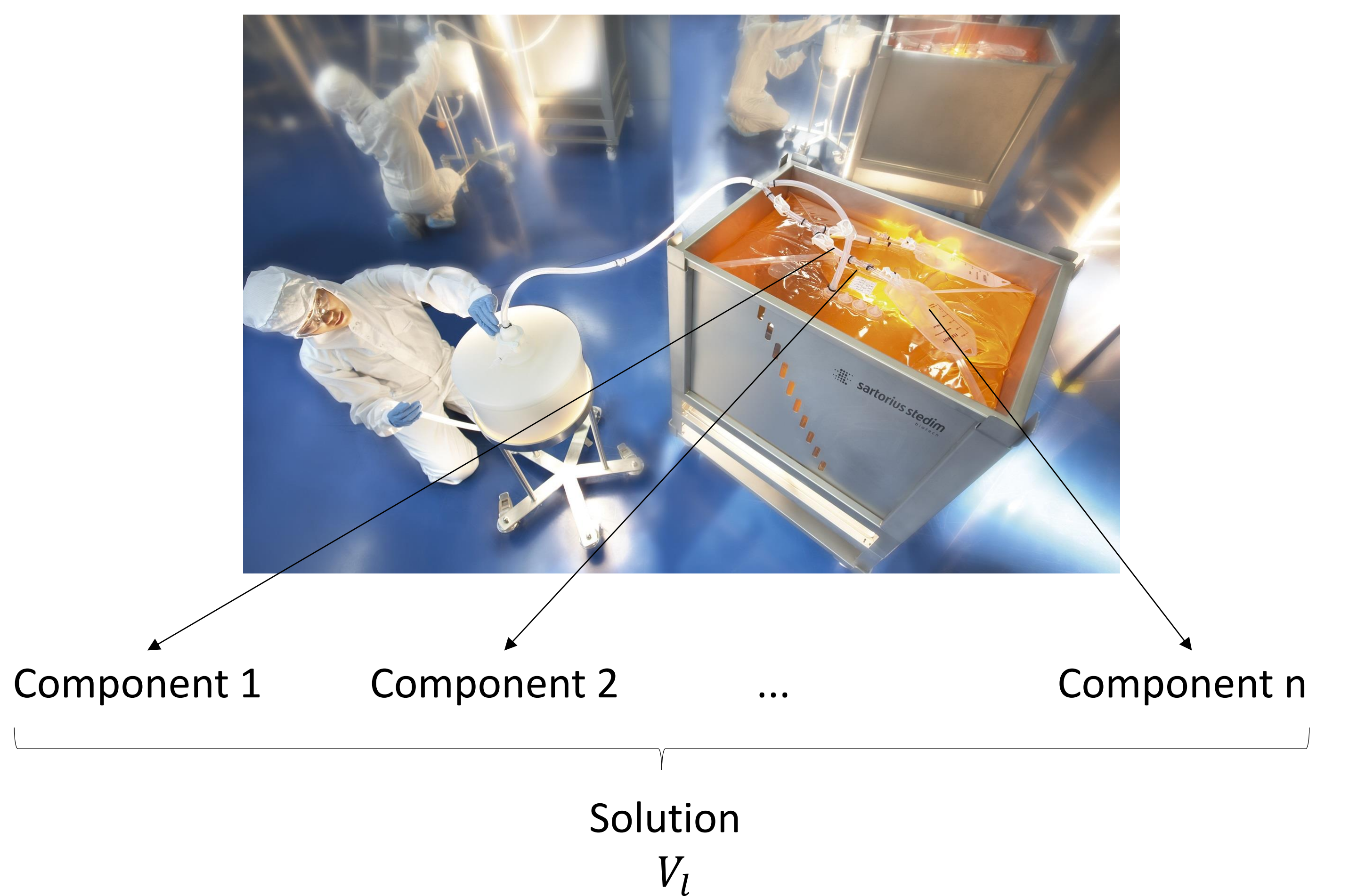
The initial quantity m_0 of a chemical in the polymer is the sum of the quantity extracted by the solvent and the remaining quantity in the polymer (condition of conservation of mass).

Based on that one can calculate the quantity of any extractables in any solvent, n , as it only depends on $K_{p/l, n}$ and m_0 [1]:

$$C_{l,n} = \frac{m_0}{V_l + K_{p/l,n} * V_p}$$

Multi-component assembly

In real conditions, a product is made of several parts (bag, tubing, connectors...) which will have product contact. It is possible to determine the extractables concentrations of the entire device:



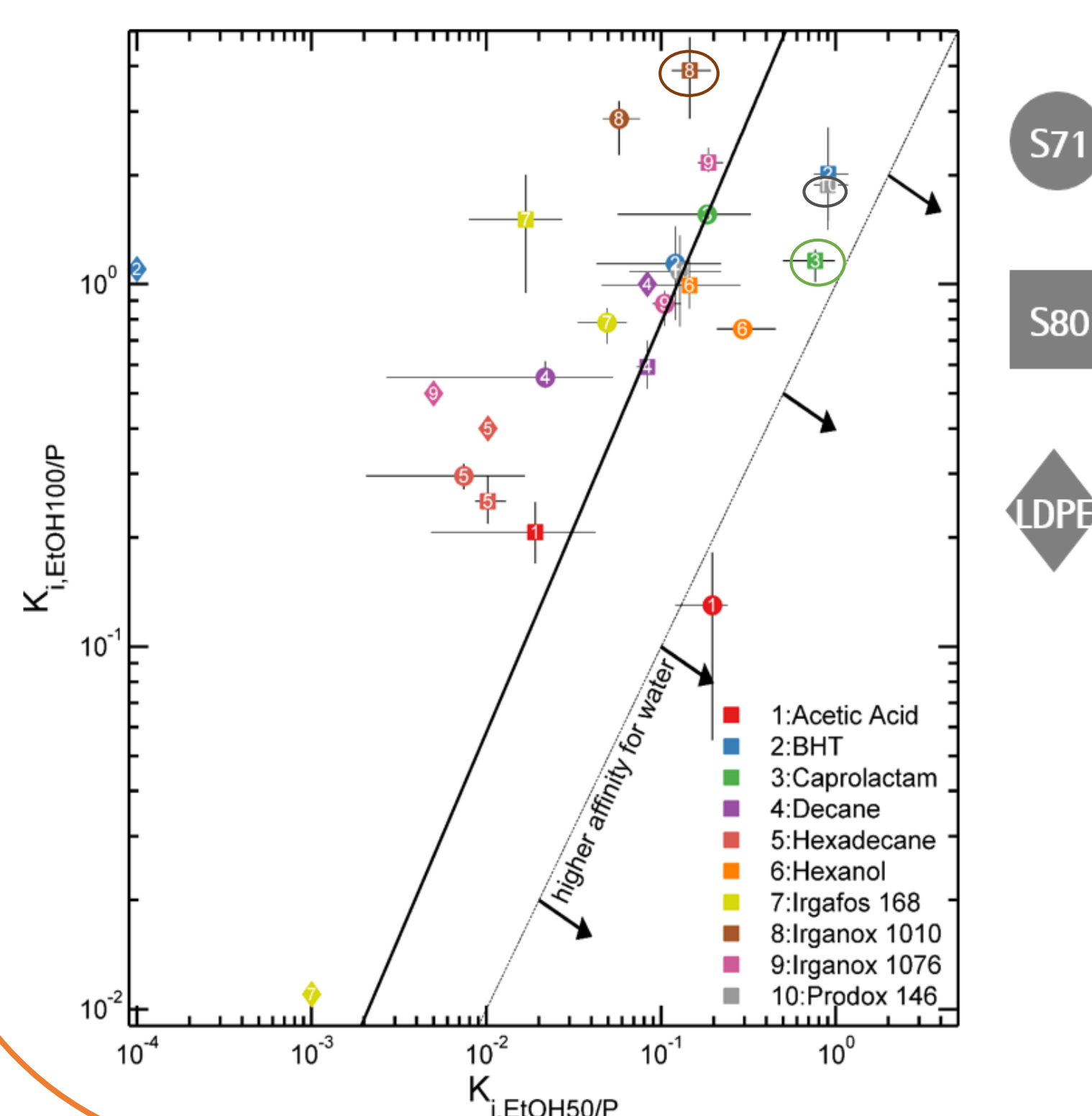
We have developed an algorithm based on the following equation allowing us to calculate the partitioning of extractables in the whole systems:

$$C_l = f(m_{tot}; K_{p/l}; V_p; V_l)$$

Experimental determination of $K_{p/l}$

When not taken from literature, $K_{p/l}$ values can be estimated experimentally, using different methods:

- direct measurement of C_l and C_p
- doping (or fortifying) of the extraction solution, and measurement of C_l after equilibrium is reached
- correlation methods (e.g. based on HPLC retention times [2])



This graph shows the $K_{l/p}$ of ten compounds which were experimentally determined by doping in pure ethanol and in a 50% ethanol/50% water mixture, for several films.

Application

We calculated the extractable concentration $C_{l,th}$ in 50% ethanol/50% water mixture from values experimentally measured $C_{l,exp}$ in pure ethanol from the S80 film (PE/EVOH/PE).

The initial concentrations in the film $C_{p,i}$ were calculated. Then the quantity of these compounds that would be extracted by a 50% ethanol/50% water mixture* was calculated $C_{l,th}$ and compared to the experimental values $C_{l,exp}$:

Compound	$C_{p,i}$ (µg/g)	$C_{l,th}$ (µg/mL)	$C_{l,exp}$ (µg/mL)
Caprolactam	21.8	3.4	2.9
2,4-Di- <i>tert</i> -butylphenol (1)	24.1	4.6	3.5
Irganox® 1010 (2)	0.7	0.06	< 0.1

* Extraction conditions: 70 days, 40°C, S/V = 6 cm²/ml.

(1) Prodox 146

(2) Irganox is a registered trademark of BASF Group: Pentaerythritol tetrakis(3,5-Di-*tert*-butyl-4-hydroxyhydrocinnamate)

Considering equilibrium conditions are achieved, we can estimate the E&L profile from different solvents, different systems of diverse sizes and even combination of devices. The use of $K_{p/l}$ combined to experimental extractable measurement in pure ethanol allows us to obtain a good estimation of the extractable quantity with a 50% ethanol/50% water mixture. This methodology will be generalizable to other solvents.

References:[1] D. R. Jenke, B. E. Rabinow, *Proper Accounting for Surface Area to Solution Volume Ratios in Exaggerated Extractions*, PDA J Pharm Sci and Tech, 2017, 71 225-233.

[2] Test No. 121: Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC), OECD Guidelines for the Testing of Chemicals, Section 1, OECD Publishing, Paris.

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