Solvent selection tool

Principles and guidance

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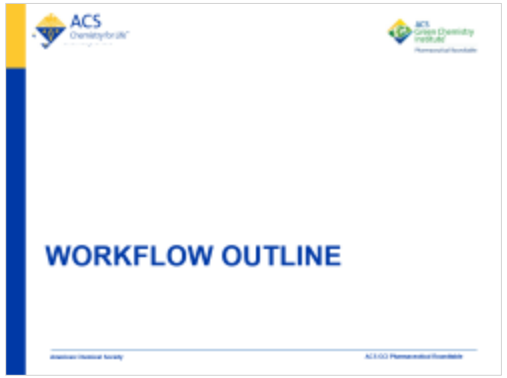
BACKGROUND TO SOLVENT SELECTION
American Chemical Society


HOW CAN WE COMPARE SOLVENTS?
American Chemical


WORKFLOW OUTLINE


USING THE TOOL


WHAT HAPPENS NEXT?

BACKGROUND TO SOLVENT SELECTION

Solvent selection – why worry?

- Solvents are critical participants in chemical processing
  - Promoting chemistry (S_N2, $E1_{cb}$…)
  - Dissolving reactants
  - Modifying solute properties
    - pKa
    - Redox potential
    - H-bonding
  - Removing impurities / byproducts (partitioning)
  - Isolating products (crystallisation…)

The right solvent can be the difference between straightforward processing and a world of pain

Solvent Selection

A common question during chemical processing is:

'What could replace…'

For solvents the obvious action is to consider homologues e.g. butyl acetate for ethyl acetate but:

1. Is butyl acetate the best alternative?
2. Was ethyl acetate the best start point?

What is required is a means of defining whether solvents are 'similar' or 'different' in behaviour and this extends beyond chemical functionality

The question that should be asked is:

'What does my application need from a solvent?'

Solvent Selection Guides

- Solvent selection guides offer assistance in identifying solvents
- Most support post-selection comparison between solvent options.
- Objective selection decisions for comparison can sometimes be compromised in such situations:
  - What is in the lab solvent cupboard?
  - What did I use last time?
  - What other esters are available commercially?
- The choice of solvent is often restricted to simple consideration of the chemistry
  - Polarity, incompatible functional groups, temperature window

Principles of the Solvent Selection Tool

Solvent Selection Tool reverses this philosophy by focussing on molecular properties rather than solvents:

What properties will interfere with your application?

What properties will facilitate your process?

Ideal solvent will provide optimal support across chemistry, work-up and isolation

User identifies the necessary properties (from ~100 options)

Tool dynamically shortlists appropriate solvents (from set of 272 candidates).

HOW CAN WE COMPARE SOLVENTS?

How can we define a solvent?

- Many different descriptors of solvent can be identified
  - Chemical functionality (alcohol, ketone, amide…)
  - Molecular descriptors (Abraham…)
  - Physical properties (m.pt, viscosity…)
  - Regulatory classification (ICH…)
  - Legal controls (REACH, TSCA…)
  - Environmental impact (VOC potential…)
  - Health and safety performance (mutagenicity, LD_{50}…)

Any or all of these may be important in choosing a solvent so where to start?

Bringing Simplicity For The User

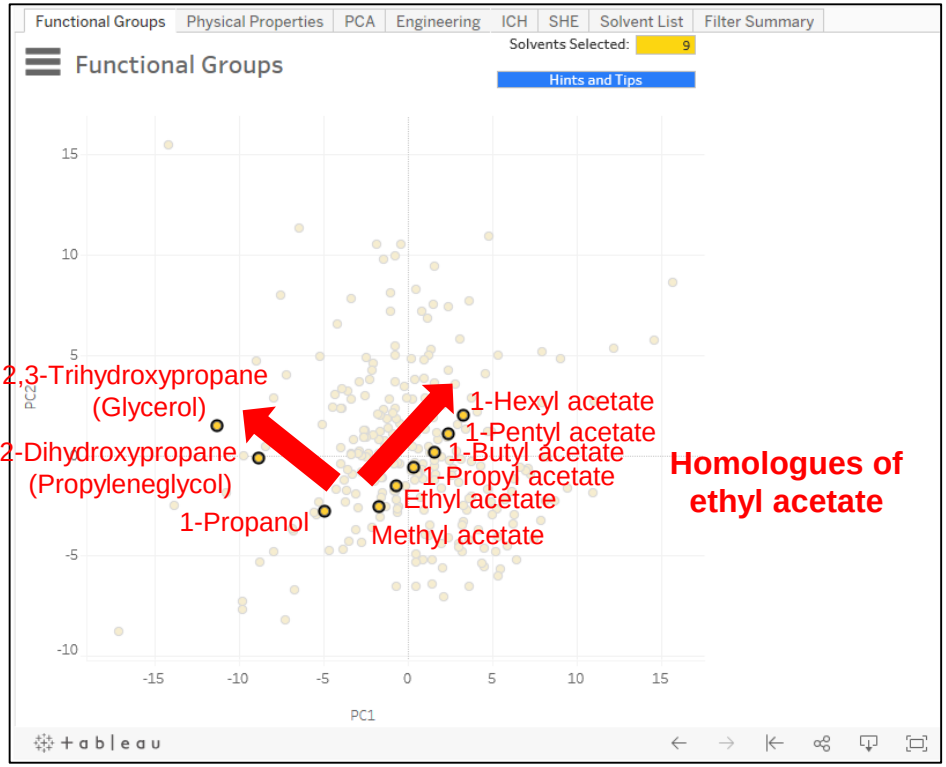
- Making comparisons across a wide range of parameters is challenging
- To identify ‘similar’ and ‘different’ options, it is necessary to represent the solvent set at a level beyond individual molecular properties
- Multivariate technique (Principal Component Analysis, PCA) allows large number of potentially correlated parameters to be reduced to small number of descriptors
- PCA identified 5 Principal Components (PCs) for solvent data
  - Model provides distribution of solvents in 5-dimensional space (PC1→PC5)
  - Default view in tool is the projection in plane of of most dominant descriptors (PC1, PC2)
  - PCs can approximate different high level property eg hydrophobicity

For most users the PCA map simply provides a convenient graphical view of the solvent shortlist

Is The PCA Map Valid?

PCA map successfully validated against observed chemical phenomena:

- Chemical series (see below)
- Keto-enol tautomerisation
- *O*- vs. *C*-alkylation of phenols
- Rates of S_NAr reactions



Oxidation analogues of 1-propanol

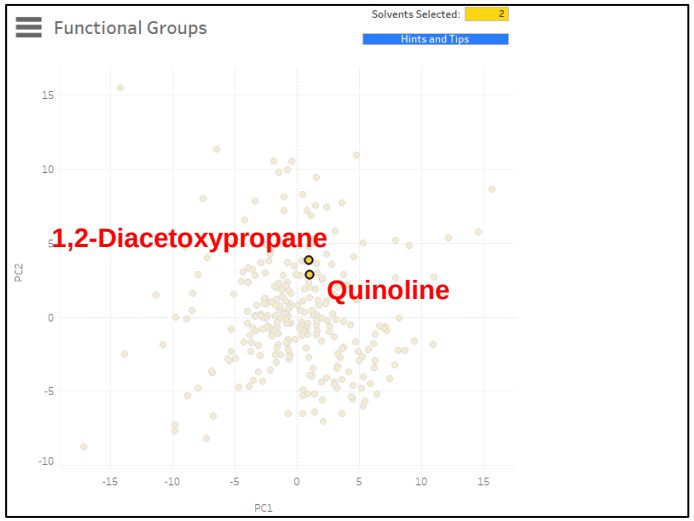
Homologues of ethyl acetate

Does map location mean anything?

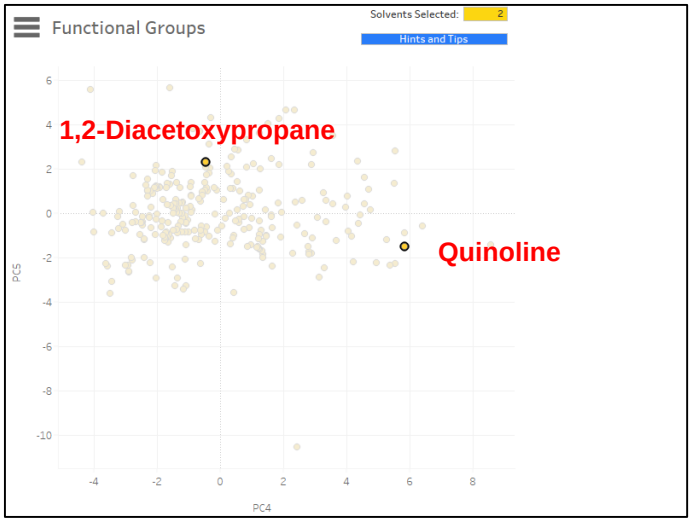
We can infer that solvents in close proximity are similar but this may not be the case in all dimensions

This simply reflects that apparently very different solvents may offer more similarities than chemical functionality might suggest

PC1 vs.PC2



PC4 vs. PC5



WORKFLOW OUTLINE

What are we looking to achieve?

- Before considering the process workflow, it is appropriate to consider what do we want to achieve

- We can identify 2 high level scenarios

Screening

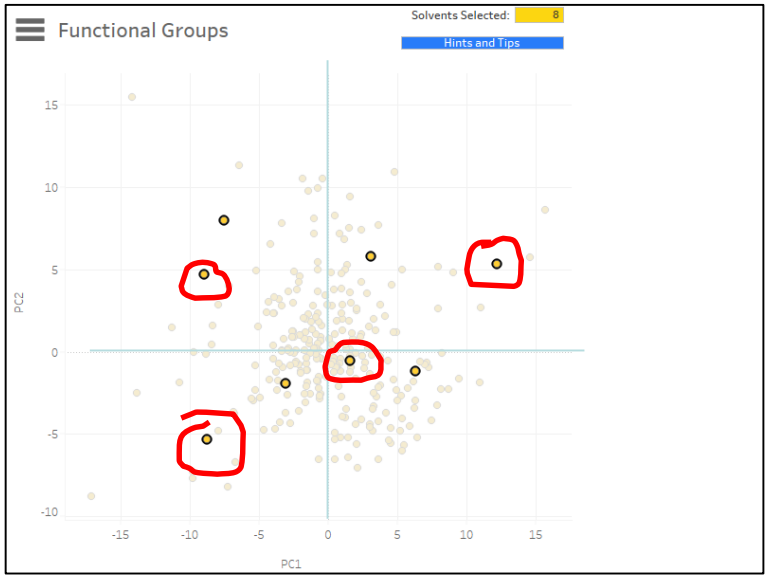
- We are considering a new reaction and don't know what might be required

Optimisation

- We have a lead already and either want to identify others or must find a replacement (eg due to legislative restrictions)

Screening

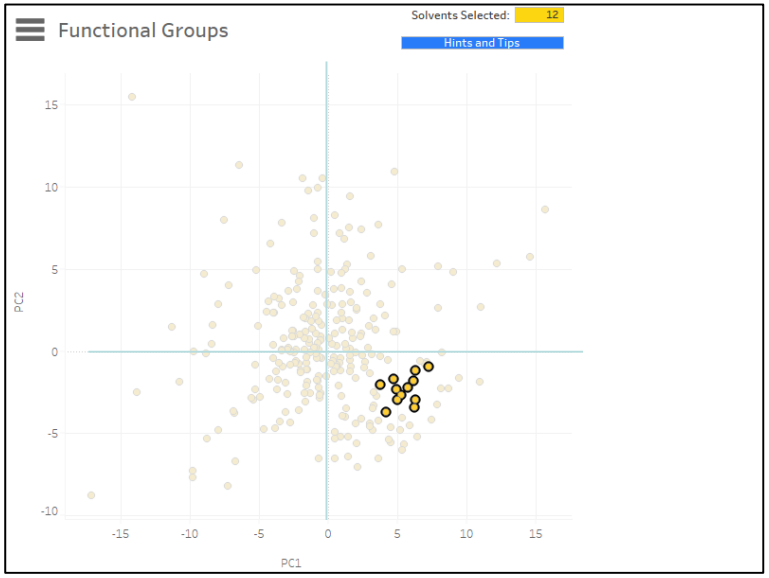
- Screening implies there is limited information to start our search (or we are being truly holistic)



- We may simply want to identify an initial hit
- Applying any appropriate filters will provide a shortlist
- It may not be beneficial to too aggressive in applying filters

- Once we have a selection shortlist we might identify a small number of representative candidates across the different quadrants as a first pass

Optimisation



- Optimisation implies an initial hit is available
  - From a previous screen
  - Due to the need for replacement
- It is reasonable to expect proximal solvents to provide some degree of ‘similar’ behaviour
- Applying filters to a localised subset may provide a reasonable start point
- The initial subset can be expanded or reduced to suit needs

2 step process to selecting solvents.

1. **Define the generic solvent requirements for the process**

   Properties that support the general needs of the application are defined such as:

   - Chemical incompatibilities
   - Temperature windows
   - Equipment or processing area restrictions e.g. area zone ratings
   - Regulatory constraints or guidance

This defines the shortlist of solvents that ***could*** support the process

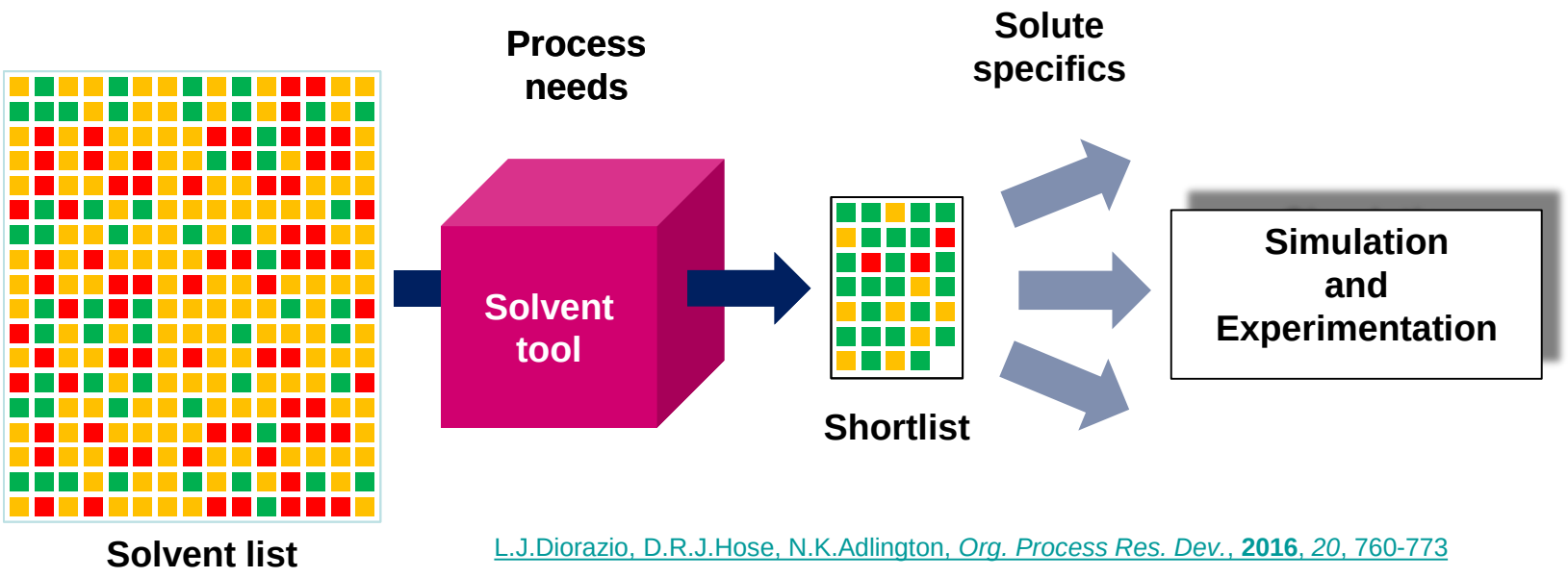
2. **Consider solute specific refinements**

   Refine the list to take account of the specific materials used

Outline workflow

The objective nature of the tool is reinforced since solvents are not explicitly identified until a shortlist is reached. This facilitates opportunities for solvents that are less obvious but potentially advantageous to the specific application.

The tool can be used for both screening and optimisation / replacement



L.J.Diorazio, D.R.J.Hose, N.K.Adlington, *Org. Process Res. Dev.*, **2016**, *20*, 760-773

Filter groups

Applicable filters are based on molecular properties and associated metadata that are grouped in clusters for visualisation :

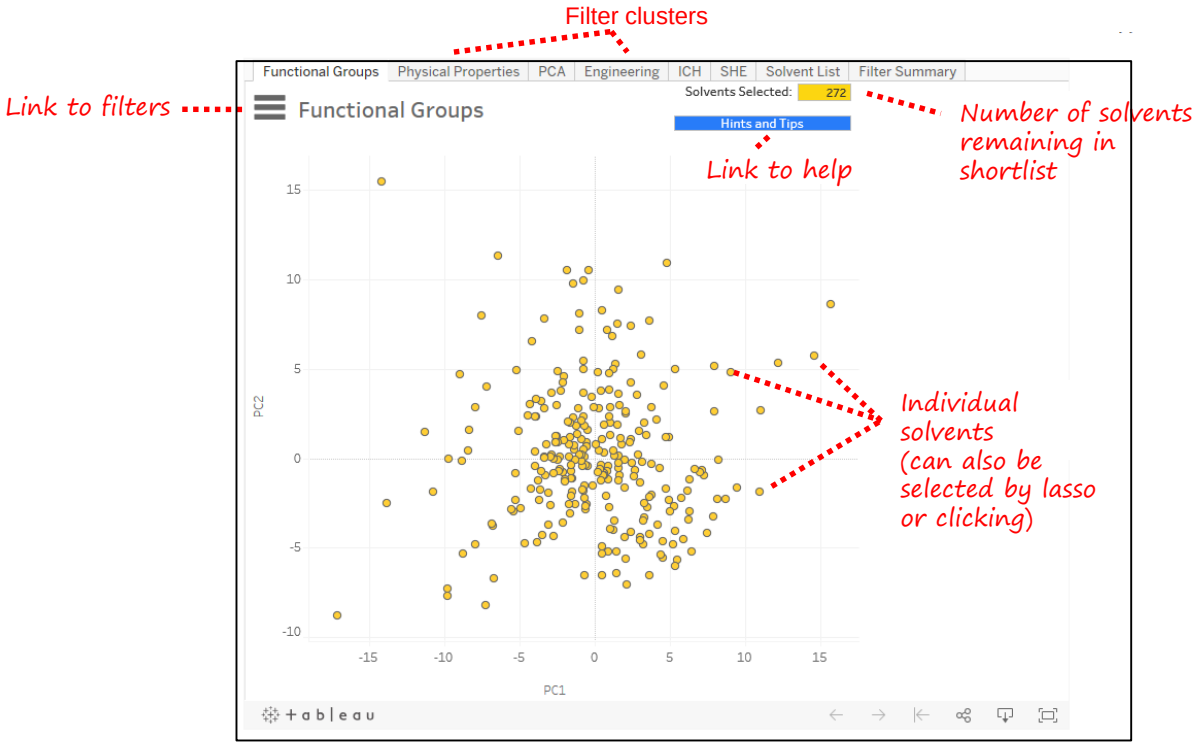
Functional Groups
Physical Properties
Engineering
ICH
SHE

Other visualisations that are provided are:

Quadrant distribution of the current shortlist
Current shortlist
Complete set of filters

The user interface

- The tool is built around Tableau™, users are not required to have this installed on their device. The user sees a graphical distribution of solvents across the 2 main principal components PC1 and PC2.



USING THE TOOL

- Here we will demonstrate use of the tool with respect to the Chemical Functionality and Physical Properties tabs

- We will also introduce the other tabs
  - Engineering
  - ICH
  - SHE
  - Quadrant
  - Solvent Shortlist
  - Filter Summary

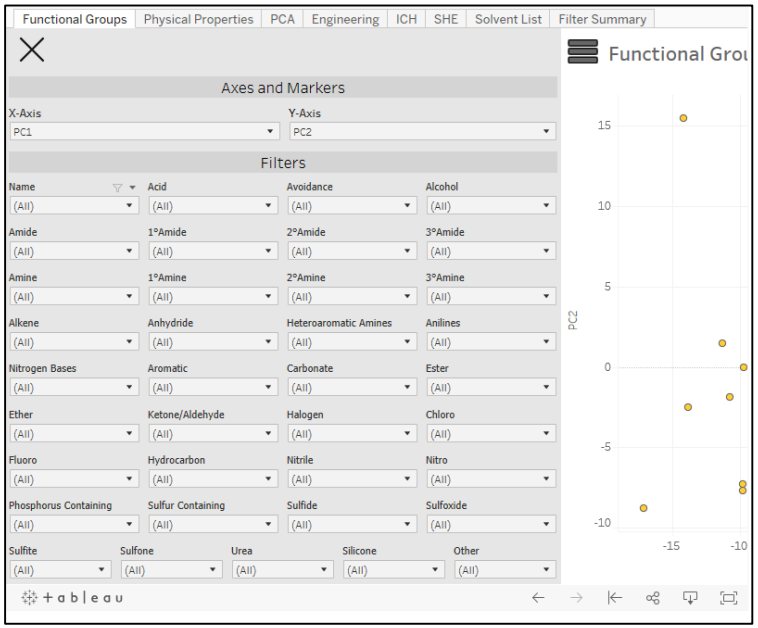
Avoiding chemical incompatibility

Consider a reductive amination process

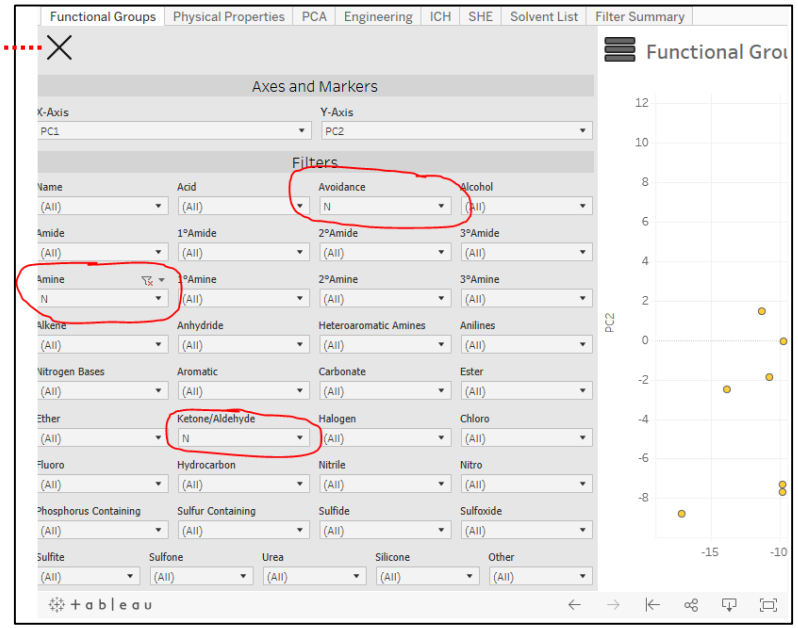
We may want to avoid Aldehyde / Ketone or Amine solvents.

Change the relevant filters in the Functional Groups from ***ALL*** to ***N***.

We might also omit solvents such as HMPA, CCl_4 - grouped as Avoidance*.

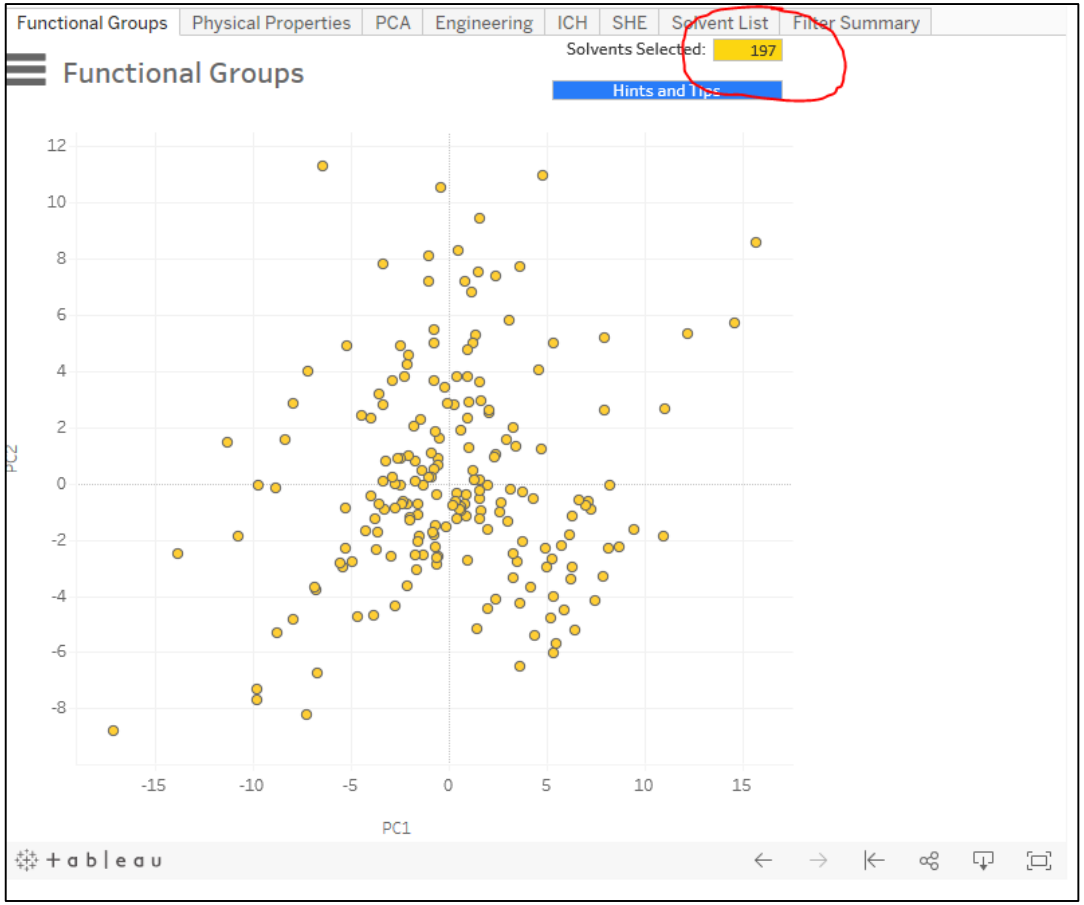


Click here ..... to exit filter view



** Avoidance solvents are included to support PCA construction and also to accommodate their replacement if encountered in older literature*

- Removing those functional groups reduces the number of solvents to 197
- Solvents that contain multiple functional groups are affected by changes to any relevant filter
- Tableau rescales the PC1/PC2 axes to maximise the distribution

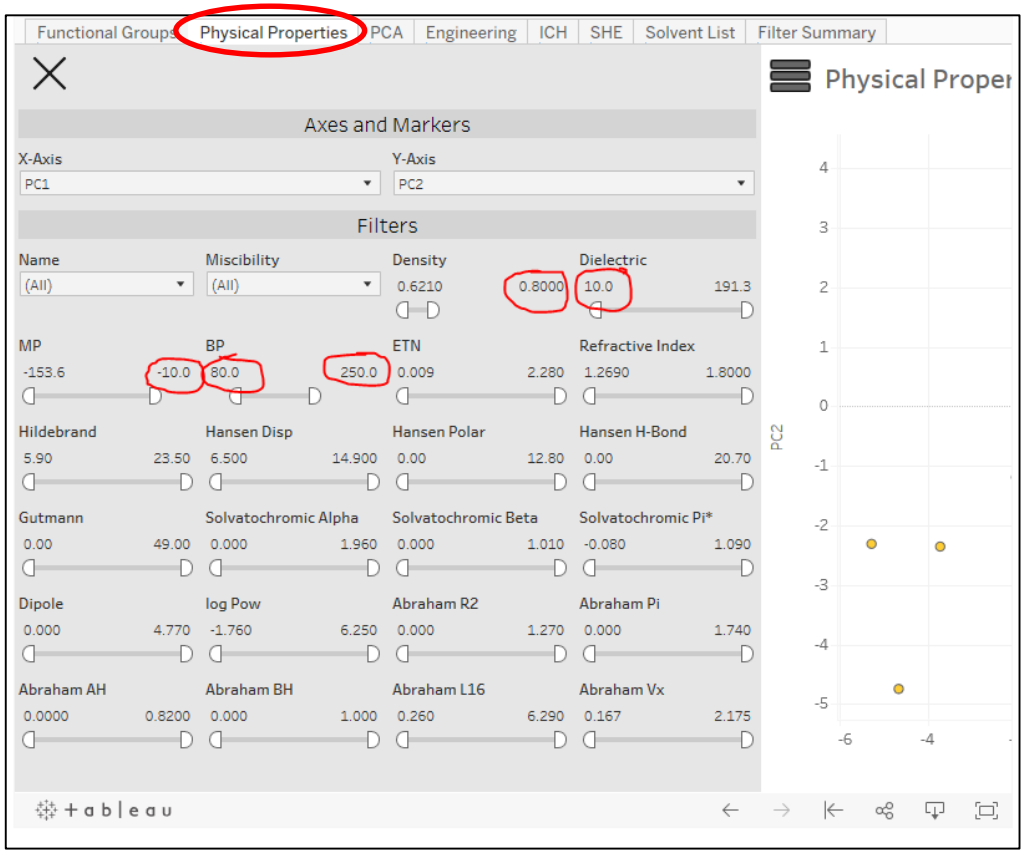


Physical Properties

Alter numerical filters by moving slider on the scale or clicking and over-writing limits

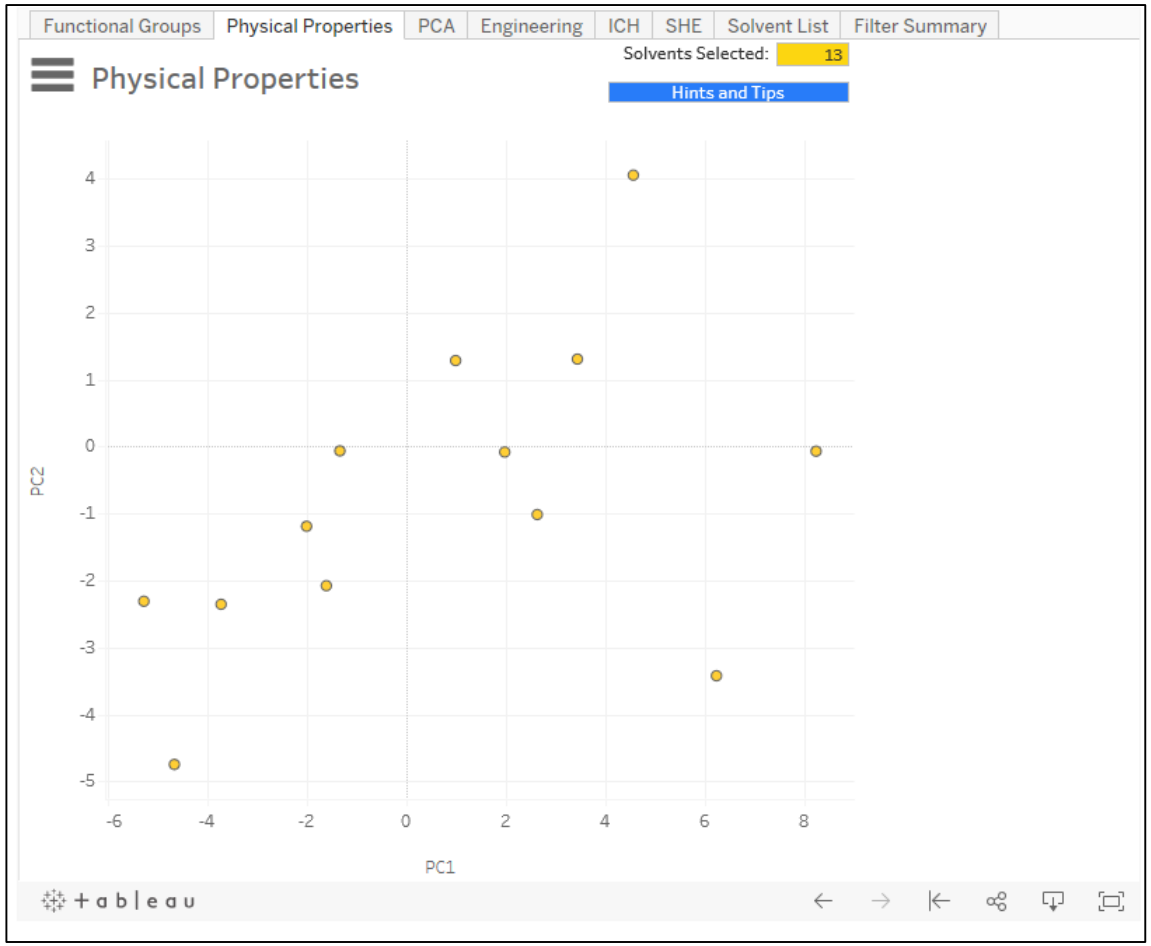
Restrict

- Density £ 0.8
  To facilitate aqueous washing
- Dielectric constant [3] 10.0
  To provide some polarity
- M.pt. £ -10°C
  To avoid melting / freezing during isolation
- B.pt. 80-250°C
  To avoid solvent loss and facilitate removal



Restriction of Physical Properties

- Shortlist reduced from 197 to 13 solvents
- PC1/PC2 axes rescale to match the shortlist

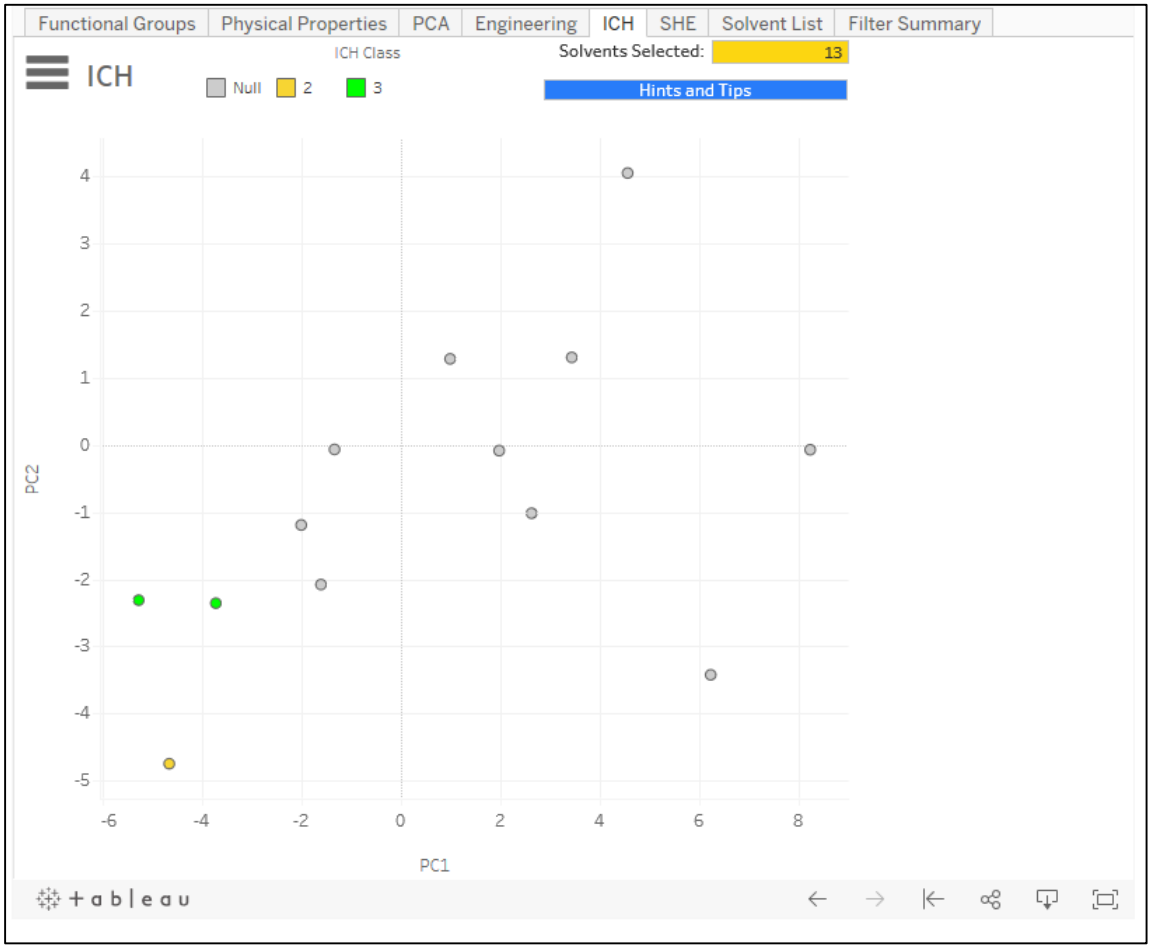


Engineering Visualisation

- Engineering shows some representations as bar charts rather than PCA maps
- Each property can be restricted as before using drop-down options, sliders or over-writing

ICH Classification

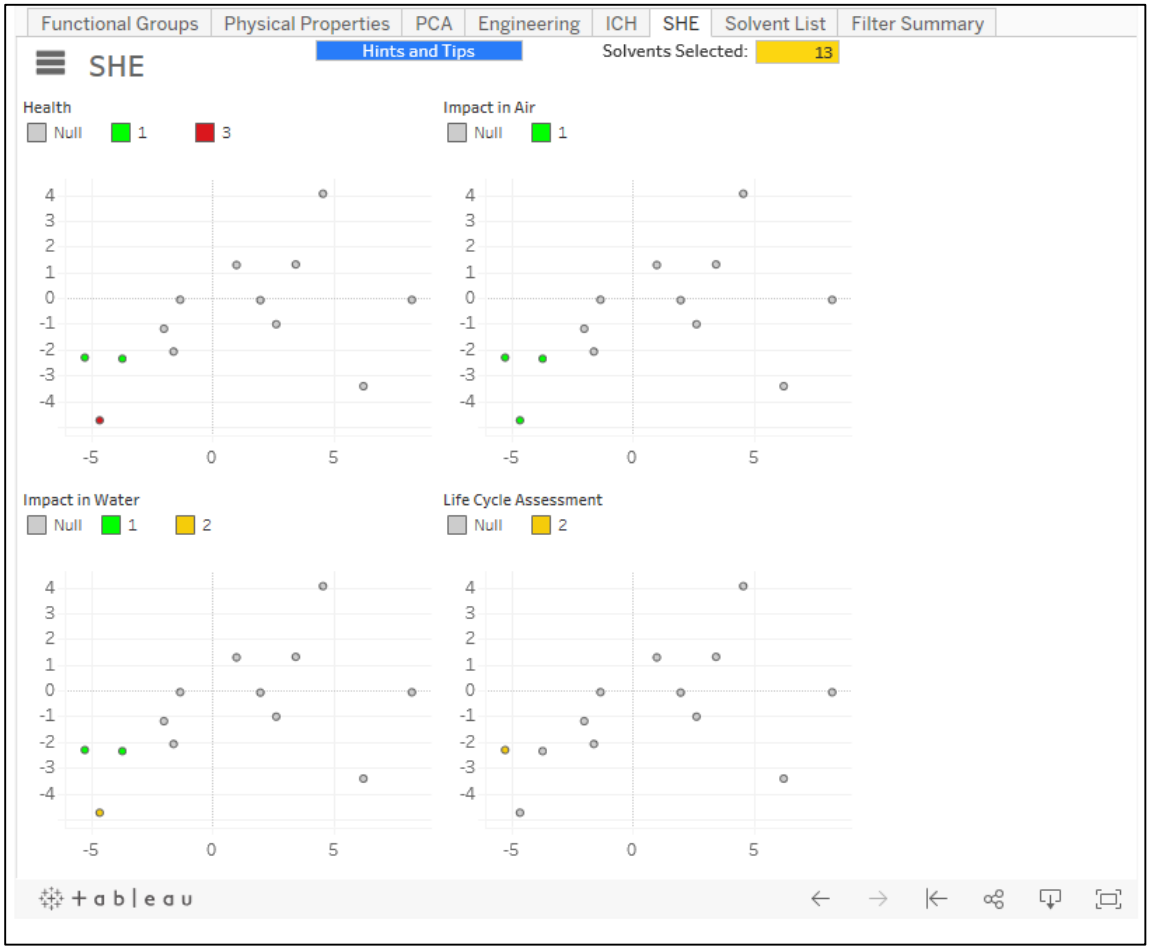
- International Conference on harmonisation (ICH) Guideline Q3C mandates control of solvent residues in pharmaceutical processing
- Many solvents are not classified (but can still be used with appropriate support)
- Filter : Classes 1,2,3 or Null



SHE Assessment

- Can restrict solvents on basis of :

- Health
- Impact in air
- Impact in water
- Life Cycle Assessment



Solvent Shortlist

- Solvents clustered on basis of distribution across quadrants of the PCA map
  - Clustering can facilitate discussion with respect to screening / Optimisation activities

Functional Groups | Physical Properties | PCA | Engineering | ICH | SHE | Solvent List | Filter Summary

Quadrant: (All)

Solvents Selected: 13

Hints and Tips

List of Select Solvents

Quadrant	ID	Name	Oct..	PC1	PC2	PC3	PC4	PC5	MP	BP	Density
0	263	2-Ethylhexanol	8	1.0	1.3	4.4	-0.6	-0.6	-70.0	184.6	0.7
	264	2-Methyl Buta..	5	-2.0	-1.2	2.5	-1.6	-1.3		128.7	0.7
	265	Methyl Isobuty..	5	-1.3	-0.1	2.4	-1.2	-0.4		131.7	0.7
	267	Ethyl 3-Ethoxy..	0	2.0	-0.1	0.2	-2.7	1.7		169.7	0.8
1	21	iso-Butanol [2-..	5	-3.7	-2.4	1.9	-1.5	-0.8	-108.0	107.8	0.8
	30	Acetonitrile	1	-4.7	-4.7	-3.3	-0.3	4.3	-43.8	81.6	0.8
	42	Butyronitrile	1	-1.6	-2.1	-1.8	-0.9	3.8	-111.9	117.5	0.8
	98	IPA [Propan-2-..	5	-5.3	-2.3	1.0	-2.4	-1.2	-88.0	82.4	0.8
2	122	TAME [tert-am..	2	2.6	-1.0	-1.2	-2.5	-1.0	-80.0	86.3	0.8
	177	Ethylcyclohexa..	6	6.2	-3.4	0.4	-1.4	-0.9	-111.3	129.9	0.8
	237	Hexamethyldis..	6	8.2	-0.1	1.7	-1.5	0.0	-68.0	100.5	0.8
4	266	n-Propyl Propio..	8	4.6	4.1	1.8	-0.7	0.7	-75.9	122.4	0.7
	269	n-Pentyl Propio..	8	3.4	1.3	0.5	-1.7	1.2		165.0	0.7

- Shortlist can be downloaded in various formats

Filter Summary

- Contains all filter selections
- Can also be used to apply changes without moving between screens

WHAT HAPPENS NEXT?

What Happens Next?

- Different applications can support different sizes of shortlist
  - Synthetic studies may require <5 solvents
  - Predictive activities may accommodate 100's
- Can apply further rounds of restriction with tighter ranges / additional filters
  - No limits to how many iterations can be applied
- Output from tool can be applied in DoE studies or material properties predictive packages for further refinement
- Provide feedback for the tool