**American Chemical Society** 

ACS GCI Pharmaceutical Roundtable





ACS Green Chemistry Institute

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## Solvent selection tool

Principles and guidance

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## **BACKGROUND TO SOLVENT SELECTION**

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#### Solvent selection – why worry?

- Solvents are critical participants in chemical processing
  - Promoting chemistry ( $S_N 2$ ,  $E1_{cb}$ ...)
  - 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?

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#### 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 <sub>50</sub> )

# 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 ( $PC1 \rightarrow PC5$ )
  - 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

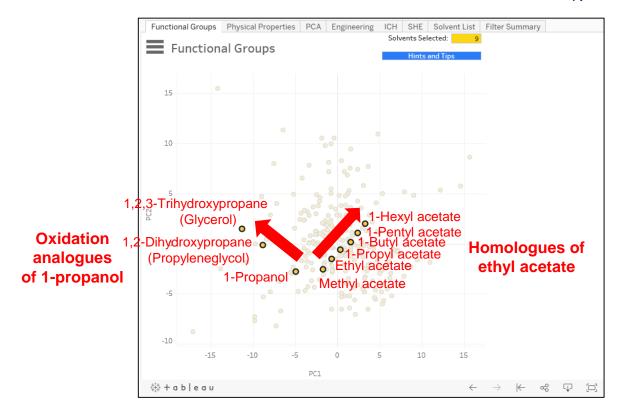
# For most users the PCA map simply provides a convenient graphical view of the solvent shortlist





#### Is The PCA Map Valid?

PCA map successfully validated against observed chemical phenomena:<br/>Chemical series (see below)O- vs. C-alkylation of phenols<br/>Rates of S<sub>N</sub>Ar reactions





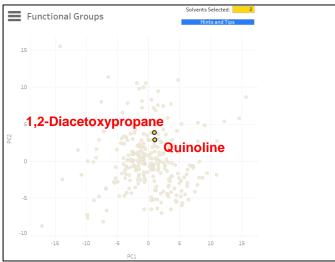


### **Does map location mean anything?**

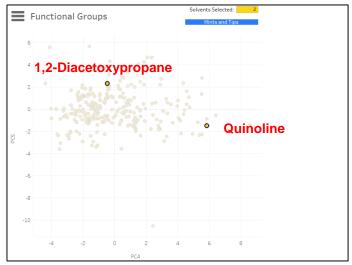
We can infer that solvents in close proximity are similar but this may not be the case in all dimensions

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**

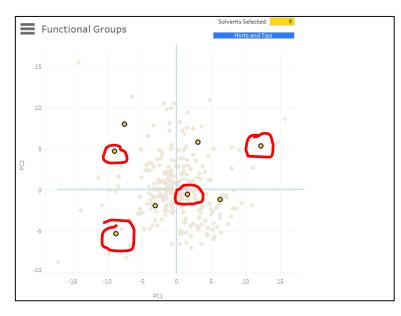
• We have a lead already and either want to identify others or must find a replacement (eg due to legislative restrictions)





#### Screening

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

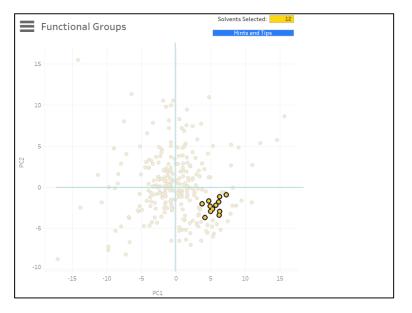


- We may simply want to identify an initial hit
- Applying any appropriate filters will provide a shortlist
- It may not be beneficial to too aggressive in applying filters
- Once we have a selection shortlist we might identify a small number of representative candidates across the different quadrants 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

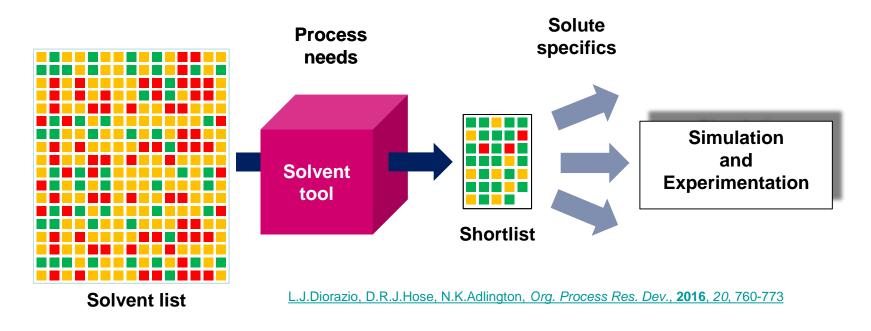




#### **Outline workflow**

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







#### **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:

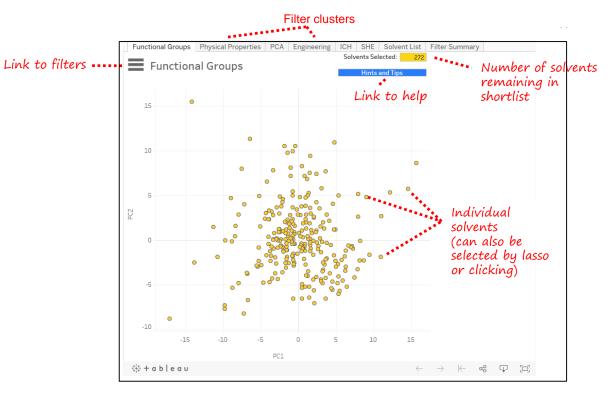
Quadrant distribution of the current shortlist Current shortlist Complete set of filters





#### The user interface

• The tool is built around Tableau<sup>™</sup>, 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<sub>4</sub> - grouped as Avoidance\*.

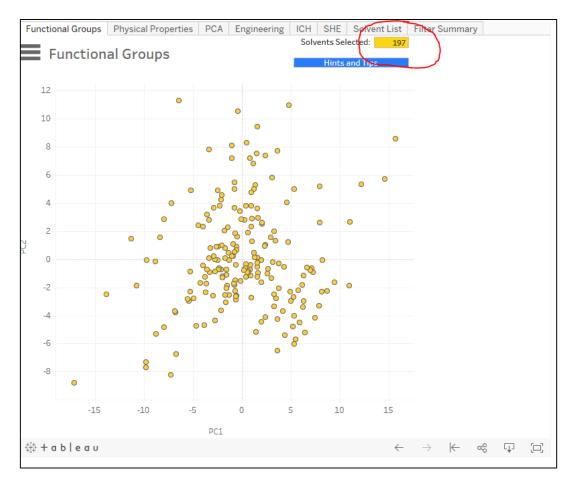
Functional Gro	ups	Physical Properties	PC	A Engineering ICH	H SHE	Solvent			mary unction	al Grou	Click here to exit	Functional Group	s Phys	vsical Properties P	CA Engineering I	СН	SHE Solvent List				nal Grou
		Axes a	nd I	Markers			· · ·		anceron					Axes and	Markers			1			
X-Axis				Y-Axis					•		filter view	X-Axis			Y-Axis				12		
PC1			•	PC2			*	15				PC1		•	PC2			•	10		
		F	ilte	ers										Fjilt	ers						
Name	∀ •	Acid	,	Avoidance	Alcohol							Name	Acid	4 (	Avoidance	~	Alcohol		8		
(AII)	٣	(All)	•	(AII) •	(All)		¥	10				(AII)	• (Al	1) -	N	•	(Ju)	•			
Amide		1°Amide	-	2°Amide	3°Amide							Amide	1°Ar	mide	2ºAmide	-	3°Amide		6		
(AII)	*	(AII)		(AII) •	(All)		•					(AII)	• (AI	II) •	(All)	•	(AII)	•	4		
Amine		1ºAmine		2°Amine	3°Amine			5				Amine s	⊼ <b>~</b> PAr	mine	2°Amine		3°Amine				
(AII)	*	(AII)		(AII) •	(AII)		•	-				N	• )(AI	II) •	(AII)	*	(AII)	•	2		
Alkene		Anhydride		Heteroaromatic Amines	Anilines			22			,	Alkene	Anhy	nydride	Heteroaromatic Amines		Anilines	2			Ŭ
(AII)	*	(All)		(AII) •	(All)		*			•		(AII)	• (AI	II) •	(AII)	*	(AII)	*	0		0
Nitrogen Bases		Aromatic		Carbonate	Ester			0				Nitrogen Bases		matic	Carbonate		Ester		-2		•
(AII)	*				(AII)		*			•		(AII)	• (AI	II) •	(AII)	*	(AII)	*			•
Ether		Ketone/Aldehyde		Halogen	Chloro							Ether	Keto	one/Aldehyde	Halogen		Chloro		-4		
(AII)	Ŧ				(AII)		•	-5				(AII)	• N	•	(AII)	*	(AII)	•			
Fluoro		Hydrocarbon (All)		Nitrile (AII) •	Nitro (All)							Fluoro		drocarbon	Nitrile		Nitro		-6		
(All)		Sulfur Containing		Sulfide	Sulfoxid					8		(AII)	• (AI				(AII)	•	-8		8
Phosphorus Containin (AII)	-				(AII)	2	•	-10	•			Phosphorus Containing		fur Containing	Sulfide		Sulfoxide			•	
Sulfite	Sulfo			Silicone		her			-15	-10		(AII)	• (AI			•	(AII)	•		-15	10
	(All			<ul> <li>(AII)</li> </ul>	• (		¥						Sulfone	Urea	Silicone		Other	-		-15	-10
。 + a b l e d							~	$\rightarrow$ $\models$	- <u>~</u> C	, c			(AII)	▼ (AII)	• (AII)		▼ (AII)	•			
+;+ 100[e1	, 0						`		~~ ~	+- LL		∰;+ab ea	J				<del>(</del>		>	αÔ	

\* 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 <sup>3</sup> 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

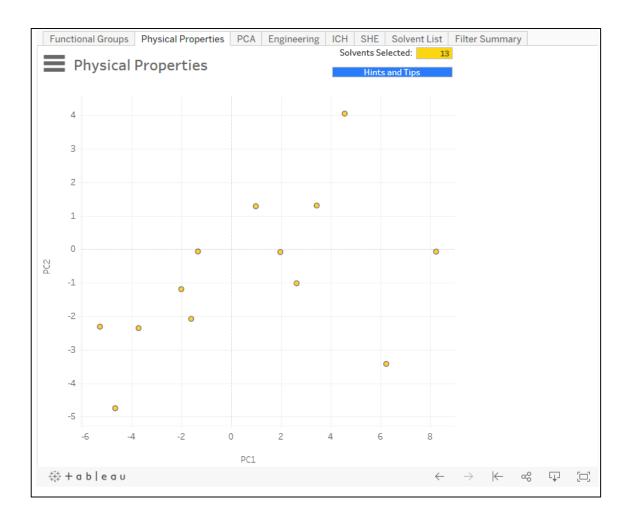
Functional C	Groups	Physical Proper	ties P	CA Engineeri	ng ICH	SHE So	olvent List	Filter Sum	mary	
$\times$									hysica	l Prope
								_	-	
		A	xes and	Markers						
X-Axis				Y-Axis				4		
PC1			•	PC2			•			
			Filt	ers				3		
Name		Miscibility		Density		Dielectric				
(AII)	•	(AII)	•	0.6210	0.8000	10.0	191.3	2		
				O-D	$\smile$		D			
MP		BP		ETN		Refractive I	ndex	1		
-153.6	-10.0	80.0	250.0	0.009	2.280	1.2690	1.8000			
0		D D		0	D	0	D	0		
Hildebrand		Hansen Disp		Hansen Polar		Hansen H-B	ond	5C2		
5.90	23.50	6.500	14.900	0.00	12.80	0.00	20.70	-1		
0	D	0	D	0	D	0	D			
Gutmann		Solvatochromic	Alpha	Solvatochromic	Beta	Solvatochro	omic Pi*	-2		
0.00	49.00	0.000	1.960	0.000	1.010	-0.080	1.090		•	•
0	D	0	D	0	D	0	D	-3		
Dipole		log Pow		Abraham R2		Abraham Pi				
0.000	4.770	-1.760	6.250	0.000	1.270	0.000	1.740	-4		
0	D	0	D	0	D	0	D	-4		
Abraham AH		Abraham BH		Abraham L16		Abraham Vx	c	-5	•	
0.0000	0.8200	0.000		0.260	6.290	0.167	2.175	-5		
0	D	0	D	0	D	0	D		-6	-4
∰ + a b	eau						$\leftarrow$	$\rightarrow$ k	- ~	ф (d)
									0	





#### **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

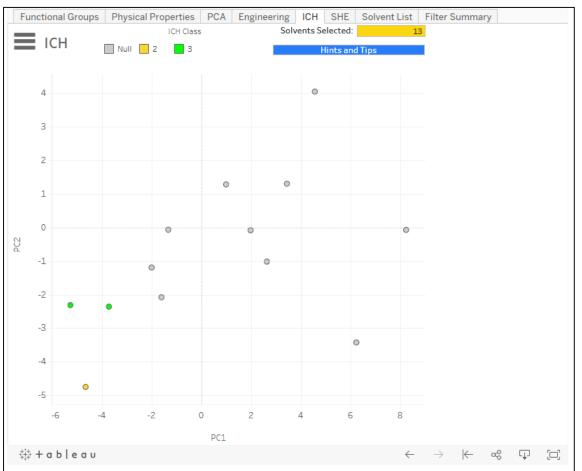






#### **ICH Classification**

- 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 S	olvent List	Filter Summary				
				Q	uadrant				Solvents Selected:				
List of Select Solvents					AII)		,	•		Hints a	nd Tips		
Quadrant	ID	Name	0ct 😐	PC	1 PC2	PC3	PC4	PC5	MP	BP	Density		
0	263	2-Ethylhexanol	8	1.0	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	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	-3.1	7 -2.4	1.9	-1.5	-0.8	-108.0	107.8	0.8		
	30	Acetonitrile	1	-4.1	7 -4.7	-3.3	-0.3	4.3	-43.8	81.6	0.8		
	42	Butyronitrile	1	-1.0	5 -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.	5 -1.0	-1.2	-2.5	-1.0	-80.0	86.3	0.8		
	177	Ethylcyclohexa	6	6.3	2 -3.4	0.4	-1.4	-0.9	-111.3	129.9	0.8		
	237	Hexamethyldis	6	8.3	2 -0.1	1.7	-1.5	0.0	-68.0	100.5	0.8		
4	266	n-Propyl Propio.	8	4.	5 4.1	1.8	-0.7	0.7	-75.9	122.4	0.7		
	269	n-Pentyl Propio	8	3.4	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

Functional	Groups	Physical I	Properties	S PCA	Eng	ineering	g ICH	I SHE	Solv	vent List	Filte	er Summa	ary		
							Hints a	nd Tips				Solvent	s Sele	ected:	13
Name	Functiona	al Avo	idance	Acid		Alcohol		Alkene		Anhydride		Amide		1°Amide	2
(AII) 🔹			•	(AII)	•	(AII)	•	(AII)	•	(AII)	•	(AII)	•	(AII)	•
2°Amide	3°Amide	Ami	ne	1ºAmin	e	2°Amine		3°Amine		Heteroarom	ati	Anilines		Nitroger	n Bases
(AII) •	(AII)	• N	•	(AII)	•	(AII)	•	(AII)	•	(AII)	•	(AII)	•	(AII)	•
Aromatic	Carbonate	Este	er	Ether		Ketone//	Aldehy	Halogen		Chloro		Fluoro		Hydroca	rbon
(AII) 🔹	(AII)	• (AI	I) 🔻	(AII)	•	Ν	•	(AII)	•	(AII)	•	(AII)	•	(AII)	•
Nitrile	Nitro	Pho	sphorus C	Sulfur (	Contain	Sulfide		Sulfoxide		Sulfite		Sulfone		Urea	
(AII) 🔹	(AII)	• (AI	I) 🔻	(AII)	•	(AII)	•	(AII)	•	(AII)	•	(AII)	•	(AII)	•
Silicone	Other		-		Miscibility	,	MP		BP		Den	sity	D	ielectric	
(AII)	• (AII)	•	Physical Property F	iltore	(AII)	•	-153.6	-10.0	80.0	250.0	0.6	210 0.800	00 1	10.0	191.3
			Fropercyr	licers			0	D	G	D		D		n –	D
ETN	Refracti	ive Index	Hildebrand		Hansen D	Disp	Hansen	Polar	Hans	en H-Bond	Gut	mann	0	Dipole	
~	80 1.2690	0 1.8000	5.90	23.50	6.500	14.900	0.00	12.80	0.00	20.70	0.0	0 49.		0.000	4.770
(   Solvatochromic		D	Columbusha	()		D	Abrahar	0		am Pi		aham AH	-	() Abraham I	
-0.080 1.0		hromic 1.960	Solvatochro		og Pow	6.250	Abrahar	п кz 1.270	Abran			000 0.82		0.000	1.000
-0.080 1.0	D (1	D.300	0.000	D	-1.760	0.250	0.000	D	0.00	0 1.740 D	0.0	000 0.82	D	0.000	1.000
Abraham L16	Abrahar	m Vx			PC1		PC2		PC3				10	CH Class	
0.260 6.2	90 0.167	2.175	PCA Filters	5	-17.11	15.68	-8.81	11.30	-4.42	11.96	ICH	Filters		(AII)	•
0	DO	D			<u>ا</u>	D	0	D		D					
Quadrant	Octant		Engineerin	ıg	T-Rating		Flamma	ability		mability Sc		C Potential		Static	
(AII)	• (AII)	•	Filters		(AII)	•	(AII)	•	(AII)	) •	(AI	II)	•	(AII)	*
Viscosity Score	Hvap		Heat Capa	city			Health		Impa	ct in Air	Imp	act in Wate	er L	.CA	
(AII)	• 81	2,180	425	8,526	SHE Filte	ers	(AII)	•	(AII)	•	(Al	II)	•	(AII)	•
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## WHAT HAPPENS NEXT?





#### What Happens Next?

- Different applications can support different sizes of shortlist
  - Synthetic studies may require <5 solvents</li>
  - 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