

**ELECTRONIC SUPPLEMENTARY INFORMATION**

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## 1. General Remarks:

The 36 solvents were selected by combining two criteria: 1) the inclusion of all solvents necessary for discussing the API examples presented in the text, and 2) the inclusion of solvents already listed in the CHEM21 solvent selection guide. The solvents (present in the CHEM21 list) that were omitted were excluded because certain fundamental information required for calculating the indices, such as the Henry's law constant or toxicity data, was unavailable.

The aggregated BI/SHI values are not weighted by the quantity of solvent used. The reported values represent the sum (Andraos's  $\Omega$ ) of the various indices, considering both environmental (BAP, BCP, INHTP, INGTP, GWP, SFP, CPP) and safety/hazard (FP, CGP, CLP, OELP, RPP) potentials. The decision to decouple the solvent quantity stems from the fact that comparing batch and flow processes often involves very different reaction scales and volumes. Therefore, our goal is to provide a quantification based on the intrinsic environmental, safety, and hazard impact.

Consequently, the interpretation of the final values for multi-step syntheses should be considered as weighted by the number of different solvents utilized, rather than by the relative total quantity of solvent.

The calculation and normalization of the solvent metrics were performed through the following workflow (see Sections 2–6):

1. Solvent Ranking: The  $\Omega$  values were calculated for the defined set of 36 solvents. These solvents were displayed in ascending order based on their  $\Omega$  values and divided into three broad tertiles (12 solvents per group) to map general solvent performance.

2. Normalization: To generate the numerical scale, water (ordered 1st) was established as the ideal baseline and assigned a score of 1. The remaining solvents were then sequentially grouped into bins of three along the ordered list, with the score increasing by 1 for each subsequent bin. Specifically, solvents in positions 2–4 received a score of 2, positions 5–7 received a score of 3, and so forth, up to the final two solvents (positions 35 and 36), which both received a maximum score of 13.

3. Application to Case Studies: For each synthetic example analyzed in the main text, the specific solvents used in both the reaction and work-up phases were recorded. The corresponding normalized BI and SHI scores for these solvents were then applied.

4. Aggregation: The BI and SHI scores across all steps of a given synthesis were summed independently. These separate totals represent the final BI and SHI metrics shown in the graphical outputs of the main text. Finally, as presented in Table 1, the cumulative BI and SHI scores for each example were added together to yield a single, overall aggregate score (BI + SHI).

**2. Solvent list ordered by  $\Omega$  value for Benign Index (BI) considering GWP, BAP, BCP, INHTP, INGTP, SFP, CPP**

	BI
1 water	4.832319
2 DEC	5.00656
3 EtOAc	6.766969
4 CPME	7.584528
5 Et <sub>2</sub> O	8.517349
6 Toluene	9.214792
7 DMSO	9.906033
8 DCM	10.39511
9 DME	10.82026
10 Cyclohexane	14.11057
11 Chloroform	17.37096
12 DMA	17.86752
13 2-MeTHF	21.82315
14 NMP	21.9607
15 EtOH	23.90467
16 IpOH	24.78137
17 Hexane	26.46306
18 Acetone	27.71469
19 <sup>t</sup> BuOH	32.80135
20 THF	33.0971
21 DMF	40.06585
22 AcOH	40.97836
23 MeOH	41.49365
24 BuOAc	49.45761
25 ACN	49.58848
26 MTBE	58.65339
27 Propanol	64.41618
28 Nitromethane	94.29384
29 <i>n</i> BuOH	117.7983
30 Heptane	118.3417
31 Formic Acid	234.1125
32 TFE	384.2374
33 HCl	400.4764
34 DCE	762.83
35 Dioxane	1177.002
36 Pyridine	4622.881

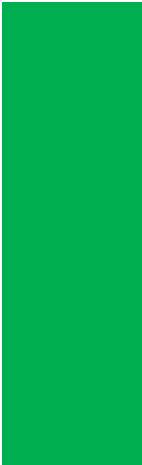
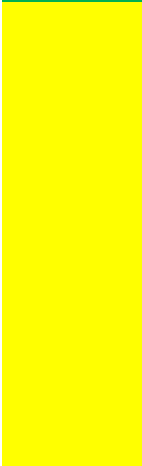

**3. Solvent list ordered by  $\Omega$  value for Benign Index (BI) grouped by color (green, yellow, red) and sub-grouped by rank number (1-13)**

	BI		
1	water	4.832319	1
2	DEC	5.00656	2
3	EtOAc	6.766969	2
4	CPME	7.584528	2
5	Et <sub>2</sub> O	8.517349	3
6	Toluene	9.214792	3
7	DMSO	9.906033	3
8	DCM	10.39511	4
9	DME	10.82026	4
10	Cyclohexane	14.11057	4
11	Chloroform	17.37096	5
12	DMA	17.86752	5
13	2-MeTHF	21.82315	5
14	NMP	21.9607	6
15	EtOH	23.90467	6
16	IpOH	24.78137	6
17	Hexane	26.46306	7
18	Acetone	27.71469	7
19	<sup>t</sup> BuOH	32.80135	7
20	THF	33.0971	8
21	DMF	40.06585	8
22	AcOH	40.97836	8
23	MeOH	41.49365	9
24	BuOAc	49.45761	9
25	ACN	49.58848	9
26	MTBE	58.65339	10
27	Propanol	64.41618	10
28	Nitromethane	94.29384	10
29	<i>n</i> BuOH	117.7983	11
30	Heptane	118.3417	11
31	Formic Acid	234.1125	11
32	TFE	384.2374	12
33	HCl	400.4764	12
34	DCE	762.83	12
35	Dioxane	1177.002	13
36	Pyridine	4622.881	13

**4. Solvent list ordered by  $\Omega$  value for Safety and Hazard Index (SHI) considering FP, CGP, CLP, OELP, RPP**

	SHI
1 water	0.007067
2 DMSO	1.162461
3 EtOH	1.536533
4 DEC	1.709431
5 DME	1.958211
6 Heptane	1.976973
7 EtOAc	2.230841
8 Acetone	2.337288
9 Cyclohexane	2.43307
10 IpOH	2.446678
11 MTBE	2.641472
12 Propanol	3.175206
13 Et <sub>2</sub> O	3.275441
14 THF	3.312572
15 CPME	3.345011
16 <sup>t</sup> BuOH	3.53953
17 BuOAc	3.563165
18 MeOH	3.770748
19 <i>n</i> BuOH	3.938655
20 2-MeTHF	4.228783
21 DCM	4.362703
22 Toluene	4.842132
23 NMP	5.254519
24 Hexane	5.393727
25 ACN	7.179491
26 Nitromethane	7.76704
27 TFE	9.038474
28 AcOH	12.04108
29 DMF	12.60752
30 DMA	13.49476
31 DCE	14.4921
32 Pyridine	22.61473
33 Formic Acid	24.6435
34 Dioxane	30.32521
35 Chloroform	52.2277
36 HCl	55.01152

**5. Solvent list ordered by  $\Omega$  value for Safety and Hazard Index (SHI) grouped by color (green, yellow, red) and sub-grouped by rank number (1-13)**

		SHI		
1	water	0.007067		1
2	DMSO	1.162461		2
3	EtOH	1.536533		2
4	DEC	1.709431		2
5	DME	1.958211		3
6	Heptane	1.976973		3
7	EtOAc	2.230841		3
8	Acetone	2.337288		4
9	Cyclohexane	2.43307		4
10	IpOH	2.446678		4
11	MTBE	2.641472		5
12	Propanol	3.175206		5
13	Et <sub>2</sub> O	3.275441		
14	THF	3.312572	6	
15	CPME	3.345011	6	
16	<sup>t</sup> BuOH	3.53953	6	
17	BuOAc	3.563165	7	
18	MeOH	3.770748	7	
19	<i>n</i> BuOH	3.938655	7	
20	2-MeTHF	4.228783	8	
21	DCM	4.362703	8	
22	Toluene	4.842132	8	
23	NMP	5.254519	9	
24	Hexane	5.393727	9	
25	ACN	7.179491		9
26	Nitromethane	7.76704		10
27	TFE	9.038474		10
28	AcOH	12.04108		10
29	DMF	12.60752		11
30	DMA	13.49476		11
31	DCE	14.4921		11
32	Pyridine	22.61473		12
33	Formic Acid	24.6435		12
34	Dioxane	30.32521		12
35	Chloroform	52.2277		13
36	HCl	55.01152	13	

**6. Solvent list ordered by rank value as sum of Safety and Hazard Index (SHI) rank and Benign Index (BI) rank grouped by color (green, yellow, red)**

1	Water	2	Green
2	DEC	4	
3	DMSO	5	
4	EtOAc	5	
5	DME	7	
6	EtOH	8	
7	Cyclohexane	8	
8	Et <sub>2</sub> O	8	
9	CPME	8	
10	IpOH	10	
11	Acetone	11	
12	Toluene	11	
13	DCM	12	Yellow
14	<sup>t</sup> BuOH	13	
15	2-MeTHF	13	
16	Heptane	14	
17	THF	14	
18	MTBE	15	
19	Propanol	15	
20	NMP	15	
21	BuOAc	16	
22	MeOH	16	
23	Hexane	16	
24	DMA	16	
25	<i>n</i> BuOH	18	Red
26	ACN	18	
27	AcOH	18	
28	Chloroform	18	
29	DMF	19	
30	Nitromethane	20	
31	TFE	22	
32	DCE	23	
33	Formic Acid	23	
34	Pyridine	25	
35	Dioxane	25	
36	HCl	25	

## 7. Equations used for E-factor, RME and STY and experimental boundaries considerations

All the masses outlined in patents and literature procedures were used to calculate the E-factor, including water.

$$E - factor = \frac{\text{mass of all reagent and solvents} - \text{mass of product}}{\text{mass of product}}$$

Unified RME (Andraos) was regarded as having thoroughly considered mass efficiency. Specifically, the relationship between RME and E-factor is given as follows using Andraos derivatization:<sup>1</sup>

$$RME = \frac{1}{1 + E - factor} * 100$$

Since reactor size is not typically reported in some procedures, the values were estimated as twice the volume of all solvents listed for each reaction step.

$$STY = \frac{\text{mass of product}}{\text{reactor volume} * \text{reaction time}}$$

### Experimental boundaries considerations:

**Work-up solvent:** All the work-up solvents listed in the related procedure were considered throughout the calculation without any exclusions. In particular, whether saturated solutions were listed, the specific density was considered to allow an accurate description of the weight of the material used. No assumptions were made in the accounting of work-up solvents.

**Isolation solvent:** If the isolation solvent comprises a description of crystallization, precipitation, or liquid/liquid separation, all amounts stated in the reported procedure were considered without any exclusions or assumptions. Whether the isolation procedure is performed using a chromatographic column, as no quantification was reported for these solvents and the related material (stationary phases), they were not considered in the calculations.

**Incomplete information:** As we aim for a broader and more meaningful review, it is worth noting that an initial screening and consideration of the API to be treated were also based on procedures that contain as much information as possible (in terms of solvent, auxiliary, boundary materials, purification materials, reactor volumes, and reagent descriptions), excluding *a priori* patent or

literature procedures that, even if valuable, do not contain enough information to allow the desired calculations. Since reactor size is sometimes not reported in some procedures, especially for very old patent batch processes, the values were estimated (for STY calculations) as twice the volume of all solvents listed for each reaction step.

## **8. References:**

1. J. Andraos, *Org. Process Res. Dev.* 2005, **9**, 149–163. doi: 10.1021/op049803n