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Solvent selection guide based on chemometrics and multicriteria decision analysis

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The selection of suitable solvents is a crucially important subject in a wide range of chemical processes. The study presents a solvent selection guide where 151 solvents were assessed, including a significant number of recently reported bio-based solvents. The assessment procedure involves grouping of solvents according to their physicochemical parameters and ranking within clusters according to their toxicological and hazards parameters. Grouping of solvents resulted in formation of three clusters – nonpolar and volatile (35 solvents), nonpolar and sparingly volatile (35 solvents) and polar ones (81 solvents). The comparison of toxicological and hazard related data indicated that solvents from the third cluster should be preferentially chosen. Within each group, a solvent ranking was performed by means of the TOPSIS procedure based on 15 different criteria. Because of lack of certain data (especially toxicological), different ranking confidence levels were introduced. The highest confidence rankings were performed only for some solvents but with all considered criteria. Low confidence rankings were created for all solvents but were based on certain criteria only. The results of our solvent selection guide (SSG) are generally in agreement with results of others but allow for finer ranking of solvents. The assessment procedure is easy to be adapted to individual chemist's needs and allows to include new solvents to the ranking.

Introduction

Green chemistry is the concept introduced by Paul Anastas and John Warner.[1] It means the application of chemistry techniques and methodologies that reduce or eliminate the use or generation of feedstocks, products, by-products, solvents, reagents, etc. that are hazardous to human health or the environment. The fifth principle of green chemistry states that the application of solvents should be avoided if possible and they should be benign when they necessary.[2] Solvents are used in large quantities and the most feasible way to reduce hazards related to their application is probably substitution of hazardous ones with more environmentally benign.[3]

Novel solvents are often automatically called "green". Ionic liquids at the beginning of intensive research on them were acclaimed as environmentally friendly but now are more cautiously labelled "green" as recent research gives substantial information that they might be harmful.[4] It is clear that newly developed solvents should be easily assessed for their potential to be called green. The need for substitution of problematic solvents and necessity to assess novel solvents are the two main reasons to develop and apply guides to select harmless solvents for green chemistry and green analytical chemistry.[5]

Several SSGs have been reported in the literature with the aim of selecting greener alternatives to conventional organic solvents and promoting more sustainable practices in chemical and engineering processes. In general terms, SSGs are derived from the evaluation of environmental, health and safety (EHS) issues (and some other additional constraints) associated to the use of solvents. A number of companies and institutions have made significant contributions toward the development of these valuable tools, as briefly described below.

- Pfizer presented a SSG for medicinal chemistry which included 39 solvents.[6] Solvents were classified as preferred, usable or undesirable (and highlighted in green, amber or red, respectively) depending on their EHS issues. A solvent replacement table with alternatives to undesirable solvents was also provided.
- AstraZeneca's guide included seven environmental criteria, one health criterion and two safety criteria for ranking solvents in terms of greenness.[7] A score from 1 (few issues) to 10 (most concern) was assigned to each solvent under each category, enabling the classification of up to 46 solvents by means of red, amber and green rating codes.
- GlaxoSmithKline (GSK) guide was consecutively improved by increasing the number of solvents from 35 to 110 and including the life cycle assessment perspective and additional aspects to the EHS criteria considered in its first report

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published in 1999.[8-10] Solvents were scored from 1 (red) to 10 (green) in each EHS and additional criteria in the expanded GSK guide.[10]

- The American Chemical Society Green Chemistry Institute® Pharmaceutical Roundtable (ACS GCI-PR), created in 2005, has also proposed a joint SSG for greening pharmaceutical industry activities.[11] The ACS GCI-PR guide included three environmental criteria, one health criterion and one safety criterion for the classification of 63 solvents, following the same scoring system and colour coding applied in AstraZeneca and GSK guides.

- Sanofi, a current member of the ACS GCI-PR, has recently reported its own SSG.[12] Solvent classification depended on their corresponding EHS issues, as well as their quality, industrial constraints, cost and recyclability. Sanofi's SSG classified 96 solvents in four categories according to the overall recommendation, namely recommended solvent, substitution advisable, substitution requested and banned solvent (highlighted in green, yellow, red and brown, respectively).

Remarkably, the overall rankings for 51 solvents evaluated by different SSGs have been compared by Prat et al. under the CHEM21 project, showing an acceptable agreement between the guides.[13] It should be noted, however, that 17 out of the 51 solvents were not unequivocally ranked into four categories, namely recommended, problematic, hazardous and highly hazardous.

The most of the existing SSGs give only quasi-quantitative information about solvent greenness. We would like to propose more quantitative and informative approach to solvent selection. We rank more than 150 solvents according to their toxicological endpoints, hazards, potential to be appropriately disposed after utilisation and the potential to be obtained from renewable feedstock. Because we find inappropriate to compare all the solvents together due to their significantly different properties, we suggest grouping according to their physicochemical properties first. Clustering by physicochemical parameters defines engineers' basic needs regarding solvents, can make initial greenness assessment and reduces the initial range of searches regarding finding appropriate solvent.

Materials and methods

Input data

The SSG is based on assessment of 151 solvents that makes the dataset being one of the largest one among already published SSGs. The compounds investigated originate from different chemical classes: aliphatic and aromatic hydrocarbons, alcohols, aldehydes, ketones, ethers, esters, organic acids, terpenes and chlorinated solvents. Water, carbon disulphide, dimethyl sulphide and acetonitrile were also included in the dataset. Among these 151 solvents, there were some traditional solvents, commonly considered as non-green, some of them being even banned, and there were commonly recognized as "novel" or "green" ones.

The main criterion to include a solvent in the study is the completeness of available physicochemical data. Completeness of data forming input matrix is the requirement of application chemometric techniques. The initial classification is based on very basic physicochemical parameters as only those are easily available. Many other solvents might be included in the study but, unfortunately, their inclusion was not possible because of the lack of available data. For instance, ionic liquids[14] cannot be described in terms of boiling points and they are scarcely described in terms of toxicological data. Deep eutectic solvents[15] are in fact mixtures of two or more compounds that are still poorly described in terms of physicochemical and toxicological parameters. Their parameters depend on the mole ratio of their constituents. Similarly, parameters of supercritical CO_2 strongly depend on temperature and pressure and the presence of other compounds.[16] Because of scarcity and ambiguousness of data available we did not include these solvents in the assessmen (although they are potentially recognized as green).

The input data to solvent selection procedure are physicochemical parameters, toxicological endpoints, environmental persistence parameters, safety related parameters and possibility to manage them after utilization. We have found 151 compounds that could be fully described in terms of their physicochemical properties. The details and additional explanations are presented in the Table 1. Some non-numerically described criteria, like feedstock renewability or combustion products hazards, had to be translated to the numbers.

Cluster analysis and principal component analysis

For the classification of solvents a well-described multivariate statistical approach is used, namely cluster analysis (CA).19 CA is a widely used tool for environmetric, food and various other products characterization purposes. In order to cluster objects characterized by a set of variables (in this case physicochemical parameters of solvents, presented in Table 1), their similarity has to be determined. A preliminary step of data transformation is necessary (e.g., autoscaling or z – transform, range scaling), where normalized dimensionless numbers substitute the real data values. Thus, even serious differences in absolute values, expressed in various units, are scaled to similar ranges. Then, the similarity between the objects in the multidimensional space can be determined. Very often the Euclidean distance is used as a measure for clustering purposes. Thus, from the raw data input matrix a similarity matrix is obtained. Ward's method was selected as the method for linkage of similar objects into clusters. The presentation of the CA results is performed by a treelike scheme, called dendrogram that clearly comprises a hierarchical structure of the initial dataset. In case of this study clustering was performed by means of Ward's mode of linkage and calculation of distances with squared Euclidean distance.

Table 1 The parameters describing the solvents

Variable/criterion	Description	Percentage of data found
Variables for solvents classification		
melting point	expressed in °C	100%
boiling point	expressed in °C	100%
Density	expressed in g cm^{-3}	100%
water solubility	expressed in mg L^{-1} at 25 °C	100%
vapour pressure	expressed in Pa at 25 °C	100%
Henry's law constant	expressed in Pa m^3 mol^{-1}	100%
log K_{OW}	unitless	100%
log K_{OA}	unitless	100%
surface tension	expressed in dyn cm^{-1}	100%
Criteria for solvents ranking within clusters		
oral LD_{50}	The solvent concentration that kills half of population of rats after oral administration of single dose. If oral LD_{50} for rat was unavailable, the values for other rodents were used. Expressed in mg of solvent per kg of rats (or other rodent) body mass	79.5%
inhalation LC_{50}	The solvent air concentration that kills half of population of rats when exposed for inhalation for 4 h. If oral LD_{50} for rat was unavailable, the values for other rodents were used. Expressed in ppm	64.2%
IACR cancer class	International Agency for Research on Cancer (IARC) human carcinogenicity classification translated into numbers – group 1 (5), group 2A (4) and group 2 B (3.5)	82.1%
other specific effects	Score of 1 was given for each effect - mutagenicity, developmental effects, reproductive effects, neurotoxicity and other chronic effects	78.1%
fish LC_{50}	Water concentration of solvent that causes death of 50% of the fish population in a 96-h test. Fathead minnow endpoint values were selected first if available	65.6%
fish NOEL	The highest dose that causes no observable effects to fish. If not available it was calculated from K_{OW} and LC_{50} as described before[17]	65.6%
BOD $t_{1/2}$	Time needed to decrease initial compound concentration by half due to biodegradation process	62.3%
hydrolysis $t_{1/2}$	Time needed to decrease initial compound concentration by half due to hydrolysis process	68.2%
log BCF	Logarithm of bioconcentration factor	98.7%
recycling by distillation	The number of other solvents in the dataset within boiling point range ± 5 °C. The potential to form azeotropes with other compounds is not considered.	100%
feedstock renewability	Indicates if solvent can be easily obtained from renewable resource (1) or not (0)	100%
flash point	Expressed in °C	100%
flammability	Indicates solvent flammability – flammable (1), non-flammable (0) or flammable at high temperatures (0.5)	100%
combustion products	Indicates hazards related to formation of combustion products – carbon oxides (1), nitrogen oxides (3), sulphur oxides (4) and hydrogen chloride (5)	100%
POCP	Photochemical tropospheric ozone formation potential related to ethene (100) applied for European conditions, if not available then for North American[18]	38.4%

TOPSIS analysis

The TOPSIS (Technique for Order of Preference by Similarity to Ideal Solution) is a multiple-criteria decision analysis technique that was developed by Hwang and Yoon.[20,21] TOPSIS is the tool dedicated to choose the best alternative by calculation of the shortest distance to the positive ideal solution and at the same time the longest distance from the negative ideal solution. The methodology is successfully used in various areas of managerial practices, such as human resources, energy, engineering and manufacturing systems, chemical engineering, water resources, business, public administration, safety and environmental management.

TOPSIS gets advantage of information on the criteria and provides a cardinal ranking of alternatives and does not require independent preferences over the criteria.[22,23] To apply this technique the values describing the criteria must be numerical or easily transformable into calculable units. The input data is the matrix consisting of *n* alternatives (in CA, as a chemometric technique, they are called objects, in this study they are solvents) described by *m* criteria (again in CA they are called variables). The criteria applied for ranking are

summarized in the Table 1. The TOPSIS algorithm can be described in several simple steps as follows:

Determination of the normalized decision matrix. The normalized value r_{xy} is calculated:

$$r_{xy} = x_{xy} \div \sqrt{\sum_{x-1}^{m} x_{xy}^2}\ ,\ \text{x= 1,2,…,m and y=1,2,…,n} \quad (1)$$

where x_{xy} and r_{xy} are original and normalized score of decision matrix, respectively.

Determination of the weighted normalized decision matrix. The weighted normalized value $v^{xy}$is calculated:

$$v_{xy} = r_{xy} \times w_y\ ,\ \text{x =1, 2,..., m and y= 1, 2, ..., n} \quad (2)$$

where w_y is the weight of the criterion and $\sum_{y-1}^{n} w_y = 1$.

Determination of the positive ideal solution (A^*) and negative ideal solution (A^-).

$$A^* = \{(\max_x v_{xy} | y \in C_b), (\min_x v_{xy} | y \in C_c)\} = \{v_y^* | y = 1,2,\dots,m\}\ \text{Positive ideal solutions} \quad (3)$$

$$A^- = \{(\min_x v_{xy} | y \in C_b), (\max_x v_{xy} | y \in C_c)\} = \{v_y^- | y = 1,2,\dots,m\}\ \text{Negative ideal solutions} \quad (4)$$

Determination of the separation measures using the m-dimensional Euclidean distance. The separation measures of each alternative from the positive ideal solution and the negative ideal solution, respectively, are calculated:

$$S_x^* = \sqrt{\sum_{y=1}^{m} (v_{xy} - v_y^*)^2}\ \text{y= 1,2,…,m} \quad (5)$$

$$S_x^- = \sqrt{\sum_{y=1}^{m} (v_{xy} - v_y^-)^2}\ \text{y= 1,2,…,m} \quad (6)$$

Determination of the relative closeness to the ideal solution. The relative closeness of the alternative A_x with respect to A^* is defined:

$$C_x^* = \frac{S_x^-}{S_x^* + S_x^-}\ ,\ \text{x=1,2,…,n and } 0 < C_x^* < 1 \quad (7)$$

Selection of the alternative with C_x^* closest to 1.

The result of alternatives (in this case solvents) ranking can be the ordering itself or the closeness to the ideal solution. Both outputs, ranking itself and the numerical values of the closeness to the ideal solution, are beneficial for obtaining information in solvent ranking. For the details of TOPSIS algorithm please refer to the article describing its fundamentals and applications.[24] All the calculations regarding TOPSIS in this study were performed in Excel program (Microsoft 2010).

Every solvent is compared to the others, so greenness assessment is performed in relation to the given population. Because TOPSIS procedure is based on toxicological and environmental persistence measurements data as an input, there is no place for subjectivity, only measurement uncertainty. In some SSGs there are quite subjective scores as an input what can potentially mislead the results.

The TOPSIS algorithm includes the possibility to apply weights to the criteria. In this study we apply equal weights to the criteria, giving equal importance to all of them. Curious and conscious users can modify weights to adapt the ranking to their needs, what of course would result in different similarity to the ideal solution scores, than presented in this study.

Results and discussion

Grouping of solvents

The set of solvents described by their physicochemical parameters was the input data to chemometric analysis. Fig. 1 shows the results of grouping and it is clear that three very well defined groups have been formed. These results have been confirmed by principal component analysis (data not presented).

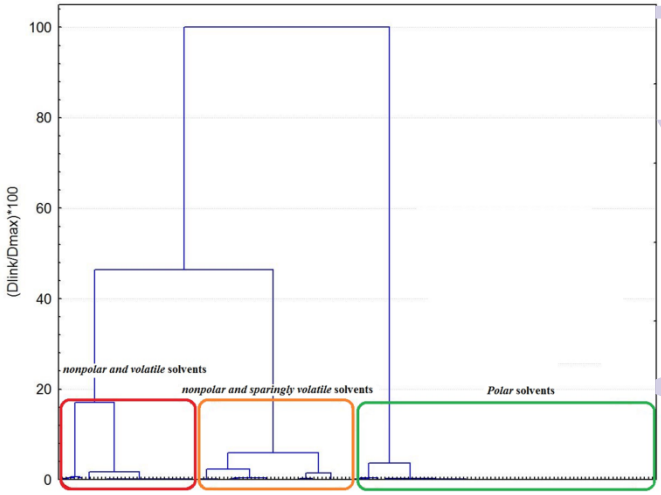

Fig. 1 Clustering of the solvents, based on their 9 physicochemical properties.

A closer look at the compounds grouped in all three clusters gives answer to what are the factors responsible for solvents grouping (discriminators). Solvents grouped to the three clusters differ substantially with their parameters (details presented in the Table 2):

Cluster 1: the compounds grouped in this cluster are characterized by low melting and boiling points. Their vapour pressures are considerably higher than for other two clusters. Most of them are denser than water and they are slightly soluble in water. Their Henry's law constants have average values. The cluster can be named *rather nonpolar and volatile* compounds. The compounds grouped into this cluster are very light alkanes and alkenes, aromatic hydrocarbons, the most of the chlorinated solvents and carbon disulphide and dimethyl sulphide.

Cluster 2: the compounds grouped in this cluster are non-soluble in water, characterized by high boiling points and low vapour pressures. They have high log K_{OW} and log K_{OA} constants and are lighter than water. Henry's constant values are very high. The name describing the cluster can be *non-polar and sparingly volatile* solvents. The compounds present

in this cluster are >C_6 alkanes, >C_7 alkenes, C_9 alcohols and terpenes. There are also long chain esters and hexachlorobutadiene.

Cluster 3: the solvents grouped in this cluster are characterized by high water solubility and low values of Henry's constants. They are moderately dense and of moderate vapour pressures. The name given to the cluster can be *polar* solvents. The group consists of water, (short chain) alcohols and phenols, aldehydes, ketones, organic acids, some of the esters, two of the chlorinated solvents and acetonitrile.

Table 2 Mean ± standard deviation values of solvent physicochemical parameters for each cluster

	Cluster 1	Cluster 2	Cluster 3
melting point	-72.9 ± 44.5	-31.7 ± 43.5	-34.4 ± 46.9
boiling point	80.3 ± 40.6	185.6 ± 58.6	148.2 ± 63.2
density	1.075 ± 0.3	0.84 ± 0.178	0.947 ± 0.151
water solubility	4962 ± 10817	12 ± 29	229852 ± 315803
vapour pressure	27599 ± 29254	1350 ± 3751	9844 ± 32276
Henry law constant	7288 ± 22624	258174 ± 518059	11 ± 49
log KOW	2.281 ± 0.812	5.795 ± 1.696	0.681 ± 1.087
log KOA	2.814 ± 0.687	5.313 ± 2.366	4.806 ± 1.822
surface tension	27.1 ± 5.2	27.9 ± 5.33	30.4 ± 8.6

Investigation of the mean values of solvents hazards values, presented in Table 3, can give the first information about greenness of solvents present in each cluster. Rodent oral LD_{50} are at comparable level in all clusters but compounds present in cluster 1 seem to be more toxic. Oppositely, cluster 3 compounds are characterized by slightly larger inhalation toxicity. There is clear distinction between clusters based on carcinogenicity and other biological effects, considerably more compounds present in cluster 1 are suspected to be or are human carcinogens and cause other undesired biological effects. Compounds grouped in cluster 3 are significantly less toxic to fish than compounds from other two clusters. They are also less persistent as they are characterized by low BOD $t_{1/2}$ and hydrolysis $t_{1/2}$. They also do not undergo bioaccumulation as easily as compounds present in clusters 1 and 2. Significantly higher percentage of solvents present in this group can originate from renewable feedstock. Compounds in all three clusters are considered to be flammable but cluster 1 compounds are characterized by lower flash points and produce more dangerous combustion products. Solvents grouped in clusters 1 and 2 have potential to form tropospheric ozone.

It has to be emphasized that this summary is based on incomplete data but still it gives clue about the initial solvent selection direction. The first choice of chemists should be solvents from cluster 3.

Table 3 Mean ± standard deviation values of solvent toxicological, environmental persistence and hazard-related criteria for each cluster

	Cluster 1	Cluster 2	Cluster 3
Oral LD_{50}	2982 ± 3283	6499 ± 7043	4155 ± 11577
Inhalation LC_{50}	15404 ± 23355	11715 ± 24950	8632 ± 13434
IACR cancer class	1.39 ± 1.97	0.12 ± 0.64	0.23 ± 0.91
other specific effects	1.59 ± 0.91	0.18 ± 0.61	0.8 ± 0.75
fish LC_{50}	136 ± 496	320 ± 494	20207 ± 135898
fish NOEL	36 ± 125	16 ± 25	18930 ± 136028
BOD $t_{1/2}$	84 ± 84	25 ± 43	18 ± 41
hydrolysis $t_{1/2}$	770 ± 373	925 ± 217	695 ± 445
log BCF	1.23 ± 0.56	2.51 ± 0.69	0.55 ± 0.65
recycling by distillation	5.91 ± 2.49	5.89 ± 3.02	7.19 ± 3.11
feedstock renewability	0.029 ± 0.169	0.571 ± 0.502	0.864 ± 0.345
flash point	4.2 ± 41.1	80.6 ± 60.5	53.1 ± 46.9
flammability	0.83 ± 0.32	0.986 ± 0.085	0.95 ± 0.17
combustion products	3.286 ± 2.585	1.143 ± 0.845	1.272 ± 1.049
POCP	33 ± 29	58 ± 31	15 ± 32

Ranking of solvents within groups

As it is stated before, cluster 3 compounds are the most environmentally safe and should be the first preference. However, they are 85 compounds clustered together and the standard deviations presented in Table 3 suggest that there might be huge differences within this group. For assessment within group, a tool with easy to read output and fine ranking capacity is needed.

Ranking of solvents in each group was performed with TOPSIS tool. A major issue with this step was the availability of data. Much of the rodent oral LD_{50}, rodent inhalation LC_{50}, fish LC_{50} or degradation data are missing. Therefore, we have decided to introduce ranking within confidence levels. They are based on the amount of missing data, very high confidence rankings are performed with all of criteria presented in the Table 2, and high confidence rankings with all criteria except POCP. For fully described solvents we have performed high confidence ranking, for those with a lot of data missing we have performed low or very low confidence ranking.

The numerical values presented in the Tables 4-6 are similarities to ideal solutions, with value 1 being ideal solution and value 0 being nonideal solution. These values give information what are the differences between solvents. As an example, and according to high confidence ranking within *nonpolar and volatile solvents*, the difference between diethyl ether and 1,1,1-trichloroethane is much higher than between 1,1,1-trichloroethane and pentane. It has to be clearly stated that the values of similarity to ideal solutions presented in different tables are not comparable among each other. These values can be compared for solvents present in single cluster and ranked within the same confidence ranking.

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Table 4 Ranking of *rather nonpolar and volatile solvents* (cluster 1) within different confidence levels

Solvent	the highest confidence ranking	high confidence ranking	medium confidence ranking	low confidence ranking	comparison with other SSGs					
					Pfizer[6]	GCI-PR[11]	GlaxoSmithKline[10]	AstraZeneca[7]	Sanofi[12]	CHEM21[13]
diethyl ether	0.556	0.499	0.221	0.273	undesirable	undesirable	undesirable	undesirable	banned	highly hazardous
1,1,1-trichloroethane	0.440	0.307	0.384	0.610	-	-	-	-	banned	-
pentane	0.432	0.374	0.271	0.317	undesirable	-	undesirable	-	banned	Hazardous
1-hexene	0.374	0.309	0.297	0.276	-	-	-	-	-	-
cyclohexane	0.373	0.301	0.313	0.225	usable	undesirable	usable	undesirable	substitution advisable	to be confirmed
m-xylene	0.367	0.276	0.302	0.413	usable	usable	usable	usable	substitution advisable	problematic
tetrachloroethene	0.361	0.230	0.274	0.452	-	-	-	-	-	-
p-xylene	0.356	0.275	0.279	0.413	usable	usable	usable	usable	substitution advisable	problematic
o-xylene	0.348	0.264	0.294	0.415	usable	usable	usable	usable	substitution advisable	problematic
dichloromethane	0.346	0.244	0.217	0.318	undesirable	-	undesirable	-	substitution advisable	to be confirmed
chloroform	0.342	0.233	0.215	0.346	undesirable	undesirable	undesirable	-	banned	highly hazardous
toluene	0.320	0.252	0.269	0.331	usable	undesirable	usable	undesirable	substitution advisable	problematic
trichloroethene	0.294	0.180	0.224	0.343	-	-	-	-	-	-
benzene	0.292	0.202	0.203	0.263	undesirable	undesirable	undesirable	-	banned	highly hazardous
1,1-dichloroethene	0.285	0.191	0.176	0.208	-	-	-	-	-	-
pentachloroethane	-	0.364	0.442	0.720	-	-	-	-	-	-
furan	-	0.355	0.518	0.449	-	-	-	-	-	-
chlorobenzene	-	0.258	0.260	0.380	-	usable	preferred	undesirable	substitution advisable	highly hazardous
styrene	-	0.250	0.304	0.426	-	-	-	-	-	-
1,3-dichloropropene	-	0.239	0.268	0.401	-	-	-	-	-	-
trans-1,2-dichloroethene	-	0.219	0.219	0.300	-	-	-	-	-	-
carbon disulphide	-	0.202	0.200	0.246	-	-	undesirable	-	-	-
1,2-dichloroethane	-	0.185	0.236	0.374	-	undesirable	undesirable	-	banned	-
carbon tetrachloride	-	0.180	0.213	0.348	undesirable	-	undesirable	-	banned	highly hazardous
cyclopentane	-	-	0.305	0.254	-	-	-	-	-	-
1,1,1,2-tetrachloroethane	-	-	0.254	0.414	-	-	-	-	-	-
dimethyl sulphide	-	-	0.253	0.355	-	-	-	-	-	-
methoxycyclopentane	-	-	0.250	0.348	-	-	usable	-	substitution requested	-
1-chloropropane	-	-	0.206	0.247	-	-	-	-	-	-
1,1-dichloroethane	-	-	0.197	0.255	undesirable	-	-	-	-	highly hazardous
1-chlorobutane	-	-	0.184	0.209	-	-	-	-	substitution advisable	-
dioxolane	-	-	-	0.420	-	-	-	-	-	-
cis-1,2-dichloroethene	-	-	-	0.287	-	-	-	-	-	-
1-pentene	-	-	-	0.263	-	-	-	-	-	-

Table 5 Ranking of *nonpolar and non-volatile* (cluster 2) solvents within different confidence levels

solvent	high confidence ranking	medium confidence ranking	low confidence ranking	comparison with other SSGs					
				Pfizer[6]	GCI-PR[11]	GlaxoSmithKline[10]	AstraZeneca[7]	Sanofi[12]	CHEM[13]
dodecane	0.619	0.625	0.640	-	-	-	-	-	-
undecane	0.605	0.613	0.613	-	-	-	-	-	-
heptane	0.596	0.511	0.546	usable	usable	usable	usable	substitution advisable	problematic
methyl laurate	0.565	0.658	0.784	-	-	-	-	-	-
p-cymene	0.550	0.616	0.655	-	-	-	-	-	-
nonanol	0.546	0.636	0.723	-	-	-	-	-	-
(R)-(+)-limonene	0.543	0.612	0.651	-	-	-	-	substitution advisable	-
hexane	0.540	0.469	0.607	undesirable	undesirable	undesirable	-	substitution requested	hazardous
β-pinene	0.539	0.621	0.667	-	-	-	-	-	-
α-pinene	0.526	0.598	0.628	-	-	-	-	-	-
isooctane	0.515	0.583	0.553	usable	preferred	preferred	undesirable	-	-
hexachlorobutadiene	0.272	0.460	0.277	-	-	-	-	-	-
tributyl 2-acetylcitrate	-	0.822	0.792	-	-	-	-	-	-
tetradecane	-	0.691	0.661	-	-	-	-	-	-
methyl caprylate	-	0.686	0.701	-	-	-	-	-	-
pentadecane	-	0.654	0.708	-	-	-	-	-	-
decanol	-	0.654	0.753	-	-	-	-	-	-
neryl acetate	-	0.649	0.744	-	-	-	-	-	-
methyl oleate	-	0.643	0.752	-	-	-	-	-	-
methyl myristate	-	0.641	0.694	-	-	-	-	-	-
tridecane	-	0.631	0.652	-	-	-	-	-	-
1-octene	-	0.628	0.596	-	-	-	-	-	-
3-carene	-	0.621	0.666	-	-	-	-	-	-
decane	-	0.609	0.606	-	-	-	-	-	-
1-heptene	-	0.598	0.588	-	-	-	-	-	-
nonane	-	0.578	0.587	-	-	-	-	-	-
benzyl benzoate	-	-	0.809	-	-	-	-	-	-
isopropyl palmitate	-	-	0.809	-	-	-	-	-	-
oleic alcohol	-	-	0.718	-	-	-	-	-	-
methyl stearate	-	-	0.718	-	-	-	-	-	-
methyl linoleate	-	-	0.712	-	-	-	-	-	-
methyl palmitate	-	-	0.712	-	-	-	-	-	-
isopropyl myristate	-	-	0.694	-	-	-	-	-	-
octane	-	-	0.588	-	-	-	-	substitution requested	-
1-nonene	-	-	0.564	-	-	-	-	-	-

Table 6. Ranking of *polar* (cluster 3) solvents within different confidence levels

solvent	high confidence ranking	medium confidence ranking	low confidence ranking	very low confidence ranking	comparison with other SSGs					
					Pfizer[6]	GCI-PR[11]	GlaxoSmithKline[10]	AstraZeneca[7]	Sanofi[12]	CHEM21[13]
water	0.849	0.849	0.778	0.668	preferred	-	preferred	-	recommended	recommi
glycerol	0.451	0.379	0.499	0.659	-	-	preferred	-	-	-
propanol	0.416	0.349	0.424	0.676	preferred	preferred	Preferred	-	recommended	-
ethanol	0.407	0.359	0.449	0.696	preferred	preferred	Preferred	-	recommended	recommended
methanol	0.382	0.305	0.350	0.546	preferred	preferred	usable	usable	recommended	to be con
acetone	0.382	0.328	0.385	0.603	preferred	usable	preferred	usable	recommended	recommended
acetic acid	0.381	0.332	0.393	0.634	usable	usable	preferred	preferred	substitution advisable	to be con
formic acid	0.375	0.329	0.385	0.622	-	usable	-	usable	substitution requested	to be confirmed
benzyl alcohol	0.372	0.329	0.378	0.590	-	preferred	preferred	-	substitution advisable	recomme
hexanoic acid	0.369	0.325	0.386	0.603	-	-	-	-	-	-
butyl lactate	0.368	0.320	0.382	0.590	-	-	-	-	-	-
butyric acid	0.368	0.320	0.381	0.604	-	-	-	-	-	-
isobutyric acid	0.368	0.321	0.366	0.584	-	-	-	-	-	-
furfural	0.367	0.315	0.370	0.595	-	-	-	-	-	-
valeric acid	0.366	0.321	0.378	0.602	-	-	-	-	-	-
isopropanol	0.364	0.306	0.355	0.539	preferred	usable	preferred	preferred	recommended	recomme ded
hexanol	0.364	0.317	0.358	0.562	-	-	-	-	-	-
methyl formate	0.364	0.310	0.349	0.536	-	undesirable	-	-	-	-
ethyl lactate	0.361	0.312	0.367	0.535	preferred	-	preferred	-	substitution advisable	recommended
methyl acetate	0.361	0.314	0.358	0.544	-	preferred	usable	-	substitution advisable	to be con
heptanol	0.360	0.317	0.358	0.530	-	-	-	-	-	-
cyclohexanone	0.360	0.311	0.364	0.572	-	preferred	preferred	-	substitution advisable	to be confirmed
2-heptanone	0.359	0.317	0.362	0.568	-	-	-	-	-	-
tetrahydrofuran	0.359	0.315	0.374	0.589	usable	usable	undesirable	undesirable	substitution advisable	to be con med
2-butanone	0.358	0.311	0.373	0.576	-	-	-	-	recommended	-
3-pentanone	0.356	0.308	0.360	0.558	-	-	preferred	-	-	-
2-hexanone	0.356	0.306	0.354	0.546	-	-	-	-	substitution requested	-
allyl alcohol	0.354	0.305	0.351	0.549	-	-	-	-	-	-
octanol	0.349	0.309	0.337	0.487	-	-	-	-	-	-
propanal	0.348	0.301	0.346	0.528	-	-	-	-	-	-
p-cresol	0.348	0.298	0.339	0.509	-	-	-	-	-	-
o-cresol	0.348	0.298	0.339	0.512	-	-	-	-	-	-
ethyl acetate	0.346	0.294	0.311	0.439	-	usable	preferred	preferred	recommended	-
phenol	0.334	0.282	0.302	0.423	-	-	-	-	-	-
m-cresol	0.328	0.276	0.288	0.378	-	-	-	-	-	-
acetonitrile	0.319	0.269	0.282	0.434	usable	preferred	usable	undesirable	recommended	problem
2-pentanone	0.297	0.244	0.351	0.541	-	-	preferred	-	-	-
methyl tert-butyl ether	0.297	0.287	0.297	0.426	usable	undesirable	undesirable	undesirable	substitution advisable	to be confi ed
ethyl acrylate	0.294	0.247	0.356	0.575	-	-	-	-	-	-
methyl isobutyl ketone	0.293	0.242	0.350	0.544	-	usable	preferred	usable	recommended	to be c nfirmed
1,1,2,2-tetrachloroethane	0.262	0.248	0.239	0.355	-	-	-	-	-	-

solvent	high confidence ranking	medium confidence ranking	low confidence ranking	very low confidence ranking	comparison with other SSGs					
					Pfizer[6]	GCI-PR[11]	GlaxoSmithKline[10]	AstraZeneca[7]	Sanofi[12]	CHEM21[13]
1,1,2-trichloroethane	0.251	0.240	0.219	0.322	-	-	-	-	-	-
tert-butyl alcohol	-	0.352	0.440	0.686	-	-	-	-	-	-
isopropylidene glycerol	-	0.341	0.408	0.638	-	-	-	-	-	-
butanol	-	0.339	0.405	0.672	preferred	preferred	preferred	preferred	recommended	recommended
propionic acid	-	0.333	0.394	0.631	-	preferred	preferred	usable	substitution advisable	-
pentanol	-	0.324	0.376	0.597	-	-	-	preferred	-	-
isobutanol	-	0.307	0.357	0.549	-	preferred	-	preferred	recommended	-
butanal	-	0.306	0.359	0.540	-	-	-	-	-	-
sec-butyl alcohol	-	0.304	0.358	0.558	-	usable	-	-	-	-
1,8-cineole	-	0.303	0.328	0.484	-	-	-	-	-	-
benzaldehyde	-	0.303	0.345	0.525	-	-	-	-	-	-
anisole	-	0.291	0.321	0.470	-	preferred	preferred	preferred	recommended	recom
ethanal	-	0.246	0.353	0.541	-	-	-	-	-	-
glycerol triacetate	-	-	0.416	0.651	-	-	-	-	substitution advisable	-
3-n-butoxy-1-tert-butoxy-2-propanol	-	-	0.411	0.637	-	-	-	-	-	-
butyl levulinate	-	-	0.403	0.637	-	-	-	-	-	-
ethyl levulinate	-	-	0.389	0.598	-	-	-	-	-	-
γ-valerolactone	-	-	0.379	0.590	-	-	-	-	substitution advisable	-
methyl lactate	-	-	0.376	0.584	-	-	preferred	-	-	-
ethyl formate	-	-	0.348	0.535	-	-	usable	-	substitution advisable	-
diethylamine	-	-	0.299	0.465	-	-	-	-	-	-
1-n-butoxy-3-iso-propoxy-2-propanol	-	-	-	0.668	-	-	-	-	-	-
3-butoxypropane-1,2-diol	-	-	-	0.638	-	-	-	-	-	-
1,3-di-n-butoxy-2-propanol	-	-	-	0.630	-	-	-	-	-	-
3-methoxypropane-1,2-diol	-	-	-	0.628	-	-	-	-	-	-
isosorbide dimethyl ether	-	-	-	0.621	-	-	-	-	-	-
3-ethoxypropane-1,2-diol	-	-	-	0.619	-	-	-	-	-	-
1-n-butoxy-3-ethoxy-2-propanol	-	-	-	0.619	-	-	-	-	-	-
1-n-butoxy-3-methoxy-2-propanol	-	-	-	0.619	-	-	-	-	-	-
1-tert-butoxy-3-methoxy-2-propanol	-	-	-	0.604	-	-	-	-	-	-
1,3-di-iso-propoxy-2-propanol	-	-	-	0.603	-	-	-	-	-	-
1-tert-butoxy-3-ethoxy-2-propanol	-	-	-	0.599	-	-	-	-	-	-
1-ethoxy-3-iso-propoxy-2-propanol	-	-	-	0.599	-	-	-	-	-	-
1,3-dimethoxypropan-2-ol	-	-	-	0.596	-	-	-	-	-	-
methyl levulinate	-	-	-	0.596	-	-	-	-	-	-
1-methoxy-3-(propan-2-yloxy)propan-2-ol	-	-	-	0.595	-	-	-	-	-	-
1,2,3-trimethoxypropane	-	-	-	0.566	-	-	-	-	-	-
2-pyrrolidone	-	-	-	0.531	-	-	-	-	-	-
1,2,3-tri-n-butoxypropane	-	-	-	0.469	-	-	-	-	-	-
dimethyl sulfoxide	-	-	-	0.457	-	usable	usable	preferred	substitution advisable	problematic

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Certain compounds cannot be ranked with others within given confidence level (due to lack of literature data). Then it is advisable to compare such compounds with others on lower confidence levels. As an example, furan is not comparable with benzene within high confidence ranking. Their ranks can be read then within medium confidence levels, bearing in mind that medium confidence level ranking is based on fewer criteria. We advise to rely mostly on high and medium confidence rankings. Lower confidence levels ranking can just give general impression about solvents greenness. The ranking values according to the highest confidence level available are shadowed grey for every compound.

Because there are several SSGs that differ in their assessment results, we compare our results with summarized results originating from different SSGs. Those differences have been attributed to the different weighting of criteria selected in each SSG.[13] Overall rankings for GCI-PR, GSK and AstraZeneca guides were obtained by conversion of the specific numerical values given for safety, health and environmental hazards, according to ACS GCI SSG.[11] Three categories, namely preferred, usable and undesirable, were differentiated following the Pfizer guide's style.[6] Furthermore, the results of a recent survey of SSGs (not a SSG in the strict sense), were included for comparison purposes.[13]

Ranking within *rather nonpolar and volatile* group. The highest confidence ranking included all criteria, high confidence ranking all except POCP, medium confidence ranking included oral LD_{50}, log BCF, potential to be recycled, renewability of feedstock, flammability and combustion products. During low confidence ranking only log BCF, potential to be recycled, renewability of feedstock, flammability and combustion products are included.

It is worth noting that ranking of solvents in this cluster, which groups the most environmentally problematic solvents, is the choice between bad or even worse solvents. The least hazardous solvents in this ranking are diethyl ether and 1,1,1-trichloroethane. Both of them are indicated as "highly hazardous", "undesirable" and 1,1,1-trichloroethane is "banned" due to its ozone depletion potential (ODP). This criterion was not considered in this assessment as ODP values are available only for few of the 151 assessed solvents. Diethyl ether is rigorously assessed by other SSGs because of its low flash point, high volatility and flammability. In cluster 1 ranking diethyl ether obtained high score because it is less toxic to fish and to rodents via inhalation. It is also characterized by lower BCF and is readily biodegradable in the environment. Despite being highly flammable, diethyl ether was ranked higher than chlorinated solvents and aromatic hydrocarbons. However, diethyl ether is a solvent to be avoided due to the low boiling point and risk of peroxide formation.

There are just two solvents, chlorobenzene and 1,3-dioxolane, that are considered green in the literature and few others that are labelled as "usable" – i.e. xylenes. In the literature 1,3-dioxalane is reported as green solvent as it is "nontoxic, odourless, easy to evaporate and environmentally friendly".[25] Our study shows that indeed it is ranked high but with low confidence ranking and within non-green solvent cluster. For sure more data are required to properly rank this solvent. Chlorobenzene is ranked rather high with medium confidence ranking, what partially indicates that it might be a better substitute than some other compounds from this cluster, but again more evidence is required for stating that it is a green solvent. Other SSGs label this compound in extremely different way – from "highly hazardous" to "preferred".

Ranking within *nonpolar and sparingly volatile* group. High confidence ranking included all criteria except POCP, medium confidence ranking included all criteria except POCP, inhalation LC_{50}, fish LC_{50}, fish NOEL and BOD $t_{1/2}$. Low confidence ranking included only log BCF, potential to be recycled, renewability of feedstock, flammability and combustion products.

High confidence ranking shows that undecane and dodecane can be the first choice, when a nonpolar and sparingly volatile solvent is obligatory. The high rank for methyl laurate in high confidence ranking is an indication that other fatty acid esters can be interesting from green chemistry point of view. These were ranked with low confidence only but they were ranked relatively high. More research is needed to completely characterize fatty acid esters, but they seem to be promising green solvents.

(R)-(+)-limonene is considered as a green solvent and was successfully applied in moisture determination instead of toluene.[26] It originates from renewable resource, it is no health or environmentally hazardous. In our study these two solvents, (R)-(+)-limonene and toluene, are not directly comparable as they are in different clusters. Similarly, (R)-(+)-limonene was used in Soxhlet extraction, as the substitution of hexane.[27] Another terpene concerned in the literature as a green solvent is α-pinene, that has been successfully used to substitute toluene.[28] The presence of terpenes in the second cluster is not a good implication for their greenness. What is more, the ranking indicates that undecane or dodecane might be better alternatives.

Ranking within *polar* group. High confidence ranking of compounds clustered in *polar* group included all criteria except POCP, medium confidence ranking included all criteria except POCP, inhalation LC_{50}, hydrolysis $t_{1/2}$ and BOD $t_{1/2}$. Low confidence ranking included oral LD_{50}, log BCF, potential to be recycled, renewability of feedstock, flammability and combustion products, while very low confidence ranking included only log BCF, potential to be recycled, renewability of feedstock, flammability and combustion products criteria.

Water is indicated as the recommended green solvent by all of the SSGs and here the situation is the same. It is indicated that water – alcohols mixtures with high water contents are also characterized by low environmental impacts.[3] A more holistic approach to solvents assessment, such as life-cycle analysis, also indicates that the production of water production is less energy demanding that in the case of organic solvents. What is interesting, water is no longer the first preference solvent in low confidence ranking, when only waste managerial practises and renewability of feedstock are concerned. In fact, water is relatively hard to be recycled because many solvents have similar boiling points. Although it was not considered in the assessment procedure, water easily forms azeotropes, for example with alcohols, what creates further problems with recycling by distillation. For the high confidence ranking, water is not indicated as ideal solvent, as it does not have the score equal to one. There are solvents that are more easily recycled and, although water does not cause harm to organisms, the water log BCF is higher than for some of the other solvents.

The second preference in high confidence ranking is glycerol, that is concerned as preferable solvent in the light of green chemistry.[29] Glycerol is non-toxic and safe, available from renewable feedstock and able to dissolve many organic and inorganic compounds, what makes it the solvent of choice for various applications.[30,31] It is worth to notice that the difference in assessment score between water and glycerol is significant and there is no such a difference between two other following solvents. This is an implication that water is unquestioned number one when green solvents are selected.

Alcohols, acetone and carboxylic acids are ranked next. Other SSGs indicate that they are labelled as “recommended”, some of them as “recommended or problematic”. They are in fact, relatively non-toxic, originate from renewable resources, are rather safe in use and are not persistent in the environment. Isopropanol, as an example, is advised to substitute tetrahydrofuran for polydimethylosiloxane dissolution.[32] Ethanol, acetone and isopropanol are green solvents examined to extract oil from passion fruits and acceptable extraction yields were obtained, when extraction was ultrasound or microwave-assisted.[33] Ethyl acetate, recommended by other SSGs, is ranked rather low, among phenol and cresols. It has all toxicological and safety parameters at average levels and it is flammable, with low potential to be recycled and high (for this cluster) bioconcentration factor. On the other hand, acetonitrile is ranked at similar level to ethyl acetate but it is marked as problematic by other SSGs. Ethyl acetate, ethanol and acetone (the first ranked rather low, while two others ranked high) are advised to substitute tetrahydrofuran and acetonitrile (both ranked low) in preparative liquid chromatography as mobile phases.[34] Anisole is ranked low with medium confidence ranking although it is recommended by all other SSGs. It is assessed as non-preferable solvent because it is toxic to fish and has relatively high bioconcentration factor.

Carboxy-alcohols could be ranked within low confidence but they seem to be promising solvents in terms of green chemistry. They originate from renewable feedstock and do not bioacumulate. They are flammable but do not produce unusually toxic combustion by-products. For more accurate assessment they need to be better described with toxicological and ecotoxicological parameters.

1,1,2,2-tetrachloroethane and 1,1,2-trichloroethane are grouped to this cluster by cluster analysis algorithm as they have low Henry’s law constant and low log Kow. However, they are ranked as the most environmentally problematic solvents.

User potential modifications

The simplicity of this assessment approach allows for ease incorporation of new solvents. The requirement is that they should be fully described in terms of physicochemical parameters and described in terms of hazards parameters in a way that allows at least for low confidence ranking. New solvents in the dataset would be assigned to one of three clusters. There is also possibility of another cluster formation (or outlying solvent) in case of solvent, which physicochemical parameters significantly differ from already formed patterns. CA is a procedure simple enough to be performed by users if incorporation of new solvents is needed.

Similarly, TOPSIS is a relatively simple ranking tool that can be applied by Excel users. This gives possibility to rank solvents within higher confidence levels after adding new toxicity and other hazard related – data. Much of these data are missing at the moment but they will presumably be studied and published for new solvents, considered as “novel” or “green”, as it is in case of bio-based solvents.[35] In addition, the assessment procedure easily allows to introduce completely new ranking criteria.

The algorithm of TOPSIS involves application weights for the criteria. In this study we applied equal weights for all criteria involved in each confidence level ranking. The SSG users can apply other, non-equal weights in some cases. The weights for certain criterion can be lowered if there is substantial suspicion of low quality of input data – i.e. various source report considerably different toxicological endpoints or toxicological endpoints for some substitute organisms are input data (for example oral LD_{50} for rabbit, instead of rat). Another reason to apply lower weight for criterion might be that certain threat occurrence is highly improbable. For example, if solvent has to be chosen for the process that is very unlike to contaminate aquatic environment the weights for fish LC50 and fish NOEL can be lowered. Similarly, if there is pre-defined spent reagents management practise, like recycling of solvent by distillation, then the weight for

"potential for distillation" criterion could be increased. Ranking with TOPSIS allows the solvent selection to be fit for purpose and in such a case the results can differ from those presented in the Tables 4-6. Modification of weights requires, however, some expertise that is required to translate the importance of criteria to numerical values of weights. Another need in expertise is a clear statement of the requirements to the solvent that is selected.

Conclusions

In this study we present a new approach to select appropriate solvents according to greenness parameters. It gives general information about solvent greenness and allows for ease of comparison of many solvents in terms of greenness performance. As opposed to other SSGs, it allows for very fine ranking of solvents. We present the general scheme of the assessment procedure, but the algorithm is tuneable and allows to fit the assessment procedure to given purpose. Many of the novel, bio-based or non-traditional solvents are *a priori* classified as green. This SSG represents a systematic tool to assess the greenness of such new solvents.

The results of 151 solvents assessment show that they are grouped into three clusters according to their physicochemical parameters. The preferences for each cluster are established and it is advisable to choose solvents from *polar* solvents if possible. Ranking of solvents within each cluster generally agrees with other SSGs results.

For the better assessment of novel or bio-based solvents greenness, more toxicological data are required. Newly obtained data can be easily incorporated to the assessment algorithm.

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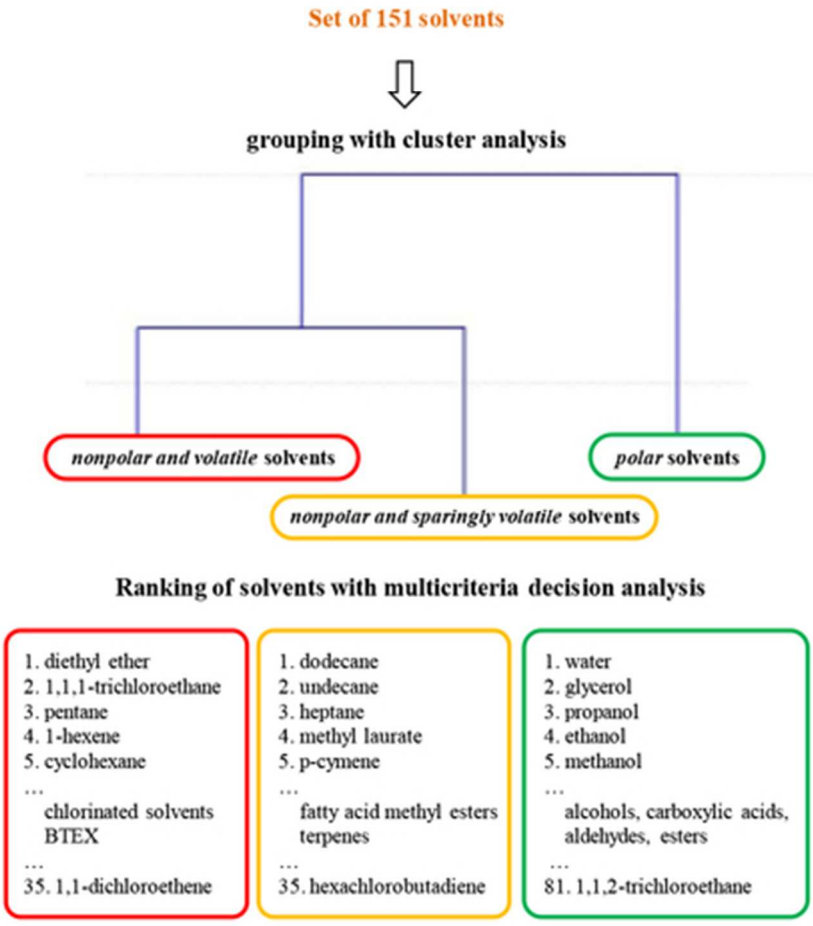

Chemometric and multicriteria decision analysis-based solvent selection guide gives more holistic view on solvents environmental impact.
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