Assessment and design of greener deep eutectic solvents – a multicriteria decision analysis

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ABSTRACT

Deep eutectic solvents (DES) are often considered as green solvents because of their properties, such as negligible vapor pressure, biodegradability, low toxicity or natural origin of their components. Due to the fact that DES are cheaper than ionic liquids, they have gained many applications in a short period of time. However, claims about their greenness sometimes seem to be exaggerated. Especially, bearing in mind lots of data gaps for DES properties as well as their individual components. To clarify the situation on their greenness status, a comprehensive assessment of commonly used hydrogen bond acceptors and donors separately and as DES is performed. The application of multicriteria decision analysis (TOPSIS ranking) with combination of biological effect modeling for DES to rank these alternatives according to greenness criteria is proposed. Also traditional organic solvents and ionic liquids as greenness reference points for better understanding are introduced. The ranking results show that many DES, which are synthetized by mixing sugars alcohols, alcohols, sugars and amides are promising environmentally friendly solvents, more than some imidazolium-based ionic liquids. Mixtures including components with metal ions and organic acids are less green.

1. Introduction

Green chemistry refers to "design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances" [1,2]. According to one of 12 principles of green chemistry, the use of harmful solvents should be avoided, replaced by more environmentally benign ones or their amount should be reduced [3]. The best replacement for conventional organic solvents is simply water, however usually more nonpolar solvents are required. Then, supercritical fluids, carbonates, bio-based solvents (from biomass or food waste), ionic liquids (ILs) or deep eutectic solvents (DES) are readily used. The last two groups of compounds have fairly similar physicochemical properties but ILs are more expensive [4] and harder to be obtained. Therefore, there is a noticeable growth of interest in DES, which are mixtures of two or more compounds with particular molar ratio – hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD). In contrary to traditional organic solvents belonging to volatile organic compounds (VOCs), DES are rather nonvolatile, non-flammable due to the low vapour pressure [5]. Moreover, in comparison to ILs (as solvents of similar characteristic), apart from their low cost, they possess other advantages such as simpler synthesis and natural origin (mainly in case of natural deep eutectic solvent - NADES).

DES show excellent applicability in many areas, for instance separation processes, biodiesel production [6], electrochemistry [7], absorption and solubility of carbon dioxide [8], medical and pharmaceutics usage [9], chemical synthesis [10], activation of enzymes and biocatalysis [11]. However, despite the wide range of applications, the claims about their low harmfulness,

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48 non-toxicity or high biodegradability are not unequivocal. Several studies proved that not all

49 DES are highly biodegradable or nontoxic and lack of data may be serious problem while

50 environmental evaluations [12, 13, 14]. Estimation of DES greenness should be performed in

51 more comprehensive way.

52 The tools that are helpful in assessments according to many factors simultaneously are

53 multicriteria decision analysis algorithms (MCDA). Among many The Technique for Order of

54 Preference by Similarity to Ideal Solution (TOPSIS) gained much interest due to its

55 simplicity. MCDA methods have been already successfully applied in greenness assessments

56 of solvents [15,16], derivatization agents [17], nanoparticles [18,19] and ionic liquids [20].

57 To authors best knowledge, it is the first study that considers variety of criteria (not only

58 toxicity) to rank HBA and HBD as DES components and DES in respect to their

59 environmental benigness. The results of this study may be useful for researchers and

60 practitioners at the first stage of DES selection, especially for separation processes. The

61 presented tools allow to assess how individual compounds, as well as their molar ratios can

62 affect the greenness of DES.

2. Materials and Methods

2.1.Data collection

65 Our study includes binary and ternary DES, which have been found in numerous scientific

66 papers. An extensive search has been conducted particularly targeted library databases: ACS,

67 Elsevier, Springerlink, RSC and Wiley – till first 150 hits, when available by the keywords

68 "DES", "Deep eutectic solvents", "Green deep eutectic solvents" or "Environmentally

69 friendly deep eutectic solvents".

70 The dataset has been divided into HBAs and HBDs, as well as DES mixtures. In first case, for

71 each of HBA and HBD properties referring to environmental and safety issues as hazardous

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72 and precautionary statements, signal wording, flash point, hazardous decomposition products,

73 vapor pressure, toxicity towards *Daphnia magna*, algae, fish and rodents, octanol-water

74 partition coefficient, biodegradability and pH have been collected. Whereas, for each of

75 binary and ternary DES mixtures parameters such as melting point, density, viscosity,

76 conductivity, surface tension, pH, refractive index, Kamlet-Taft parameters, spectroscopic

77 polarity index as E_T^N, toxicity towards *Vibrio fischeri*, *Escherichia coli*, fish and cell line of

78 CCO fish and MCF-7 or HeLa human tumor, phytotoxicity towards wheat seeds - *Triticum*

79 *aestivum*, biodegradability and solubility of gases as carbon dioxide, sulphur dioxide,

80 ammonia has been gathered according to corresponding articles. All information are presented

81 in *Supplementary Information 2*. Due to many gaps in dataset some of initially collected data

82 was not included in the assessments. The criteria that have been taken for TOPSIS rankings

83 are summarized in **Table 1**.

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Table 1. Criteria for HBDs and HBAs TOPSIS rankings.

Criterion	Remarks	Source
H-stat	Descriptions are transferred into numerical values	MSDS
P-stat	Descriptions are transferred into numerical values	MSDS
Signal wording	Descriptions are transferred into numerical values	MSDS
Flash point	The temperature in which compound flashes	MSDS, papers
Hazardous decomposition products	Descriptions are transferred into numerical values	MSDS
Vapour pressure	In 25 °C	MSDS, papers, databases
Toxicity Daphnia magna	48 h test data was preferable; if not available 24 h test data was taken	Papers
Toxicity algae	72 h test data was preferable; if not available 96 h test data was taken	Papers
Toxicity fish	96 h test data was preferable; if not available 48 h data was taken	Papers
Toxicity rodents via ingestion	Rat was the preferable organism, if data was not available data for mouse was taken	Papers
logKow	Logarithm of partitioning coefficient between octanol and water	Papers, MSDS, databases
Biodegradability	28 day test	Papers, MSDS,

			databases
pH		-	MSDS, papers
Solubility in water		In 25 °C	MSDS

85 For the specific references to paper, please see descriptions in Supplementary Information

86 The majority of properties are taken from scientific papers, describing chemical

87 characteristics of DES. Then information are supported by the chemical on-line databases

88 such as ECHA, PubChem, Chemspider. Moreover, data for analysis in this work is provided

89 by the Material Safety Data Sheets (MSDS) supplied by different companies, mainly Sigma-

90 Aldrich, Merck, Thermo Fisher Scientific, Santa Cruz Biotechnology Inc., Iolitec. Especially

91 information and parameters as: alternative names, CAS number, molecular formula,

92 molecular weight, signal wording, special hazards arising from the substance or

93 mixture/hazardous decomposition products.

94 The properties of DES are not fully available, so in case of lack of data, parameters have been

95 completed by predicted or estimated values (calculated in QSAR, EPISuite, etc.) or missing

96 points are substituted with the values of the chemically similar compounds / group of

97 compounds as proposed by Adler et al. [21] as summarized in **Tables S1, S5 and S7-S16**.

98 Additionally, wherever several datapoints are available (for instance toxicity values for

99 different fish / algae / rodent spices), always the most unbeneficial one is selected, according

100 to precautionary principle.

101 Traditional organic solvents and ionic liquids are included in the dataset as reference points,

102 for better understanding of a green nature of HBAs and HBDs being the DES components

103 (the same properties as for the HBAs and HBDs are collected). Some of data require

104 transformations from descriptions to numerical values, what is presented in **Tables S2-S6**.

105 **2.2.TOPSIS algorithm**

106 TOPSIS is algorithm developed by Hwang and Yoon [22], it is based on finding an

107 alternative characterised by the shortest distance from the positive ideal solution and

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108   simultaneously the furthest distance from the negative ideal solution. This mathematical

109   model allows for combination of different (often contradictory) criteria into a single score

110   leading to creation of ranking of available alternatives. The ranking is defined by the values of

111   similarity to ideal solution, for each alternative, ranged between 0 and 1. The value 0 is

112   assigned to completely non-ideal alternative (the worst values for all criteria), while the value

113   1 for an ideal solution (the best values for all criteria). Only basic information about TOPSIS

114   algorithm are described above. Its mathematical algorithm is presented in Section 2 of

115   *Supplementary Information 1*. More details may be found in the articles, including its

116   fundamentals [23, 24]. The calculations involving TOPSIS are performed in Excel program

117   (Microsoft 2016). TOPSIS was selected over other MCDA tools as it is fully applicable for

118   many alternatives assessment, its outcome is easily interpretable and its algorithm is relatively

119   simple.

120   ### 2.3.TOPSIS algorithm for DES components – HBA and HBD

121   Evaluation of HBAs and HBDs is carried out for each group separately. The number of

122   alternatives is 95 for HBA, 181 for HBD, 16 and 14 for organic solvents and 7 for ILs. The

123   difference in the amount of commercially used organic solvents is due to fact that n-butanol

124   and phenol are also a DES component in case of HBDs assessment. The selection of ionic

125   liquids is dictated by the data availability. Nevertheless, attempts are made to include salts

126   with different cations and anions. Moreover, substances like 1-butyl-3-methylimidazolium

127   chloride ($[C_4C_1im][Cl]$) and tetrabutylphosphonium bromide ($[P_{4444}][Br]$) may be classified as

128   a ILs as well as a HBD.

129   ### 2.4.TOPSIS algorithm for DES

130   Environmental assessment of DES including binary and ternary mixtures are based on results

131   obtained with TOPSIS analysis for HBAs and HBDs and calculations of common effects. Due

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132   to fact, that DES are composed of HBA and one (for binary mixtures) or two HBDs (for

133   ternary mixtures), the evaluation includes common responses, calculated with toxicological

134   model, according to the equation:

135     $E(C_{mix}) = 1 - \prod_{i=1}^{n}(1 - E(C_i))$ (1)

136   where E(Cmix) is combined effect at the mixture concentration (Cmix), and E(Ci) is the

137   similarity to ideal solution (calculated for HBA and HBD with TOPSIS) of individual mixture

138   component (i) applied at the concentration (Ci) [25]. Bearing in mind, fact that DES mixtures

139   may have different ratios of HBA and HBD, this information is introduced by fractions,

140   e.g. for HBA:HBD mixtures with ratios of 1:1 and 1:3, the fractions are equal ½ and ½ as well

141   as ¼ and ¾, respectively. Selected 35 binary and 2 ternary mixtures, considered by the

142   authors of respective publications as green solvents are evaluated. All these DES are listed in

143   **Table S18.** together with an information about areas of application and justification why

144   authors consider them green. Ionic liquids and traditional organic solvents are also included as

145   reference points. To obtain an adequate level of comparability with DES mixtures, combined

146   value of addition effect for each solvent is calculated by multiplication values of similarity to

147   ideal solution of HBA and HBD for particular solvent according to equation 1 (solvent is

148   treated as mix of two individuals).

149   *2.5. Weights and confidence rankings*

150   The advantage of MCDA tools is possibility of assigning weights to criteria to give them

151   relative importance in accordance to the purpose of the analysis. To provide a comprehensive

152   ranking thirteen criteria with different importance are simultaneously considered in the

153   assessment. Toxicity towards *Daphnia magna*, fish, algae and rats via ingestion are assessed

154   to have higher influence on the greenness character of DES components (0.14), while

155   biodegradability has weight value of 0.1. Information about hazard and precautionary

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156 statements, vapor pressure are found to be less important with weight value equal 0.06. Then

157 lower weights are considered for hazardous decomposition products (0.02), signal word

158 (0.02), flash point (0.04), pH (0.04) and $logK_{OW}$ (0.04). The toxicity criteria are assigned with

159 the highest weights as they refer more to the greenness assessment than other criteria. Hazards

160 and precautionary statements, signal wordings, decomposition products, flash point, pH and

161 $logK_{OW}$ are given low weights as they are characterized by lower variability and the criteria

162 translated from descriptions can be treated as semi-quantitative information.

163 *2.6.Sensitivity Analysis*

164 The sensitivity analysis is performed to investigate how changes in input values and/or

165 weights influence the final ranking results. It is also applied to consider measurement errors of

166 input variables. The input values are changed randomly for +10% or -10% and next analysis

167 is performed to see if differences in ranking are significant.

168 **3. Results and discussion**

169 *3.1.Results of TOPSIS ranking of HBA*

170 The results of TOPSIS analysis for HBAs with proposed criteria and assigned weight values

171 are presented in **Table 2**. Traditional organic solvents and ionic liquids are highlighted light

172 blue and light green, respectively.

173 It is found that the best alternative is triethylene glycol (0.5883), which is nontoxic to all

174 evaluated organisms. Moreover, it does not undergo bioaccumulation due to low value of log

175 K_{OW} and it is easily biodegradable. This DES component is also described by small number of

176 hazard and precautionary statements and in case of its decomposition there is no risk of

177 arising hazardous products. Then for next 5 compounds the values of similarities to ideal

178 solutions decrease from 0.18 to ~0.14. These compounds are mainly amino acids (betaine

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179 hydrochloride, betaine, histidine) and traditional organic solvents such as methanol and

180 heptane. The high position of amino acids in the ranking is due to low toxicities towards at

181 least two of organisms, high flash points, small values of log K_{OW} and ease of biodegradation.

182 These two organic solvents are highly ranked because of low toxicity towards rats via

183 ingestion and good biodegradability. Moreover, methanol is characterized by low value of

184 logK_{OW} and is rather non-toxic towards other analyzed organisms.

185 The ranking scores for latter compounds are gradually decreasing from 0.0962 for serine to

186 0.0244 for glycerol. These compounds are monosaccharides, such as mannose, D-glucose and

187 D-fructose, which are characterized by small number of hazardous statements and low value

188 of K_{OW}, as well as by the high values of flash point and low toxicity towards majority of test

189 organisms. Moreover, mannose is favorable due to high biodegradability. Within this part of

190 ranking ethyl acetate is localized, because of low toxicities towards the most of evaluated

191 organisms and low risk of bioaccumulation. All ionic liquids included are located in the

192 second half of this ranking. For these salts the common features are low biodegradability and

193 considerable toxicities towards all organisms, as well as high number of decomposition

194 products and. Also HBA that are organometallic compounds are located in the second part of

195 the ranking. For the last ranks the scores change to <0.007 for ammonium and phosphonium

196 salts, dodecanoic acid and solvents, like chlorobenzene, tetrahydrofuran and diethyl ether.

197 They are ranked low because of high toxicity in all included tests, in case of organic solvents

198 also high volatility.

199 **Table 2.** Results of TOPSIS analysis for HBA and comparison with traditional organic
200 solvents and ionic liquids combined with sensitivity analysis for changes in range of ±10%

No.	Substance name (HBA/organic solvent/IL)	CAS number	Similarity to ideal solution	Ranking difference for ±10% changes
1	triethylene glycol	112-27-6	0.5880	0
2	betaine hydrochloride	590-46-5	0.1812	3
3	betaine	107-43-7	0.1734	1

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4	heptane	142-82-5	0.1644	2
5	histidine	71-00-1	0.1485	-3
6	methanol	67-56-1	0.1459	-3
7	serine	56-45-1	0.0962	0
8	mannose	3458-28-4	0.0900	1
9	L-proline	147-85-3; 609-36-9	0.0597	-1
10	citric acid	77-92-9	0.0542	0
11	potassium carbonate	584-08-7	0.0532	0
12	D-glucose	50-99-7	0.0383	0
13	D-fructose	57-48-7	0.0381	0
14	acetamide	60-35-5	0.0317	3
15	ethylene glycol	107-21-1	0.0293	-1
16	ethyl acetate	141-78-6	0.0280	0
17	glycerol	56-81-5	0.0244	-2
18	hexane	110-54-3	0.0209	0
19	uea	57-13-6	0.0183	0
20	calcium chloride hexahydrate	7774-34-7	0.0129	3
21	alanine	302-72-7	0.0124	3
22	sodium glutamate	6106-04-3	0.0123	-2
23	cyclohexane	110-82-7	0.0117	-2
24	toluene	108-88-3	0.0115	1
25	L-carnitine	541-15-1	0.0115	-3
26	polyethylene glycol	25322-68-3	0.0111	1
27	monoethanolamine hydrochloride	2002-24-6	0.0109	23
28	acetic acid	64-19-7	0.0108	-2
29	ethylammonium chloride	557-66-4	0.0107	-1
30	glycine	56-40-6	0.0106	0
31	lithium perchlorate	7791-03-9	0.0104	1
32	β-alanine	107-95-9	0.0103	-1
33	triethanolamine hydrochloride	637-39-8	0.0103	4
34	malonic acid	141-82-2	0.0102	-1
35	ethylammonium bromide	593-55-5	0.0100	-1
36	magnesium chloride hexahydrate	7791-18-6	0.0100	2
37	dimethylurea	598-94-7	0.0100	4
38	chloroethyltrimethylammonium chloride	999-81-5	0.0100	1
39	1-ethyl-3-methylimidazolium	65039-03-4	0.0098	-3
40	L-menthol	2216-51-5	0.0097	0
41	anisole	100-66-3	0.0096	12
42	lithium nitrate	7790-69-4	0.0096	7
43	dimethylammonium chloride	506-59-2	0.0095	31
44	tetraethylammonium chloride	56-34-8	0.0094	73
45	tetramethylammonium chloride	75-57-0	0.0094	15
46	cyclohexanone	108-94-1	0.0094	16
47	DL-menthol	89-78-1; 1490-04-6	0.0093	-5
48	malic acid or DL-malic acid	617-48-1	0.0093	-5
49	1,2-decanediol	1119-86-4	0.0093	-3
50	tert-butanol	75-65-0	0.0092	-2
51	diethylamine hydrochloride	660-68-4	0.0092	-4

52	caprolactam	105-60-2	0.0092	4
53	n-butanol	71-36-3	0.0091	-9
54	lithium chloride	7447-41-8	0.0091	1
55	zinc nitrate hexahydrate	10196-18-6	0.0091	2
56	furoic acid	88-14-2	0.0091	3
57	lithium hexafluorophosphate	21324-40-3	0.0091	-12
58	1-butyl-3-methylimidazolium bromide	85100-77-2	0.0089	30
59	1-butyl-3-methylimidazolium nitrate	179075-88-8	0.0089	-5
60	choline iodide	2260-50-6	0.0089	-2
61	1-tetradecanol	112-72-1	0.0088	7
62	choline chloride	67-48-1	0.0088	1
63	1-ethyl-3-methylimidazolium chloride	65039-09-0	0.0088	-2
64	tetrapropylammonium bromide	1941-30-6	0.0088	2
65	methyltriphenylphosphonium bromide	1779-49-3	0.0088	-1
66	potassium thiocyanate	333-20-0	0.0088	1
67	1-butyl-3-methylimidazolium hexafluorophosphate	174501-64-5	0.0088	-16
68	lactic acid	79-33-4	0.0087	2
69	guanidine	113-00-8	0.0087	14
70	imidazole	288−32−4	0.0086	1
71	iron(III) chloride hexahydrate	10025-77-1	0.0086	-19
72	N-benzyl-2-hydroxy-N,N-dimethylethanaminium chloride	7221-40-1	0.0086	-7
73	1-butyl-3-methylimidazolium trifluoromethanesulfonate	174899-66-2	0.0085	-4
74	acetylcholine chloride	60-31-1	0.0085	5
75	guanidine hydrochloride	50-01-1	0.0085	12
76	tetraethylammonium bromide	71-91-0	0.0085	34
77	1-butyl-3-methylimidazolium chloride	79917-90-1	0.0085	39
78	zirconyl chloride octahydrate	13520-92-8	0.0085	2
79	decanoic acid	334-48-5	0.0085	5
80	manganese(II) chloride tetrahydrate	13446-34-9	0.0084	-8
81	butyltriphenylphosphonium bromide	1779-51-7	0.0084	1
82	4-methyl-imidazole	822-36-6	0.0084	-4
83	xylenes	1330-20-7	0.0084	-10
84	chromium(III) chloride hexahydrate	10060-12-5	0.0084	6
85	1-ethyl-3-methylimidazolium acetate	143314-17-4	0.0083	-8
86	thymol	89-83-8	0.0083	-10
87	triethylmethylammonium chloride	56375-79-2	0.0083	-6
88	benzyltriethylammonium chloride	56-37-1	0.0082	-13
89	benzyltrimethylammonium chloride	56-93-9	0.0082	22
90	lidocaine	137-58-6	0.0081	-1
91	atropine	51-55-8	0.0081	-6
92	tetraheptylammonium chloride	10247-90-2	0.0080	1
93	pyrazole	288-13-1	0.0080	-2
94	tetraoctylammonium bromide	14866−33−2	0.0079	-2
95	tin(II) chloride	7772-99-8	0.0079	-9
96	guanidine thiocyanate	593-84-0	0.0079	4
97	tetrabutylphosphonium bromide	3115-68-2	0.0078	-3

98	tetrabutylammonium bromide	1643-19-2	0.0078	-3
99	ethyltriphenylphosphonium iodide	4736-60-1	0.0078	-2
100	iron(III) chloride	7705-08-0	0.0078	3
101	1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide	174899-83-3	0.0077	12
102	zinc bromide	7699-45-8	0.0077	0
103	aluminum trichloride	7446-70-0	0.0077	-7
104	tetrabutylphosphonium chloride	2304-30-5	0.0076	3
105	1-butyl-3-methylimidazolium tetrafluoroborate	174501-65-6	0.0076	-7
106	phenol	108-95-2	0.0076	-7
107	1-napthol	90-15-3	0.0076	-6
108	tetrahexylammonium bromide	4328-13-6	0.0075	-3
109	lithium bis[(trifluoromethyl)sulfonyl]imide	90076-65-6	0.0074	-5
110	benzyltributylammonium chloride	23616-79-7	0.0074	-1
111	tetrabutylammonium chloride	1112-67-0	0.0073	-5
112	zinc chloride	7646-85-7	0.0073	-4
113	chlorobenzene	108-90-7	0.0072	-1
114	benzyltriphenylphosphonium chloride	1100-88-5	0.0068	1
115	methyltrioctylammonium chloride	5137-55-3	0.0068	-1
116	dodecanoic acid	143-07-7	0.0063	2
117	tetrahydrofuran	109-99-9	0.0038	-82
118	diethyl ether	60-29-7	0.0014	-89

3.2.Results of TOPSIS ranking of HBD

The results of TOPSIS analysis for HBD including proposed criteria and assessed weight values are presented in **Table 3.** ILs and organic solvents, which are also highlighted with light green and light blue, respectively.

The first rank is mannitol (0.5743), which is characterized by very low toxicities towards all evaluated organisms. Moreover, this sugar is not bioaccumulative and does not decompose to form harmful products and is described only by very few hazard and precautionary statements and no signal wording. The second, the third and the fourth ranks are disaccharides: isomaltose (0.4024), maltose (0.4009), D-sucrose (0.3675) which are non-toxic to *Daphnia magna* and rodents via ingestion, highly biodegradable. Furthermore, they are characterized by high flash point, low value of $logK_{OW}$.

213 After few alternatives with clearly higher values of similarities to ideal solution, there are

214 betaine, m-aminobenzoic acid, serine, L-proline, citric acid and stearic acid with score values

215 0.11-0.23. These amino acids and are favorable due to low toxicity towards at least two of

216 tested organisms, higher flash point, small value of $logK_{OW}$ and average to high percentage of

217 biodegradation. Organic acids also appear in this range and the reason for their high positions

218 is high biodegradability and each of compound has low and average toxicity towards tested

219 organisms.

220 Then, straight-chain alcohols (1,2-propanediol, 1,4-butanediol), sugar alcohols (glycerol,

221 sorbitol), sugars (D-fructose, D-glucose) and their derivatives (glucosamine) are placed in the

222 ranking. They are characterized by high to average toxicity endpoints at least for two

223 organisms, low values of $logK_{OW}$ and acceptable to high biodegradability level for almost all

224 sugar-like HBDs. Between these compounds there are also traditional organic solvents as

225 ethyl acetate, hexane or acetic acid, which are rather green solvents. Gradually, aminoacids

226 appear, which begin the dominance of compounds containing an amino group as amino acids

227 (e.g. alanine), amines (e.g. triethanolamine) and amides (e.g. urea). The majority of these

228 chemicals have small values of $logK_{OW}$, average level of toxicity, pH value close to neutral

229 and are biodegradable. In the next part of the ranking organic acids occur (nicotinic, myristic,

230 L-tartaric, succinic, itaconic), which are characterized by certain greenness issues, related to

231 pH value, toxicity and hazards or precautionary statements.

232 In lower part ranking ionic liquids are located, indicating that they cause more problems than

233 the most of HDB. Imidazolium salts owe their low position due to unfavourable toxicity

234 endpoints, as well as great numbers of hazard and precautionary statements together with

235 hazardous decomposition products. The ranking is closed with diethyl ether that is non-

236 biodegradable and toxic to algae, flammable and very volatile. The majority of inorganic salts

237 with metal cations as magnesium chloride hexahydrate, chromium(III) chloride hexahydrate,

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238 iron(III) chloride, zinc bromide, zinc chloride, zinc chloride hydrate, cobalt(II) chloride

239 hexahydrate are localized in latter parts of HBD ranking.

240 **Table 3.** Results of TOPSIS analysis for HBD and comparison with traditional organic
241 solvents and ionic liquids combined with sensitivity analysis for changes in range of ±10%.
242 Comparison of different toxicity evaluation – marked by colors: green, yellow, red (more
243 details in *Discussion – Comparison of obtained results* section)

No.	Substance name (HBD/organic solvent/IL)	CAS number	Similarity to ideal solution	Ranking difference for ±10% changes
1	mannitol	69-65-8	0.5743	0
2	isomaltose	499-40-1	0.4024	1
3	maltose	6363-53-7	0.4009	-1
4	D-sucrose	57-50-1	0.3675	0
5	betaine	107-43-7	0.2353	2
6	m-aminobenzoic acid	99-05-8	0.2208	-1
7	heptane	142-82-5	0.1979	-1
8	serine	56-45-1	0.1455	1
9	L-proline	147-85-3; 609-36-9	0.1293	-1
10	citric acid	77-92-9	0.1230	0
11	stearic acid	57-11-4	0.1120	0
12	methanol	67-56-1	0.0463	1
13	xylose	58-86-6	0.0447	1
14	methionine	63-68-3	0.0332	-2
15	tricarballylic acid	99-14-9	0.0297	0
16	ethyl acetate	141-78-6	0.0290	1
17	aconitic acid	499-12-7	0.0282	2
18	lanthanum(III) chloride hexahydrate	17272-45-6	0.0251	-2
19	D-glucose	50−99−7	0.0249	-1
20	D-fructose	57−48−7	0.0246	2
21	glucosamine	3416-24-8	0.0242	-1
22	meso-erythritol	149-32-6	0.0230	-1
23	1,2-propanediol	57-55-6	0.0221	0
24	D-sorbitol	50-70-4	0.0214	1
25	α-cyclodextrin	10016-20-3	0.0206	-1
26	cis-9-octadecenoic acid	112-80-1	0.0205	2
27	L-sorbose	87-79-6	0.0203	2
28	1,2-butanediol	26171-83-5	0.0196	-1
29	pentaerythritol	115-77-5	0.0195	-3
30	alanine	302-72-7	0.0189	0
31	hexane	110-54-3	0.0189	1
32	diethylene glycol	111-46-6	0.0182	3
33	raffinose	512-69-6	0.0179	0
34	phytic acid	83-86-3	0.0178	0
35	adonitol	488-81-3	0.0176	5
36	toluene	108-88-3	0.0174	1

14

37	mannose	3458-28-4	0.0173	1
38	calcium chloride hexahydrate	7774-34-7	0.0172	7
39	urea	57-13-6	0.0172	9
40	polyethylene glycol	25322-68-3	0.0170	1
41	D-trehalose	99-20-7	0.0168	2
42	cyclohexane	110-82-7	0.0167	-3
43	acetamide	60-35-5	0.0166	1
44	ethylene glycol	107-21-1	0.0165	-8
45	acetic acid	64-19-7	0.0163	-14
46	D-isosorbide	652-67-5	0.0162	0
47	triethanolamine	102-71-6	0.0161	6
48	DL-glutamic acid	617-65-2	0.0161	-1
49	glycerol	56-81-5	0.0159	0
50	β-alanine	107-95-9	0.0159	10
51	1,4-butanediol	110-63-4	0.0158	0
52	D-galactose	59-23-4	0.0157	0
53	nicotinic acid	59-67-6	0.0156	3
54	arginine	74-79-3	0.0155	-4
55	zinc nitrate hexahydrate	10196-18-6	0.0155	11
56	threonine	72-19-5	0.0155	2
57	1,3-propanediol	504-63-2	0.0155	-3
58	magnesium chloride hexahydrate	7791-18-6	0.0154	4
59	myristic acid	544-63-8	0.0154	2
60	1,6-hexanediol	629-11-8	0.0154	9
61	formamide	75-12-7	0.0154	14
62	DL-aspartic acid	617-45-8	0.0154	15
63	L-tartaric acid	87-69-4	0.0153	11
64	N-methylacetamide	79-16-3	0.0153	-7
65	succinic acid	110-15-6	0.0153	-23
66	malonic acid	141-82-2	0.0152	2
67	itaconic acid	97-65-4	0.0152	4
68	triethylene glycol	112-27-6	0.0152	8
69	L-diethyl tartrate	87-91-2	0.0152	17
70	1,3-dimethylurea	96-31-1	0.0152	10
71	p-hydroxybenzaldehyde	123-08-0	0.0151	-1
72	aluminum trichloride	7446-70-0	0.0151	-9
73	N-methyldiethanolamine	105-59-9	0.0151	0
74	A-L-rhamnose	3615-41-6; 116908-82-8	0.0151	7
75	vanillin	121-33-5	0.0150	-11
76	malic acid or DL-malic acid	617-48-1	0.0150	3
77	suberic acid	505-48-6	0.0150	5
78	1,5-pentanediol	111-29-5	0.0150	-11
79	glutaric acid	110-94-1	0.0150	-1
80	gallic acid	149-91-7	0.0149	-25
81	p-ethylphenol	123-07-9	0.0149	-16
82	adipic acid	124-04-9	0.0149	-23
83	anisole	100-66-3	0.0148	-11

84	phenylacetic acid	103-82-2	0.0148	1
85	propionamide	79-05-0	0.0148	7
86	methylurea	598-50-5	0.0148	-3
87	1-butyl-3-methylimidazolium nitrate	179075-88-8	0.0147	15
88	o-chlorobenzoic acid	118-91-2	0.0147	6
89	glycolic acid	79−14−1	0.0147	-5
90	3-amino-1-propanol	156-87-6	0.0147	15
91	caffeic acid	331-39-5	0.0146	6
92	p-chlorobenzoic acid	74-11-3	0.0146	-1
93	coumarin	91-64-6	0.0146	11
94	pyruvic acid	127-17-3	0.0146	1
95	ammonium thiocyanate	1762-95-4	0.0145	-7
96	tetramethylammonium chloride	75-57-0	0.0145	3
97	DL-lactic acid	50-21-5	0.0145	17
98	DL-mandelic acid	90-64-2; 611-72-3	0.0144	13
99	1-butyl-3-methylimidazolium bromide	85100-77-2	0.0144	9
100	1-butyl-3-methylimidazolium hexafluorophosphate	174501-64-5	0.0144	15
101	chromium(III) chloride hexahydrate	10060-12-5	0.0143	-12
102	allylurea	557-11-9	0.0143	-2
103	p-toluenesulfonic acid	104-15-4	0.0143	3
104	guaiacol	90-05-1	0.0143	-14
105	succinonitrile	110-61-2	0.0143	4
106	p-coumaric acid	7400-08-0	0.0143	12
107	lactic acid	79-33-4	0.0143	-6
108	benzamide	55-21-0	0.0143	4
109	furoic acid	88-14-2	0.0143	-6
110	oxalic acid	144-62-7	0.0143	-23
111	m-chlorobenzoic acid	535-80-8	0.0143	-18
112	DL-menthol	89-78-1; 1490-04-6	0.0142	-14
113	pentaethylenehexamine	4067-16-7	0.0142	13
114	levulinic acid	123−76−2	0.0142	-18
115	cinnamic acid	621-82-9	0.0142	-5
116	copper(II) chloride dihydrate	10125-13-0	0.0141	6
117	p-hydroxybenzoic acid	99-96-7	0.0141	13
118	trans-cinnamic acid	140-10-3	0.0141	-11
119	decan-1-ol	112-30-1	0.0140	-2
120	oxalic acid dihydrate	6153-56-6	0.0140	7
121	2,2,2-trifluoroacetamide	354-38-1	0.0139	-2
122	triazole	288-88-0	0.0139	6
123	1-hexadecanol	36653-82-4	0.0139	13
124	caprolactam	105-60-2	0.0139	22
125	butanoic acid	107-92-6	0.0139	39
126	dodecyl alcohol	112-53-8	0.0139	-2
127	aminomethylpropanol	124-68-5	0.0138	-11
128	octanol	111-87-5	0.0138	-15
129	diethanolamine	111-42-2	0.0138	-8
130	diethylene triamine	111-40-0	0.0138	12

131	cyclohexanone	108-94-1	0.0138	1
132	1-tetradecanol	112-72-1	0.0138	1
133	sulfolane	126-33-0	0.0137	2
134	1-butyl-3-methylimidazolium chloride	79917-90-1	0.0137	5
135	chloroethyltrimethylammonium chloride	999-81-5	0.0137	-15
136	potassium thiocyanate	333-20-0	0.0137	-2
137	1-butyl-3-methylimidazolium trifluoromethanesulfonate	174899-66-2	0.0137	-12
138	α-tocopherol	59-02-9	0.0136	3
139	butyltriphenylphosphonium bromide	1779-51-7	0.0136	9
140	phenylpropanoic acid	501-52-0	0.0136	0
141	ethanolamine	141-43-5	0.0135	-18
142	decanoic acid	334-48-5	0.0135	-11
143	propionic acid	79-09-4	0.0135	1
144	ibuprofen	15687-27-1	0.0135	-7
145	hexanoic acid	142-62-1	0.0134	-2
146	1-ethyl-3-methylimidazolium acetate	143314-17-4	0.0134	17
147	imidazole	288−32−4	0.0134	2
148	m-cresol	108-39-4	0.0133	2
149	hexan-1-ol	111-27-3	0.0133	5
150	lidocaine	137-58-6	0.0133	-21
151	cyclohexanol	108-93-0	0.0133	0
152	p-cresol	106-44-5	0.0133	7
153	tin(II) chloride	7772-99-8	0.0132	-6
154	resorcinol	108-46-3	0.0132	-2
155	10-undecanoic acid	112-38-9	0.0132	0
156	bis(trifluoromethylsulfonyl)imide	82113-65-3	0.0132	-11
157	acetic acid	64−19−7	0.0132	-4
158	iron(III) chloride	7705-08-0	0.0132	-1
159	xylenes	1330-20-7	0.0131	-21
160	octanoic acid	124-07-2	0.0131	-4
161	ethambutol	74-55-5	0.0131	0
162	atropine	51-55-8	0.0130	12
163	benzyltriethylammonium chloride	56-37-1	0.0130	-3
164	tert-butanol	75-65-0	0.0130	-2
165	1-butanol	71-36-3	0.0130	-7
166	furfuryl alcohol	98-00-0	0.0129	3
167	zinc bromide	7699-45-8	0.0129	0
168	valeric acid	109-52-4	0.0129	12
169	salicylic acid	69-72-7	0.0129	4
170	chloroacetic acid	79-11-8	0.0129	-4
171	tetrabutylphosphonium bromide	3115-68-2	0.0129	6
172	1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide	174899-83-3	0.0128	-7
173	1-butyl-3-methylimidazolium tetrafluoroborate	174501-65-6	0.0128	8
174	thiourea	62-56-6	0.0128	-3
175	benzoic acid	65-85-0	0.0127	0
176	thymol	89-83-8	0.0127	0

177	DL-camphor	21368-68-3	0.0127	-5
178	o-cresol	95-48-7	0.0126	-8
179	trifluoromethanesulfonic acid	1493-13-6	0.0125	3
180	p-chlorophenol	106-48-9	0.0125	-1
181	trichloroacetic acid	76-03-9	0.0125	-3
182	zinc chloride	7646-85-7	0.0124	7
183	phenol	108-95-2	0.0123	3
184	acrylic acid	79-10-7	0.0123	7
185	2,3-xylenol	526-75-0	0.0122	-1
186	tetramethyl urea	632-22-4	0.0121	-3
187	2,6-dimethylphenol	576-26-1	0.0120	-2
188	cobalt(II) chloride hexahydrate	7791-13-1	0.0120	5
189	diazabicyclo[5.4.0]undec-7-ene	6674-22-2	0.0120	3
190	zinc chloride hydrate	29604-34-0	0.0120	-3
191	1-propanol	71-23-8	0.0119	3
192	tetraethylenepentamine	112-57-2	0.0118	-2
193	chlorobenzene	108-90-7	0.0116	-5
194	ethylenediamine	100-36-7	0.0115	-26
195	DL-borneol	507-70-0	0.0111	0
196	perfluorodecanoic acid	335-76-2	0.0102	0
197	dodecanoic acid	143-07-7	0.0096	1
198	formic acid	64-18-6	0.0085	-1
199	2,2,2-trifluoroethanol	75-89-8	0.0065	0
200	tetrahydrofuran	109-99-9	0.0046	0
201	hexafluoroisopropanol	920-66-1	0.0026	0
202	diethyl ether	60-29-7	0.0018	0

3.3. Results of TOPSIS ranking of DES

The results of DES mixtures evaluation including proposed criteria and modeling of their combined greenness, calculated with equation 1, are presented in **Table 4**. ILs and organic solvents are included in the analysis and they are marked light green and light blue, respectively.

The best alternative among selected set is citric acid:D-sucrose (1:3), followed by the citric acid:D-maltose (4:1) and glycerol:L-proline:D-sucrose (9:4:1). On the other hand, last three DES are represented by the iron(III) chloride hexahydrate:ethylene glycol (2:1), choline chloride:zinc chloride (1:1.2) and tetrabutylammonium bromide:formic acid (1:1). In general, places in the ranking for DES mixtures are similar to those obtained for separate analyses of HBA and HBD. For instance, citric acid as HBA and D-maltose as HBD have high positions,

18

256   their mixture is also in the top. Tetrabutylammonium bromide and formic acid take lower

257   positions in the rankings of HBA and HBD, then their mixture is also unsatisfactorily ranked.

258   In case of DES with choline chloride as a HBA (choline chloride:1,2-propanediol, choline

259   chloride:ethylene glycol, choline chloride:1,4-butanediol), the ranking positions decrease with

260   changing ratios towards the growing presence of hydrogen bond donors in the compounds.

261   Based on values of similarities to ideal solution of HBA and HBD, DES consisting of any

262   combination of constituents, can be assessed in this way. Traditional organic solvents are

263   found along the entire list of compounds with similar order as in case of individual assessment

264   of HBA and HBD. Location of DES next to solvents of rather green character (alcohols, esters

265   or aliphatic hydrocarbons) indicates that DES are also not so problematic. On the other hand,

266   ILs are in the second half of the list.

267   **Table 3.** Results of environmental assessment for DES mixtures using toxicological model
268   and TOPSIS analysis and comparison with traditional organic solvents and ionic liquids

	DES/IL/traditional organic solvents name	Combined greenness effect
1	citric acid:D-sucrose (1:3)	0.2855
2	heptane	0.1730
3	citric acid:D-maltose (4:1)	0.1201
4	methanol	0.0944
5	glycerol:L-proline:D-sucrose (9:4:1)	0.0766
6	betaine:1,2-butanediol (1:3)	0.0574
7	betaine:ethylene glycol (1:4)	0.0474
8	ethyl acetate	0.0283
9	glycerol:xylitol:D-fructose (3:3:3)	0.0218
10	potassium carbonate:glycerol (1:7)	0.0205
11	hexane	0.0198
12	choline chloride:1,2-propanediol (1:4)	0.0194
13	choline chloride:1,2-butanediol (1:5)	0.0178
14	choline chloride:1,2-propanediol (1:2)	0.0175
15	choline chloride:polyethylene glycol (1:20)	0.0166
16	zirconyl chloride octahydrate:urea (1:5)	0.0157
17	choline chloride:1,2-propanediol (1:1)	0.0154
18	lactic acid:1,2-propanediol (1:1)	0.0154
19	choline chloride:1,4-butanediol (1:5)	0.0146
20	choline chloride:ethylene glycol (1:3)	0.0146
21	toluene	0.0144

22	choline chloride:urea (1:2)	0.0142
23	cyclohexane	0.0141
24	choline chloride:ethylene glycol (1:2)	0.0138
25	glycine:lactic acid (1:5)	0.0136
26	acetic acid	0.0135
27	choline chloride:glycerol (1:2)	0.0134
28	choline chloride:1,4-butanediol (1:2)	0.0133
29	choline chloride:p-toluenesulfonic acid (1:4)	0.0132
30	L-menthol:acetic acid (1:1)	0.0130
31	choline chloride:glycerol (1:1)	0.0123
32	choline chloride:lactic acid (1:2)	0.0123
33	choline chloride:levulinic acid (1:2)	0.0122
34	anisole	0.0122
35	choline chloride:malic acid (1:1)	0.0119
36	1-butyl-3-methylimidazolium nitrate	0.0118
37	1-butyl-3-methylimidazolium bromide	0.0116
38	choline chloride:phenol (1:4)	0.0116
39	choline chloride:tin(II) chloride (1:2)	0.0116
40	cyclohexanone	0.0115
41	1-butyl-3-methylimidazolium hexafluorophosphate	0.0115
42	choline chloride:oxalic acid (1:1)	0.0115
43	lactic acid:D-glucose (5:1)	0.0114
44	tetrabutylammonium chloride:decanoic acid (1:2)	0.0113
45	lactic acid:D-fructose (5:1)	0.0113
46	methyltrioctylammonium chloride:decanoic acid (1:2)	0.0112
47	tert-butanol	0.0111
48	1-butyl-3-methylimidazolium chloride	0.0111
49	iron(III) chloride hexahydrate:ethylene glycol (2:1)	0.0111
50	1-butyl-3-methylimidazolium trifluoromethanesulfonate	0.0111
51	n-butanol	0.0110
52	1-ethyl-3-methylimidazolium acetate	0.0108
53	choline chloride:zinc chloride (1:1.2)	0.0107
54	xylenes	0.0107
55	tetrabutylphosphonium bromide	0.0103
56	1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide	0.0103
57	1-butyl-3-methylimidazolium tetrafluoroborate	0.0102
58	phenol	0.0099
59	chlorobenzene	0.0094
60	tetrabutylammonium bromide:formic acid (1:1)	0.0081
61	tetrahydrofuran	0.0042
62	diethyl ether	0.0016

269

270 *3.4.Results of sensitivity analysis and comprehensive ranking*

271 Sensitivity analysis allows to assess the reliability of conducted analysis based on reliability

272 of input data. Results of sensitivity analysis rankings are presented in **Tables 2** and **3.** In both

273 cases, the changes of input data within ±10% of original values are insignificant, as they do

274 not affect the ranking. Therefore, the ranking results can be considered as reliable. There are

275 some shifts in HDB positions in the middle of ranking results, where the differences in values

276 of similarities to ideal solution are very low.

277 ### *3.5. Discussion - Comparison of obtained results*

278 HBD taken into evaluation are chemicals of a variety of characteristics, because they belong

279 to different groups of compounds. However, it can be seen that in the first part sugars alcohols

280 and straight-chain alcohols appear, they gradually pass through sugars and amides to organic

281 acids. These groups do not create a clear boundaries but interpenetrate gradually increasing

282 the predominance. Poor ecotoxicological profile of organic acids as a HBD is also reported by

283 Radošević et al. in *in vitro* study of cholinium-based IL and DES towards fish cell line [26].

284   Similar results are presented by Halder et al. [27] in *in silico* modeling study of HDB

285 toxicity. They divide evaluated chemicals into three groups, based on their toxicity level -

286 low, intermediate and high. Their findings are marked in **Table 3** with green (low toxicity),

287 yellow (moderate toxicity) and red (high toxicity) colours, respectively. The reason for some

288 differences in comparison to this study may be fact, that Hadler's et al. assessment involves

289 only toxicity criteria measured for different organisms (11 different mammalian cell lines -

290 and 12 different microbial organisms) what results in poor coverage of this study assessment

291 criteria. Hadler et al. also evaluate some HBA as preliminary studies, as they claim more

292 experimental data is needed: choline chloride, menthol, N,N-diethylethanol ammonium

293 chloride (DEAC), and methyltriphenyl phosphonium bromide (MTPB). MTPB and DEAC,

294 are found to impart toxicity towards the most of the organisms, while N,N-diethylethanol

295 ammonium chloride followed by choline chloride were found to be less toxic DES

296 components. However, it is difficult to compare both results due to fact that our evaluation

297 includes only choline chloride and MTPB. Nevertheless, ChCl and MTPB are ranked on

298 45th and 63rd place in the HBA list (out of 125 positions). The majority of evaluated HBA and

299 HBD that are metalorganic compounds are ranked lower. The reason is that in our assessment

300 toxicities are the most significant criteria and metal-containing DES are generally toxic to

301 different organisms [28].

302 Perales et al. (2017) evaluated toxicity endpoints in combination with some physicochemical

303 data (volatility and boiling point, flashpoint, biodegradability, bioconcentration factor, etc.)

304 using the Environmental Health and Safety Approach (EHSA) used for identification of risks

305 related to the environment and the human health) [29]. Using both types of information, each

306 chemical compound receives a score for the categories health, safety and environment, then

307 the best candidates considered as least dangerous for a short exposure time may be found.

308 Herein, glycerol (rank 17 in HBA ranking) - derived solvents as 3-ethoxy-1,2-propanediol,

309 3-butoxy-1,2-propanediol   and   1,3-diethoxy-2-propanol   are   the   most   favourable

310 (1,2-propanediol ranked 23 and 1,3-propanediol ranked 57 but ethoxy derivatives are not

311 included in ranking).

312 DES mixtures may show some effects between the DES constituents (HBA and HBD) – the

313 interactions, such as synergism and antagonism. More often synergistic effects are described

314 due greater toxicity level of a mixture than toxicity level of its constituents. However, these

315 two effects occur, which has also been discussed in the literature [30, 31]. In our study the

316 synergistic or antagonistic effects are neglected, because still little is known on these types of

317 interactions. In other words, only independent actions of the HBA and HBD are considered.

318 We also conduct evaluation of DES applications where authors claim their solvent is green

319 and these results are summarized in **Table S17**. The number of publications that describe

22

320 choline chloride-based DES application is significantly higher than the others (30 out of 46

321 examples). Then, betaine, citric acid, glycerol and lactic acid as HBA are of great interest,

322 probably due to the natural origin. NADES generally belong to plant-based primary

323 metabolites, i.e. organic acids, sugars, alcohols, amines and amino acids. Often they are

324 considered as those with lower environmental impact and low toxicity than other DES. It has

325 been reported in many papers, for instance in comparison of cytotoxicity profile of choline

326 chloride:fructose and choline chloride:glucose as NADES and N,N-diethyl ethanolammonium

327 chloride:triethylene glycol as DES towards different hepatic cell lines [32].

328 The problem with DES greenness assessment is that reports usually refer to physicochemical

329 properties, such as density, viscosity, electrical conductivity, surface tension, solvatochromic

330 parameters or refractive index [33]. Unfortunately, there is still lack of data on toxicological

331 and environmental fate parameters (biodegradability, octanol-water partition coefficients,

332 etc.). In this area DES as poorly characterized as ILs. The comparison of results on the

333 cytotoxic effects on Channel Catfish Ovary cell line indicate that the cytotoxicity of

334 cholinium-based IL and DES is generally lower than that of imidazolium- and pyridinium-

335 based IL [26]. It is an implication that cholinium-based DES are promising and beneficial

336 class of solvents in terms of ecotoxicological impact. However, it only refers to this specific

337 type of DES and single of species of tested organism. Our results show that selected ionic

338 liquids, mainly imidazolium salts, are placed in second part of list. Moreover, some choline-

339 based DES as choline chloride with oxalic acid (1:1) or zinc chloride (1:1.2) are ranked

340 between ILs.

341 All of the above-mentioned issues explain that it is not possible to unambiguously resolve the

342 dispute, which of the solvents are more green - ILs or DES. DES properties depend on the

343 specific case, criteria taken into evaluation, including tested organisms, etc. Therefore, the

344 terms as non-toxic, biodegradable, environmentally friendly must be carefully used. Each of

23

345   the mixtures should be tested and evaluated individually. Naming the solvent green because it

346   belongs to DES group is an abuse. The interpretation of data gathered in Table S18 shows that

347   only very few of authors claims about the greenness of the used DES mixture is presented

348   without justification. This is a significant improvement in a reference to greenness evaluation

349   of ionic liquids [20]. In case of DES solvents, more authors explain the use of the term

350   "green" extensively, giving solid justifications.

351   **4. Conclusions**

352   In this study, the TOPSIS algorithm combined with calculation of additive effects is applied

353   for DES components and DES ranking by their greenness. The comprehensive assessments

354   that includes simultaneously safety, biodegradability and toxicological criteria indicate that

355   DES formed by mixing sugars alcohols, straight-chain alcohol, sugars and amides may be

356   promising green solvents, in contrary to those that include metal ions and organic acids.

357   Those ranked first are more environmentally advantageous than some of the selected

358   imidazolium ionic liquids, which makes them a potential alternative solvents for many

359   applications. However, according to our results, due insufficient characteristics, especially

360   concerning toxicity level, a general flat assertion of DES mixtures as a green solvent is

361   inappropriate. Moreover, lack of data of some physiochemical properties may limit the

362   number of fields for they usage in chemical practice or industry. Therefore, additional studies

363   measuring environmental impact are required to understand the nature of DES mixtures

364   including properties and biological effects between their components.

365   Although the described approach provides general information about solvent greenness and

366   allows for ease comparison of variety of solvents in terms of greenness performance, the

367   proposed assessment procedure may be only treated as a screening tool for preliminary

368   selection of a green alternative, due to simplified model of additivity that is used for DES

369 mixtures calculations. More targeted evaluation for specific purpose is also possible, but need

370 providing more newly obtained data (variety of properties and environmental fate of

371 particular chemical) that may be easily incorporated into the performed algorithm.

372 **Conflict of interests**

373 There are no conflicts of interests to declare.

374 **Supplementary Information**

375 Supplementary Information 1 – Summary of different authors claims on DES being green,

376 numerical transformation involved criteria and alternative substances (objects) taken into

377 consideration in case of lack of data.

378 Supplementary Information 2 – Gathered data concerning physiochemical and environmental

379 properties as a evaluated criteria of DES components and their mixtures.

380 **References:**

[1] Collins, T. J.; Gordon-Wylie, S. W.; Bartos, M. J.; Horwitz, C. P.; Woomer, C. G.; Williams, S. A.; Patterson, R. E.; Vuocolo, L. D.; Paterno, S. A.; Strazisar, S. A.; Peraino, D. K. Green chemistry: *Macmillan encyclopedia of chemistry*, **1997**, *2*, 691-697.

[2] Anastas, P. T.; Warner, J. C. Theory and Practice. In *Green Chemistry*; Oxford University Press: New York, 1998.

[3] Anastas, P. T.; Warner, J. C. Principles of green chemistry. *Green chemistry: Theory and practice*, 1998, 29-56.

[4] Smith, E. L.; Abbott, A. P.; Ryder, K. S. Deep eutectic solvents (DESs) and their applications. *Chem. Rev.*, **2014**, *114*(21), 11060-11082, DOI 10.1021/cr300162p.

[5] García, G.; Aparicio, S.; Ullah, R.; Atilhan, M. Deep eutectic solvents: physicochemical properties and gas separation applications. *Energ. Fuel.*, **2015**, *29*(4), 2616-2644, DOI 10.1021/ef5028873.

[6] Zhou, H.; Shen, Y.; Lv, P.; Wang, J.; Fan, J. Degradation of 1-butyl-3-methylimidazolium chloride ionic liquid by ultrasound and zero-valent iron/activated carbon. *Sep. Purif. Technol.*, **2013**, *104*, 208-213, DOI 10.1016/j.seppur.2012.11.029.

[7] Taubert, J.; Keswani, M.; Raghavan, S. Post-etch residue removal using choline chloride–malonic acid deep eutectic solvent (DES). *Microelectron. Eng.*, **2013**, *102*, 81-86, DOI 10.1016/j.mee.2011.11.014.

[8] Leron, R. B.; Li M. H. Solubility of carbon dioxide in a choline chloride–ethylene glycol based deep eutectic solvent. *Thermochim. Acta*, 2013, *551*, 14-19, DOI 10.1016/j.tca.2012.09.041.

[9] Morrison, H. G.; Sun, C. C.; Neervannan, S. Characterization of thermal behavior of deep eutectic solvents and their potential as drug solubilization vehicles. *Int. J. Pharm.*, **2009**, *378*(1-2), 136-139, DOI 10.1016/j.ijpharm.2009.05.039.

[10] Singh, B. S.; Lobo, H. R.; Pinjari, D. V.; Jarag, K. J.; Pandit, A. B.; Shankarling, G. S. Ultrasound and deep eutectic solvent (DES): a novel blend of techniques for rapid and energy efficient synthesis of oxazoles. *Ultrason. Sonochem.*, **2013**, *20*(1), 287-293, DOI 10.1016/j.ultsonch.2012.06.003.

[11] Durand, E.; Lecomte, J.; Baréa, B.; Piombo, G.; Dubreucq, E.; Villeneuve, P. Evaluation of deep eutectic solvents as new media for Candida antarctica B lipase catalyzed reactions. *Process Biochem.*, **2012**, *47*(12), 2081-2089, DOI 10.1016/j.procbio.2012.07.027.

[12] Radošević, K.; Bubalo, M. C.; Srček, V. G.; Grgas, D.; Dragičević, T. L.; Redovniković, I. R. Evaluation of toxicity and biodegradability of choline chloride based deep eutectic solvents. *Ecotox. Environ. Saf.*, **2015**, *112*, 46-53, DOI 10.1016/j.ecoenv.2014.09.034.

[13] Hayyan, M.; Mbous, Y. P.; Looi, C. Y.; Wong, W. F.; Hayyan, A.; Salleh, Z.; Mohd-Ali, O. Natural deep eutectic solvents: cytotoxic profile. *SpringerPlus*, **2016**, *5*(1), 913, DOI 10.1186/s40064-016-2575-9.

[14] Wen, Q.; Chen, J. X.; Tang, Y. L.; Wang, J.; Yang, Z. Assessing the toxicity and biodegradability of deep eutectic solvents. *Chemosphere*, **2015**, *132*, 63-69, DOI 10.1016/j.chemosphere.2015.02.061.

[15] Tobiszewski, M.; Tsakovski, S.; Simeonov, V.; Namieśnik, J.; Pena-Pereira, F. A solvent selection guide based on chemometrics and multicriteria decision analysis. *Green Chem.*, **2015**, *17*(10), 4773-4785, DOI 10.1039/c5gc01615k.

[16] Tobiszewski, M.; Namieśnik, J.; Pena-Pereira, F. Environmental risk-based ranking of solvents using the combination of a multimedia model and multi-criteria decision analysis. *Green Chem.*, **2017**, *19*(4), 1034-1042, DOI 10.1039/c6gc03424a.

[17] Tobiszewski, M.; Namieśnik, J.; Pena-Pereira, F. A derivatisation agent selection guide. *Green Chem.*, **2017**, *19*(24), 5911-5922, DOI 10.1039/c7gc03108d.

[18] Cinelli, M.; Coles, S. R.; Nadagouda, M. N.; Błaszczyński, J.; Słowiński, R.; Varma, R. S.; Kirwan, K. A green chemistry-based classification model for the synthesis of silver nanoparticles. *Green Chem.*, **2015**, *17*(5), 2825-2839, DOI 10.1039/c4gc02088j.

[19] Naidu, S.; Sawhney, R.; Li, X. A methodology for evaluation and selection of nanoparticle manufacturing processes based on sustainability metrics. *Environ. Sci. Technol.*, 2008, *42*(17), 6697-6702, DOI 10.1021/es703030r.

[20] Bystrzanowska, M.; Pena-Pereira, F.; Marcinkowski, Ł.; Tobiszewski, M. How green are ionic liquids?–A multicriteria decision analysis approach. *Ecotox. Environ. Saf.*, **2019**, *174*, 455-458, DOI 10.1016/j.ecoenv.2019.03.014.

[21] Alder, C. M.; Hayler, J. D.; Henderson, R. K.; Redman, A. M.; Shukla, L.; Shuster, L. E.; Sneddon, H. F. Updating and further expanding GSK's solvent sustainability guide. *Green Chem.*, **2016**, *18*(13), 3879-3890, DOI 10.1039/c6gc00611f.

[22] Hwang, C.L.; Yoon, K.P. *Multiple Attribute Decision Making: Methods and Applications*, Springer-Verlag, New York, USA, 1981, DOI 10.1007/978-3-642-48318-9_3.

[23] Yoon, K. A reconciliation among discrete compromise solutions. *J. Oper. Res. Soc.*, **1987**, *38*(3), 277-286, DOI 10.1057/jors.1987.44.

[24] Hwang, C. L.; Lai, Y. J.; Liu, T. Y. A new approach for multiple objective decision making. *Comput. Oper. Res.*, **1993**, *20*(8), 889-899, DOI 10.1016/0305-0548(93)90109-v.

[25] Scher S. (2013). Scenihr (2012) Opinion on the toxicity and assessment of chemical mixtures. *Toxicity and Assessment of Chemical Mixtures. Available: http://ec. europa. eu/health/scientific_committees/consultations/public_consultations/sc her_consultation_06_en. htm*. (accessed May 3, 2020)

[26] Radošević, K.; Železnjak, J.; Bubalo, M. C.; Redovniković, I. R.; Slivac, I.; Srček, V. G. Comparative in vitro study of cholinium-based ionic liquids and deep eutectic solvents toward fish cell line. *Ecotox. Environ. Saf.*, **2016**, *131*, 30-36, DOI 10.1016/j.ecoenv.2016.05.005.

[27] Halder, A. K.; Cordeiro, M. N. D. Probing the environmental toxicity of deep eutectic solvents and their components: An in silico modeling approach. *ACS Sustain. Chem. Eng.*, **2019**, *7*(12), 10649-10660, DOI 10.1021/acssuschemeng.9b01306.

[28] Marcus Y., Properties of Deep Eutectic Solvents. In *Deep Eutectic Solvents* (pp. 45-110), Springer, Cham, 2019, DOI 10.1007/978-3-030-00608-2_3.

[29] Perales, E.; García, C. B.; Lomba, L.; García, J. I.; Pires, E.; Sancho, M. C., Navarro, E.; Giner, B. Comparative ecotoxicity study of glycerol-biobased solvents. *Environ. Chem.*, **2017**, *14*(6), 370-377, DOI 10.1071/en17082.

[30] Macário, I. P.; Ventura, S. P.; Pereira, J. L.; Gonçalves, A. M.; Coutinho, J. A.; Gonçalves, F. J. The antagonist and synergist potential of cholinium-based deep eutectic solvents. *Ecotox. Environ. Saf.*, **2018**, *165*, 597-602, DOI 10.1016/j.ecoenv.2018.09.027.

[31] Macário, I. P.; Jesus, F.; Pereira, J. L.; Ventura, S. P.; Gonçalves, A. M.; Coutinho, J. A.; Gonçalves, F. J. Unraveling the ecotoxicity of deep eutectic solvents using the mixture toxicity theory. *Chemosphere*, **2018**, *212*, 890-897, DOI 10.1016/j.chemosphere.2018.08.153.

[32] Mbous, Y. P.; Hayyan, M.; Wong, W. F.; Looi, C. Y.; Hashim, M. A. Unraveling the cytotoxicity and metabolic pathways of binary natural deep eutectic solvent systems. *Sci. Rep.*, **2017**, *7*(1), 1-14, DOI 10.1038/srep41257.

[33] Abbott, A. P.; Al-Barzinjy, A. A.; Abbott, P. D.; Frisch, G.; Harris, R. C.; Hartley, J.; Ryder, K. S. Speciation, physical and electrolytic properties of eutectic mixtures based on

CrCl $_3\cdot$ 6H $_2$ O and urea. *Phys. Chem. Chem. Phys.*, **2014**, *16*(19), 9047-9055, DOI 10.1039/c4cp00057a.