

1 Diethyl carbonate as green extraction solvent for chlorophenols determination with dispersive  
2 liquid-liquid microextraction.

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8

9 ABSTRACT

10 The principles of green analytical chemistry indicate that the search for greener organic  
11 solvents for extraction applications is crucial. In this study diethyl carbonate (DEC) is proved  
12 to be green solvent, as it is relatively nontoxic, obtainable from renewable resources and it is  
13 biodegradable. Here it is applied as extraction solvent for chlorophenols determination in  
14 water samples with dispersive liquid-liquid microextraction. The multiobjective optimization  
15 for 7 chlorophenols is done with design of experiment combined with Derringers desirability  
16 function. The optimized parameters on extraction step are 300  $\mu\text{L}$  of DEC volume, 0.5 mL of  
17 methanol, 8 mL of water sample and 7.5% of inorganic salt addition. The values of LOQ are  
18 0.01 and 0.3  $\mu\text{g L}^{-1}$ , CVs are between 7.1-17.3 % for 7 CPs. In this study DEC is proved to be  
19 promising, green solvent, applicable in analytical extractions.

20

21 Keywords: DLLME; chlorophenols; green analytical chemistry; green solvent;  
22 microextraction

23

24

## 25 1. Introduction

26 One of the aims of green analytical chemistry is introduction of greener solvents to analytical  
27 practice.<sup>1</sup> Supercritical fluids application requires costly and relatively nonstandard apparatus.

28 The application of ionic liquids also requires nonstandard solutions as their lack of volatility  
29 makes them incompatible with gas chromatography. Therefore, there is strong need to  
30 develop solventless analytical methodologies<sup>2</sup> or methodologies based on extraction with  
31 greener organic solvents.<sup>3</sup>

32 The definition of green solvent is not straightforward. The three main aspects that need to be  
33 considered are: health issues in case of exposure, environmental concerns in case of their  
34 release and safety during their storage, handling and application.<sup>4</sup> Within each aspect of  
35 greenness there are few assessment criteria to be considered and because of unavailability of  
36 data the assessment is even harder to perform. There are systems that help to select the  
37 solvent within green chemistry framework, that are known as solvent selection guides. They  
38 combine many greenness criteria into easy to interpret output.<sup>5</sup> The closest homologue to  
39 diethyl carbonate – dimethyl carbonate is assessed as green solvent, causing only some  
40 problems in the safety area.<sup>6</sup> Diethyl carbonate (DEC) is a linear carbonate ester that is  
41 classified as organic carbonate.<sup>7</sup> The application of this colorless, transparent liquid mainly  
42 involves being an alternative fuel or fuel additive due to its high oxygen content.<sup>8,9,10</sup> It  
43 influences reduction CO<sub>2</sub> and particulates emissions from engines. Many studies describe  
44 DEC application as an electrolyte for lithium ion batteries.<sup>11,12</sup> It could also be an excellent  
45 solvent, that is why it is widely used in pharmaceutical products, fertilizer, pesticide and dyes  
46 manufacture.<sup>13,14</sup> Organic carbonates are characterized by many outstanding properties, for  
47 instance polarity, low toxicity, low bio-accumulation or relatively high biodegradability.

48 Dispersive liquid-liquid microextraction (DLLME) is a liquid sample preparation technique  
49 that applies the mixture of two organic solvents to perform the extraction rapidly.<sup>15,16</sup> The first



50 solvent plays the role of extractant and has to be immiscible with water. The first extraction  
51 solvents applied in DLLME were chlorinated solvents and other non green organic solvents.  
52 The development of DLLME mode applying solvents lighter than water allowed to apply  
53 more organic solvents and these solvents are of greener nature.<sup>17</sup> The examples of such  
54 solvents can be hexane, methyl tert-butyl ether or toluene. As these solvents are indicated by  
55 green solvent selection guides as problematic the search for green extraction solvents is still  
56 urgent problem. The second solvent applied in DLLME is dispersive solvent, which has to be  
57 miscible with both aqueous sample and extraction solvent. In analytical practice the most  
58 commonly applied dispersive solvents are methanol, acetone and acetonitrile,<sup>18</sup> two first are  
59 considered to be green and the third one is claimed to be problematic.

60 Chlorophenols (CPs) are group of environmental pollutants that are toxic and hardly undergo  
61 degradation processes in both aerobic and anaerobic conditions.<sup>19</sup> They are used as wood  
62 preservation agents and are substrates in pesticides production processes. They can be formed  
63 during water disinfection process or during pulp bleaching. Therefore, their occurrence is  
64 detected in surface and groundwaters.<sup>20</sup>

65 The aim of the study is to show the applicability of diethyl carbonate as analytical extraction  
66 solvent. There is a strong need to search for new, green solvents to be applied in analytical  
67 chemistry. In this study the applicability is shown at the example of chlorophenols  
68 determination with dispersive liquid-liquid microextraction.

## 70 2. Materials and Methods

### 71 2.1. Reagents

72 The analytical standards of: 2,4-dichlorophenol (2,4-DCP), 2,6-dichlorophenol (2,6-DCP),  
73 2,4,6-trichlorophenol (2,4,6-TCP), 2,3,4-trichlorophenol (2,3,4-TCP), 2,3,4,5-  
74 tetrachlorophenol (2,3,4,5-TeCP), 2,3,4,6-tetrachlorophenol (2,3,4,6-TeCP),



75 pentachlorophenol (PCP). Diethyl carbonate (anhydrous, 99%) and acetic anhydride used for  
76 derivatization were purchased from Sigma-Aldrich (Germany). 2,4,6-tribromophenol (2,4,6-  
77 TBP) was used as an internal standard and  $K_2SO_4$  were also purchased from Sigma-Aldrich  
78 (Germany).

79 Stock standard solution of CPs was prepared in methanol (1, 2 or 5 mL), with appropriate  
80 concentration levels and stored in a refrigerator in the dark. All aqueous solutions were  
81 prepared with appropriate amount of ultrapure water obtained from a Mili-Q<sup>®</sup> apparatus  
82 (Merck KGaA, Germany).

83

84

## 85 2.2. Instrumentation

86 Centrifugation of samples was carried out by centrifuge supplied from Eppendorf SG  
87 (Germany). Chromatographic analysis of CPs was performed with GC8000 Top (USA),  
88 electron capture detector ECD850 (TermoQuest, Italy) and on-column injector. Separation  
89 and identification of chlorophenols were obtained by applying the DB-5 column (30m x  
90 0.32mm x 0.25 $\mu$ m) (Agilent Technolgies, USA) and Guard Column (6 m x 0.32mm) (Zebron  
91 Phenomenex, USA). The initial temperature was 130 °C (held for 8 min) and followed by  
92 heating to 250 °C at rate 15 °C min<sup>-1</sup> held for 1 min. Hydrogen, as carrier gas, was supplied  
93 by hydrogen generator (HG2600, Claind Italy) and inlet pressure of 130 kPa was applied.  
94 Nitrogen (purity 99,999%) was used as make-up gas for ECD and detector operated at 330 °C.

95

## 96 2.3. Dispersive liquid-liquid microextraction

97 In order to perform the simultaneous DLLME and derivatization, in the optimized conditions  
98 8 mL of an aqueous solution was transferred into 10-mL glass test tube (OMNILAB,  
99 Germany) with screw cap and PTFE/silicone membrane (Agilent Technologies, USA) and



100 sample was treated with mixture of 0.5 mL of methanol and 0.3 mL of diethyl carbonate that  
 101 contained 50  $\mu\text{L}$  of acetic anhydride. Such mixture was rapidly injected into aqueous sample  
 102 with using 2-mL syringe (Polfa, Poland). A cloudy solution was formed and centrifugation for  
 103 2 min at 3200 rpm was applied to separate extraction phase from sample. A 2  $\mu\text{L}$  of extract  
 104 was carefully taken from the surface of the sample in the vial with a 10- $\mu\text{L}$  microsyringe  
 105 (Hamilton, USA) and injected into GC for analysis. For easy recovery of this light extraction  
 106 solvent from the surface of sample, specially designed sampler was applied.<sup>21</sup>  
 107 To clean the glassware after centrifugation it was rinsed with tap water and washed with soap.  
 108 Then it was soaked overnight in 5%  $\text{HNO}_3$  solution, rinsed very thoroughly with deionized  
 109 water and placed in an ultrasonic bath (Bandelin Sonorex, Germany) for ~15 minutes. Then  
 110 the glassware was oven-dried at 120 °C in furnace (Poland).

#### 112 2.4.Experimental design

113 Central composite design is used to optimize the volumes of sample, extraction and dispersive  
 114 solvents of DLLME applied for isolation and enrichment of CPs. It is designed for these  
 115 three factors as it is shown in the table 1. The type dispersive solvent optimised in previous  
 116 step in this study, while the extraction solvent is assumed to be diethyl carbonate.

118 Table 1. Factors and their values applied in experimental central composite plan

|       | -1.68 | -1  | 0    | 1   | 1.68 | units         |
|-------|-------|-----|------|-----|------|---------------|
| Vextr | 216   | 250 | 300  | 350 | 384  | $\mu\text{L}$ |
| Vdisp | 0.33  | 0.5 | 0.75 | 1   | 1.17 | mL            |
| Vsamp | 2.64  | 4   | 6    | 8   | 9.36 | mL            |

119  
 120 The structure of central design plan is presented in the table 2. All the calculations to obtain  
 121 central composite design plan and figure of response surface are drawn with Statistica  
 122 software.

123 Table 2. Design matrix for central composite plan

| No experiment | V extr | V disp | V sampl |
|---------------|--------|--------|---------|
| 4             | -1     | 1      | 1       |
| 14            | 0      | 0      | 1.68    |
| 6             | 1      | -1     | 1       |
| 1             | -1     | -1     | -1      |
| 9             | -1.68  | 0      | 0       |
| 2             | -1     | -1     | 1       |
| 12            | 0      | 1.68   | 0       |
| 15 C          | 0      | 0      | 0       |
| 18 C          | 0      | 0      | 0       |
| 8             | 1      | 1      | 1       |
| 3             | -1     | 1      | -1      |
| 13            | 0      | 0      | -1.68   |
| 17            | 0      | 0      | 0       |
| 7             | 1      | 1      | -1      |
| 16 C          | 0      | 0      | 0       |
| 5             | 1      | -1     | -1      |
| 10            | 1.68   | 0      | 0       |
| 19C           | 0      | 0      | 0       |
| 11            | 0      | -1.68  | 0       |

124

## 125 2.5.Desirability Function

126 To perform multi-objective optimization usually a desirability function was applied. In this  
127 case multi-objectiveness is expressed as selection of optimal parameters for all 7 analytes at  
128 the same time. Together with completely desirable response ( $d = 1$ ) and completely  
129 undesirable response ( $d = 0$ ), for every optimization criterion (peak area to be maximized)  
130 desirability function equation are defined. In this case linear functions between desirable and  
131 undesirable response are selected. The desirable response ( $d = 1$ ) is above 90 % of the range  
132 between minimum and maximum values of response for given analyte. The undesirable  
133 response ( $d = 0$ ) is below 10 % of the range between minimum and maximum values of  
134 response for given analyte. Then functions for every optimization goal are combined into a  
135 single score called global desirability ( $D$ ) as it is presented with equation 1. If any of  
136 optimized analytes has undesirable response, then  $D = 0$ . Application of desirability function  
137 approach allows for giving different relative importance of criteria ( $r_1, r_2 \dots r_n$ ) but in this  
138 study equal importance for all analytes is assigned.

139 
$$D = (d_1^{r_1} \times d_2^{r_2} \times \dots \times d_n^{r_n})^{\frac{1}{\sum r_i}} \quad (1)$$

140 Global desirability function is input data to draw response surface for optimization of sample  
141 volume and dispersive and extraction solvents and obtain their optimized values.

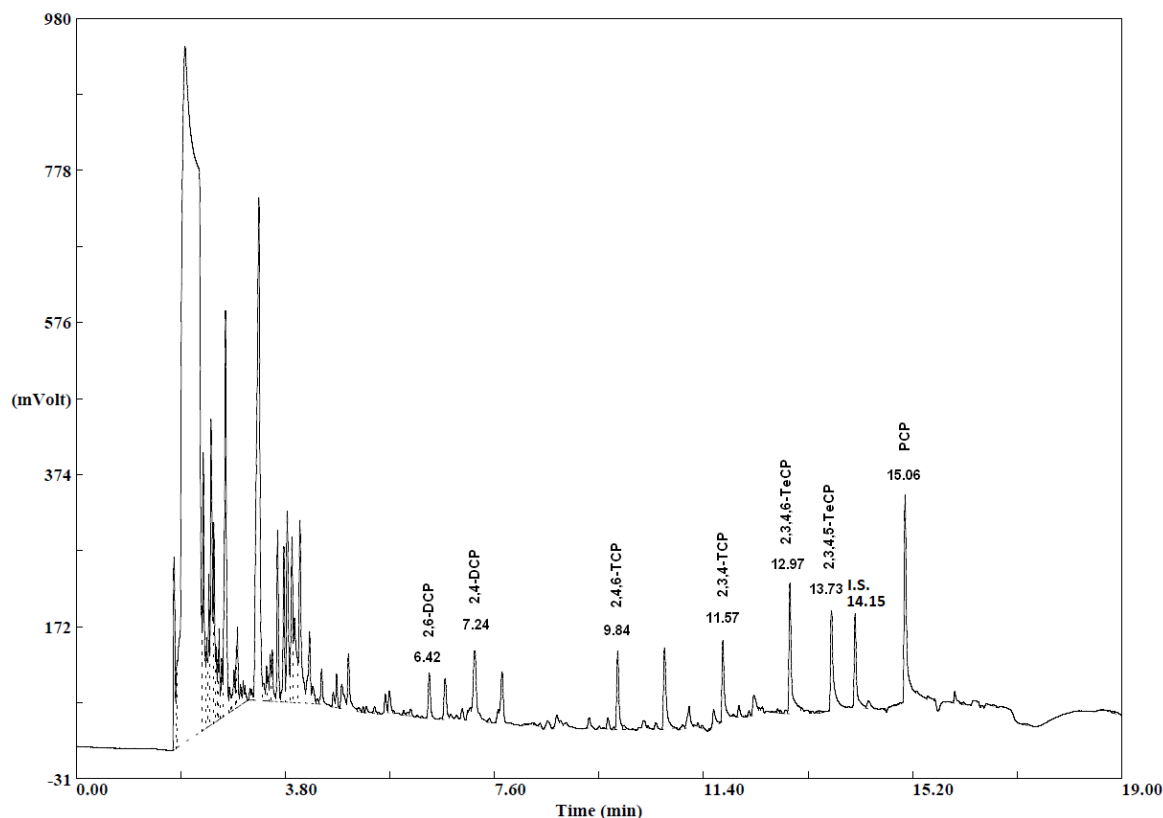
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### 143 3. Results and Discussion

144

#### 145 3.1. Chromatographic separation

146 The chromatographic separation was aimed at minimization of separation time and separation  
147 of analytes peaks from solvent peak and impurities that elute mainly at the beginning of the  
148 chromatographic run. As some impurities elute in the region of retention times of analytes, the  
149 optimization of chromatographic separation was also aimed at assurance that none of analytes  
150 co-elutes with impurities. Less ghost peaks are obtained indeed during blank sample analysis  
151 in the after 5th minute and slightly less peaks before this time. These impurities may originate  
152 from derivatization reagent and/or side reactions and from dispersive solvent.



153

154 Figure 1. Chromatogram showing separation of 7 CPs and I.S. – 2,4,6-TBP. The  
 155 concentrations are  $1\mu\text{g L}^{-1}$  (except for I.S. and PCP  $0.5\mu\text{g L}^{-1}$ ) spiked in ultrapure water.  
 156

157

158

### 3.2. Selection of dispersive solvent

159

159 The selection of dispersive solvent was based on comparison of means of peak areas for the

160 analysis of standard solutions with the concentration of  $1\mu\text{g L}^{-1}$  ( $0.5\mu\text{g L}^{-1}$  for PCP). The

161 volume of disperser solvent was 1 mL, while the volume of diethyl carbonate was 0.3 mL

162 while the volume of sample was 8 mL. Acetone gave moderate chromatographic response but

163 the precision ( $n = 3$ ) expressed as coefficient of variance (CV) was between 18.49 and 69.56

164 %. The application of acetonitrile gave poor chromatographic response but CVs were between

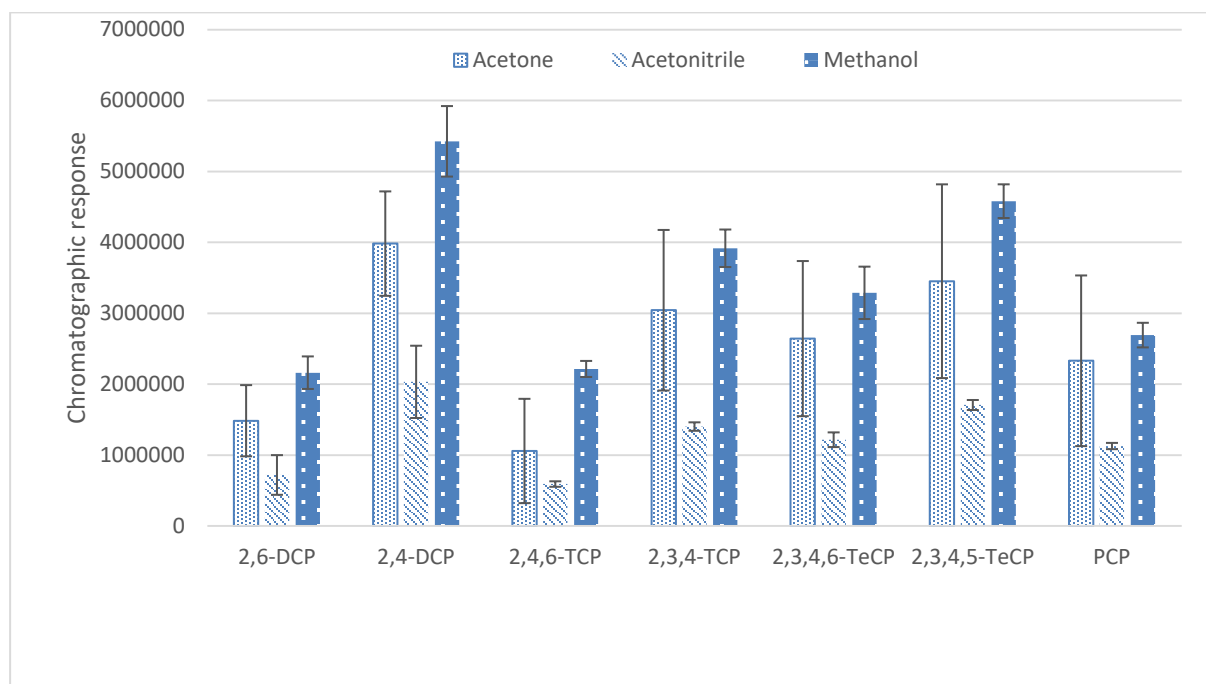
165 3.92 and 8.52 for all CPs except for dichlorophenols, for 2,6-DCP it was 38.90 % and for 2,4-

166 DCP it was 25.07 %. Methanol gave the best response and the values of CV were between

167 5.11 and 11.24 % for all analytes. Methanol was selected as the most appropriate dispersive



168 solvent and the procedure was optimized for diethyl carbonate and methanol as extraction and  
 169 dispersive solvents. The results are presented in the figure 2.



170  
 171 Figure 2. The chromatographic responses (n = 3) and standard deviations for different  
 172 dispersive solvents.

### 173 3.3. Optimization of sample, extraction solvent and dispersive solvent volumes

174  
 175 Above-described central composite design was applied to obtain the optimal volumes. The  
 176 concentration of analytes in the samples used for optimization was  $1 \mu\text{g L}^{-1}$ . The values of  
 177 global desirability for given extraction conditions are presented in the table 3. The worst  
 178 conditions are for experimental point 13 with very low volume of sample. For this point 4 out  
 179 of 7 analytes gave undesirable response.

180  
 181  
 182 Table 3. The extraction conditions with their values of calculated global desirability.

| No | V Extr. [ $\mu\text{L}$ ] | V Disp. [mL] | V Sam. [mL] | D     |
|----|---------------------------|--------------|-------------|-------|
| 4  | 250                       | 1            | 8           | 0.634 |
| 14 | 300                       | 0.75         | 9.36        | 0.894 |
| 6  | 350                       | 0.5          | 8           | 0.523 |
| 1  | 250                       | 0.5          | 4           | 0.747 |

|      |     |      |      |       |
|------|-----|------|------|-------|
| 9    | 216 | 0.75 | 6    | 0     |
| 2    | 250 | 0.5  | 8    | 0.980 |
| 12   | 300 | 1.17 | 6    | 0.915 |
| 15 C | 300 | 0.75 | 6    | 0.936 |
| 18 C | 300 | 0.75 | 6    | 0.898 |
| 8    | 350 | 1    | 8    | 0.927 |
| 3    | 250 | 1    | 4    | 0.623 |
| 13   | 300 | 0.75 | 2.64 | 0     |
| 17   | 300 | 0.75 | 6    | 0.788 |
| 7    | 350 | 1    | 4    | 0     |
| 16 C | 300 | 0.75 | 6    | 0.462 |
| 5    | 350 | 0.5  | 4    | 0.209 |
| 10   | 384 | 0.75 | 6    | 0.231 |
| 19C  | 300 | 0.75 | 6    | 0.778 |
| 11   | 300 | 0.33 | 6    | 0.610 |

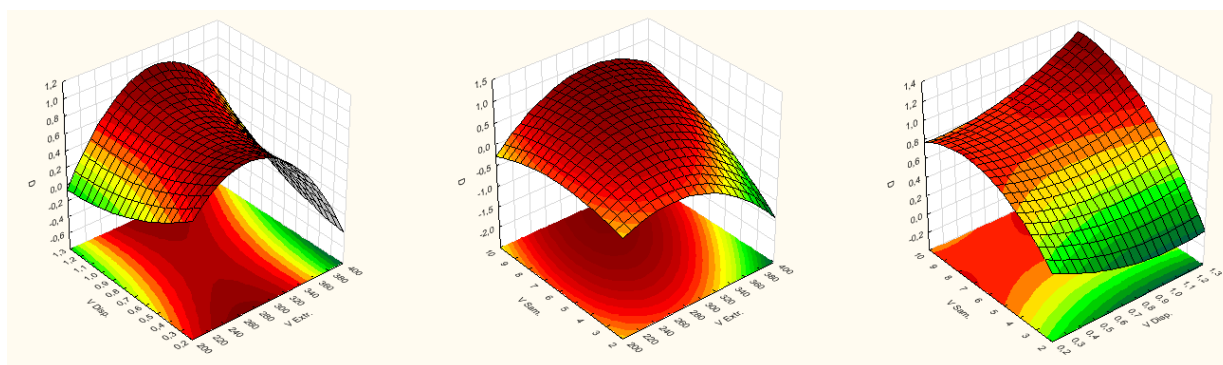
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184 Based on global desirability calculated for all experimental design conditions response

185 surface was drawn and it is presented in figure 3. The response is not desirable at low volume

186 of sample and for extreme values of extraction solvent volume. The volume of dispersive

187 solvent does not influence much the desirability of response.



188

189 Figure 3. The response surface for central composition design. Global desirability for 7 CPs.

190

191 The polynomial equation for the response function is following:

192  $D = -2.94424 + 0.0337895 * V_{extr} - 0.000079424 * V_{extr}^2 - 3.25828 * V_{disp} + 0.489155 * V_{disp}^2 -$

193  $0.0950929 * V_{sam} - 0.0202707 * V_{sam}^2 + 0.0066808 * V_{extr} * V_{disp} + 0.00124701 * V_{extr} *$

194  $V_{sam} + 0.0983837 * V_{disp} * V_{sam}$

195

196 Critical values that are obtained with solving of response surface equation are  $V_{extr.} = 297$   
197  $\mu\text{L}$ ;  $V_{disp.} = 0.51 \text{ mL}$ ;  $V_{sam.} = 7.99 \text{ mL}$ . Global desirability value obtained by the solution  
198 is  $D = 0.869$ . As a result,  $300 \mu\text{L}$  of DEC,  $0.5 \text{ mL}$  of methanol and  $8 \text{ mL}$  of water sample  
199 were selected as optimal parameters.

200

#### 201 3.4. Salting out effect

202 To investigate the effect of the salt on the extraction efficiency  $\text{K}_2\text{SO}_4$  was used. No salt  
203 added, 5 %, 7.5 % and 10 % of salt were considered as procedural options. There was no  
204 influence on the extraction efficiency however the addition of salt resulted in much easier  
205 separation of phases during centrifugation phase. Without adding of the salt dispersed system  
206 partially remained despite performing centrifugation. As a result the volume of extraction  
207 phase collected at the surface of the sample was so small that it was inconvenient or  
208 sometimes impossible to collect extract for analysis. It was decided to apply addition of salt  
209 resulting in 7.5% of salt concentration.

210

#### 211 3.5. Metrological parameters

212 Limit of detection (LOD) was estimated on the basis of signal to noise ratio. The value of  
213 LOD was for  $S/N = 3$ . Limit of quantitation (LOQ) was calculated according to the relation  
214  $\text{LOQ} = 3 * \text{LOD}$ . Coefficient of variance (CV) was determined at the level of concentration  $1$   
215  $\mu\text{g L}^{-1}$  for  $n = 5$  repetitions. Linearity range was investigated up to  $5 \mu\text{g L}^{-1}$  as these are  
216 maximal concentrations of CPs in environmental waters. The results of determination of  
217 metrological parameters of the procedure are presented in table 4.

218

219

Table 4. Basic validation parameters of the procedure

| Analyte | LOD [ $\mu\text{g L}^{-1}$ ] | LOQ [ $\mu\text{g L}^{-1}$ ] | CV [%] | Linearity range [ $\mu\text{g L}^{-1}$ ] |
|---------|------------------------------|------------------------------|--------|--|
| 2,6-DCP | 0.05                         | 0.15                         | 17.3   | LOQ – 5                                  |
| 2,4-DCP | 0.1                          | 0.3                          | 9.0    | LOQ – 5                                  |



|              |        |       |      |         |
|--------------|--------|-------|------|---------|
| 2,4,6-TCP    | 0.01   | 0.03  | 13.6 | LOQ – 5 |
| 2,3,4-TCP    | 0.01   | 0.03  | 10.5 | LOQ – 5 |
| 2,3,4,6-TeCP | 0.005  | 0.015 | 7.2  | LOQ – 5 |
| 2,3,4,5-TeCP | 0.005  | 0.015 | 9.9  | LOQ – 5 |
| PCP          | 0.0033 | 0.01  | 7.1  | LOQ – 5 |

220

### 221 3.6. Comparison with other procedures

222 Table 5 shows the comparison of LODs, CVs and extraction solvents with previously reported  
 223 analytical procedures for CPs determination, based on solvent extraction. Almost all given  
 224 procedures incorporate solvents that are commonly considered as less green ones, some of  
 225 them causing environmental problems. Other sample preparation techniques based on solvent  
 226 extraction are hollow fiber liquid phase microextraction (HF-LPME) and single drop  
 227 microextraction (SDME). The values of LODs, obtained with other than LC based  
 228 procedures, are in similar range as in this study. On the other hand, other procedures are  
 229 characterized by better precisions. This is probably due to the fact that we have selected lower  
 230 concentrations to determine CVs, but such concentration is typical for CPs present in the  
 231 environmental waters. Our methodology is characterized by poor precision for 2,6-DCP,  
 232 neglecting this analyte, the poorest precision, expressed as CV, would be 13.6 %. The detailed  
 233 investigation on extraction solvents greenness indicates that DEC can only be compared with  
 234 butyl acetate, that is recommended by solvent selection guides. Additionally, procedure with  
 235 its application presented by Bagheri et al.<sup>24</sup> is characterized by equally good and satisfactory  
 236 value of LOD. Thus, option is another available option for CPs determination in water  
 237 samples baring in mind green analytical chemistry approach.

238

239 Table 5. CPs determination in water samples - comparison with other procedures based on  
 240 solvent extraction.

| Procedure     | Analytes | Extraction solvent | LOD [ $\mu\text{g L}^{-1}$ ] | CV [%] | EF | Reference     |
|---------------|----------|--------------------|------------------------------|--------|----|---------------|
| HF-LPME-GC-MS | 4-CP     | toluene            | 3.2                          | 10     | 30 | <sup>22</sup> |



|                |  |                   |              |        |          |            |
|----------------|--|-------------------|--------------|--------|----------|------------|
| HF-LPME-GC-MS  | 2,4-DCP, PCP   | toluene           | 0.015        | < 13   | 123, 136 | 23         |
| SDME-GC-MS     | 2-CP, 4-CP, 2,4-DCP, 2,6-DCP   | butyl acetate     | 0.01 – 0.021 | < 10   | 71-134   | 24         |
| SDME-LC-UV-VIS | 2-CP, 2,4-DCP, 2,6-DCP   | methyl cyanide    | 6 – 23       | < 9    | -        | 25         |
| DLLME-GC-ECD   | 2-CP, 3-CP, 4-CP, 2,3-DCP, 2,4-DCP, 2,5-DCP, 2,6-DCP, 3,4-DCP, 3,5-DCP, 2,3,4-TCP, 2,4,5-TCP, 2,3,5-TCP, 2,3,6-TCP, 3,4,5-TCP, 2,3,4,5-TeCP, 2,3,4,6-TeCP, 2,3,5,6-TeCP, PCP | chlorobenzene     | 0.001 – 1    | < 5    | 287-906  | 26         |
| DLLME-GC-ECD   | 2,4-DCP, 2,6-DCP, 2,4,6-TCP, 2,3,4-TCP, 2,3,4,5-TeCP, 2,3,4,6-TeCP, PCP  | diethyl carbonate | 0.0033 – 0.1 | < 17.3 | ?        | This study |

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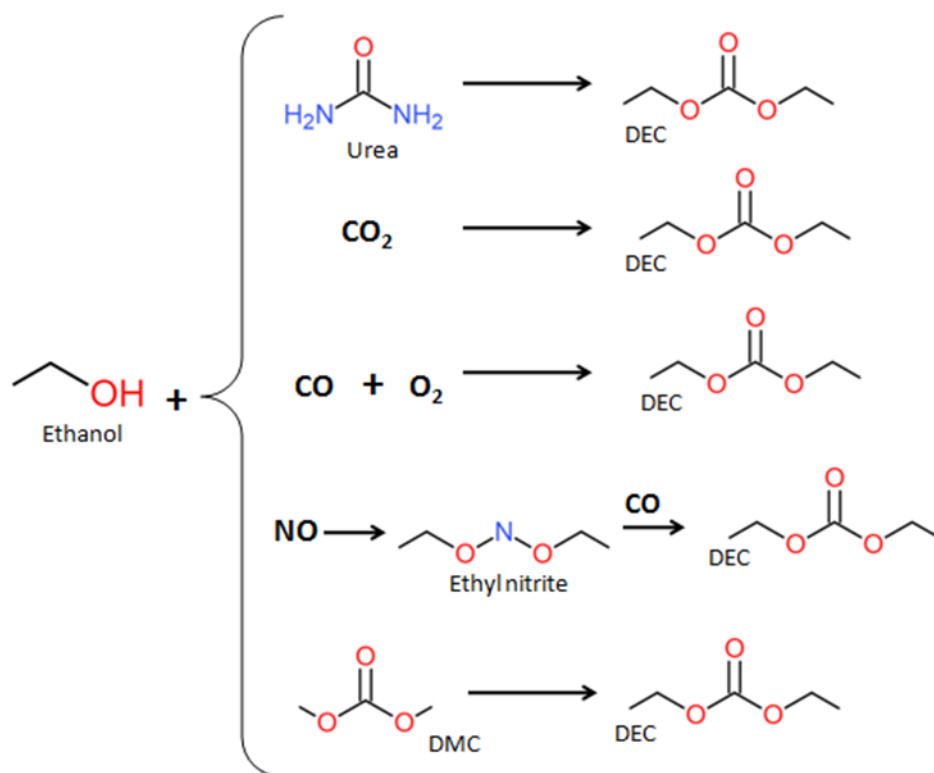
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### 243 3.7. Comparison of DEC greenness with other solvents

244 The most commonly used methods of greenness evaluation applied to solvents are EHS  
 245 (environmental, health and safety) assessment and life-cycle assessment (LCA).<sup>27,28</sup> The first  
 246 one is a screening method that aims to identify potential hazards of chemicals. The second  
 247 one is used for an assessment of emissions to the environment as well as resource use over the  
 248 full life-cycle of a solvent, including the production, the use, potential recycling, and the  
 249 disposal.

250 Beginning with LCA, the oldest known method for DEC production is phosgenation of  
 251 ethanol,<sup>29</sup> however it is undesired way of synthesis, due to toxic substrate. Since phosgene  
 252 route of organic carbonates has been abandoned, non-phosgene synthesis have been  
 253 developed. They include among others oxidative carbonylation of ethanol, transesterification of  
 254 carbonate, alcoholysis of urea, ethanolysis of CO<sub>2</sub> and decarbonylation of diethyl oxalate.  
 255 Some of them are summarized in Figure 4.<sup>30</sup> And it can be noted that there is a significant

256 growth of publications concerning DEC production via non-phosgene routes since 2009 year.  
 257 Recently, the most frequently used method of DEC production is synthesis from urea due to  
 258 its cheap and non-toxic raw materials. Considering potential recycling, and the disposal of  
 259 diethyl carbonate, it also seems to be relatively non-hazardous. When it is released into  
 260 environment, it decomposes to benign CO<sub>2</sub> and ethanol.<sup>31</sup>



261  
 262 Fig. 4. Possible non-phosgene methods for DEC production<sup>30</sup>

263  
 264 Another method of assessment is EHS data interpretation. This information mainly relies on  
 265 physical and chemical properties, toxicity, environmental and safety aspects of the substances  
 266 to be assessed. The simplest way of dealing with data is looking through the Material Safety  
 267 Data Sheets. Solvents that could be considered a green should be characterized by relatively  
 268 high flash point to prevent potential fire ignition. The boiling point ought to be between 70-  
 269 139 °C, because low temperatures may generate vapours and high ones may influence  
 270 negatively on easy solvent recycling and complicates the work-up and downstream unit

271 operations, for instance drying.<sup>6</sup> Also octanol-water partition coefficient should not exceed  
272 value  $\log K_{ow} > 3$ , which denotes high potential of bioaccumulation.<sup>32,33</sup> The best score for  
273 biodegradation in 28-days test would be 100% as for example hexane shows, however level  
274 of biodegradability of DEC is satisfactory. According to International Agency for Research  
275 on Cancer (IARC) diethyl carbonate is not classified as carcinogenic or potentially  
276 carcinogenic substance, in contrary to formerly used benzene and chloroform.

277 The first researches on DEC toxicity were carried out in 1966<sup>34</sup> and then 1978.<sup>35</sup> In the first  
278 one, 100-week study with rats consuming water containing up to 0.3% DEC was presented.  
279 No effect on survival, growth, clinical chemistry, hematology and pathology of the rats was  
280 found. Later long-term toxicity of DEC in mice was studied. During 83 weeks drinking water  
281 with 0-1000 ppm DEC was given to group of 48 male and 50 female mice. Also no effect on  
282 mortality, rate of body-weight gain or the incidence of histopathological findings, including  
283 tumors was found. The latest assessment on DEC was conducted in 2018 by  
284 Kumar Das et al.<sup>36</sup> and the potential of DEC as a green solvent and the fact that there is not  
285 much available information about it was emphasized.

286 An attempt to make a comprehensive solvents evaluation in the point of sustainable  
287 development (including DEC) for medicine chemistry was also made by GlaxoSmithKline  
288 (GSK).<sup>37,38</sup> Solvent selection guide (SSG) is the system to provide concise and useful  
289 information for scientists and engineers to help with green solvent selection decision  
290 problems. The SSG includes the most commonly used solvents within GSK operations. Its  
291 approach is based on relative ranking of associated environmental, health and safety issues for  
292 each solvent. Solvents assessment is prepared based on collected data including different  
293 areas of interest (categories), for instance incineration, recycling, biotreatment, VOC  
294 emissions, impact on aquatic and air, health hazard, exposure potential, flammability,  
295 reactivity, LCA. More details of their descriptions may be found in SSG.<sup>38</sup> Based on SSG



296 results, diethyl carbonate is classified as a green solvent. Moreover DEC is one of the  
 297 recommended solvent alternatives. In reference to mostly used solvents, DEC is characterized  
 298 by good score values within each category.  
 299 DEC is less commonly used solvent than traditional extraction solvents such as toluene,  
 300 chloroform, etc. Further research on its properties and especially toxicity endpoints is needed.  
 301 However, according to results from studies carried out so far, DEC could be considered as a  
 302 potentially green solvent. The comparison of DEC with other extraction solvents, presented in  
 303 table 6 shows that it is less toxic, biodegradable and relatively safe in handling.

304 Table 6. Comparison of parameters of DEC with other extraction solvents

| Solvent                          | MW<br>[g/mol] | F.P.<br>[°C]         | B.P.<br>[°C] | Log<br>K <sub>ow</sub> | Biodegradability<br>in % (28 day<br>test) | LD50 towards<br>rats administered<br>orally [mg kg <sup>-1</sup> ] | Toxicity<br>towards<br><i>Daphnia</i><br><i>Magna</i> EC50<br>[mg/L] |
|----------------------------------|---------------|----------------------|--------------|------------------------|---|--|--|
| Diethyl<br>carbonate<br>105-58-8 | 118.13        | 29                   | 127          | 1.21                   | 75  | 4876   | 103 mg/L/48h   |
| Hexane<br>110-54-3               | 86.18         | -25                  | 69           | 4                      | 100                                       | 25000  | 3.8 mg/L/24 h  |
| Chloroform<br>67-66-3            | 119.38        | Does<br>not<br>flash | 60           | 1.97                   | 0   | 695  | 79 mg/L/24 h   |
| Toluene<br>108-88-3              | 92.14         | 4                    | 110.5        | 2.65                   | 86  | > 5000   | 6 mg/L/48 h  |
| Diethyl ether<br>60-29-7         | 74.12         | -40                  | 34.6         | 1.05                   | 7   | 1215   | 165 mg/L/24 h  |

#### 305 4. Conclusions

306 Diethyl carbonate is greener option to be applied as extraction analytical solvent than  
 307 commonly used organic solvents. It can be obtained from renewable resources and is safer in  
 308 use and much less toxic than the most of organic solvents. It is characterized by low toxicity  
 309 and high biodegradability. DEC was applied as extraction solvent for determination of CPs in  
 310 water samples by means of DLLME. Methanol was used as dispersive solvent and optimal  
 311 extraction parameters were selected. Estimated values of LODs and CVs were comparable  
 312 with other analytical procedures for CPs determination.  
 313



314 The results of the study show that diethyl carbonate is promising green, extraction solvent for  
315 analytical chemistry. It has a potential to be applied for other extraction purposes and is worth  
316 future investigations.

317

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