

# Selection of Derivatisation Agents for Chlorophenols Determination with Multicriteria Decision Analysis

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## ABSTRACT

The paper shows very systematic method of selection of derivatisation agents for a given group of analytes. In this study 8 derivatisation agents are assessed for their capability to derivatise 8 chlorophenols. Multicriteria decision analysis is used to combine many objectives of derivatisation agents selection into single, easy to be interpreted numerical value. Three basic analyses were performed to obtain rankings with the aims to assess derivatisation reaction, chromatographic separation of derivatised analytes and greenness of derivatisation agents. The first assessment showed acetic anhydride to be the most favourable alternative, the second one indicated N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) - chlorotrimethylsilane (TMCS) mixture to give the best separation and the third proved heptafluorobutyrylimidazole (HFBI) to be the greenest agent. Fourth, comprehensive assessment showed BSTFA:TMCS to have the best total performance. Multicriteria decision

26 analysis can be successfully applied in analytical procedure multi-objective optimisation, at  
27 the stage of derivatisation agent selection.

28

29 Keywords: method optimization; TOPSIS; multicriteria decision making; gas  
30 chromatography; derivatisation; chlorophenols

31

## 32 **1. Introduction**

33 The eighth principle of Green Chemistry states that unnecessary derivatisation should be  
34 minimised or avoided whenever possible since it requires additional reagents and can generate  
35 wastes [1]. The term derivatisation is referred to chemical reactions performed to obtain  
36 analyte derivatives that can be isolated, separated and detected more easily than target  
37 compounds. Even though avoiding derivatisation reactions is advisable, the use of simple  
38 microreactions is eminently justified when enables, for instance, the sensitive determination  
39 of analytes of concern present at ultra-trace levels in environmental compartments.  
40 Notwithstanding, the chemicals used in derivatisation reactions can significantly differ in  
41 terms of environmental, health and safety (EHS) concerns, so this information should be  
42 carefully considered for appropriate selection of derivatisation agents [2].

43 Chlorophenols (CPs) are toxic, mutagenic and carcinogenic substances that have been used in  
44 the chemical and pharmaceutical industry and agriculture. As a consequence of their  
45 widespread use and recalcitrance to biodegradation, chlorinated phenols are widespread  
46 pollutants in the environment. Apart from their release to the environment as a consequence  
47 of their anthropogenic uses, CPs can also be formed during water disinfection (by  
48 chlorination) and biodegradation of herbicides such as 2,4-dichlorophenoxyacetic acid or  
49 2,4,5-trichlorophenoxyacetic acid [3–5]. Several CPs have been classified as priority  
50 pollutants by the US Environmental Protection Agency [6], and a maximum admissible



51 concentration has been set by the European Union at  $0.5 \mu\text{g L}^{-1}$  for total phenols and  
52  $0.1 \mu\text{g L}^{-1}$  for individual compounds in water, respectively [7]. Thus, a number of  
53 methodologies have been described in the literature for determination of CPs involving  
54 mainly chromatographic techniques with different detectors [7]. CPs can be determined by  
55 liquid chromatography, although they show low resolution and can be affected by the sample  
56 matrix. Alternatively, CPs can be determined by gas chromatography. In this case,  
57 derivatisation of CPs prior to their determination is recommended in order to increase  
58 analytes' volatility, to improve the chromatographic characteristics of analytes and/or to  
59 increase the detector sensitivity. Different derivatisation reactions have been reported in the  
60 literature for CPs, mainly based on acylation and silylation reactions [8–10]. Metrological  
61 aspects are usually considered when choosing derivatisation agents for CPs, whereas the EHS  
62 issues of derivatising agents are commonly overlooked.

63 Choosing the best solution is sometimes a difficult decision problem, especially if we take  
64 into consideration many alternatives, many criteria, even contradictory ones, or there is also a  
65 need to involve decision makers' preferences. In these cases making a proper, objective  
66 decision may be impossible. Therefore, it may be a good idea to use some aid of Multicriteria  
67 Decision Analysis (MCDA). MCDA is a group of methods based on mathematical algorithms  
68 which are able to formalise decision problem. They allow to analyse the problem with a  
69 reference to various points of view, i.e. technical aspects, quality, environmental aspects,  
70 security and safety, delays, ethics, economy [11]. Additionally, these methods provide  
71 assessment which includes the decision makers' preferences by giving a proper weight values  
72 to each criteria. The most popular MCDA methods are TOPSIS (Technique for Order of  
73 Preference by Similarity to Ideal Solution), AHP (Analytic Hierarchy Process),  
74 PROMETHEE (Preference Ranking Organization Method for Enrichment Evaluations),  
75 ELECTRE (Elimination and Choice Expressing the Reality), and MAUT (Multi-Attribute



76 Utility Theory). MCDA methods are successfully used to solve complex problems in many  
77 areas such as management, business, engineering, science and other areas of human activity  
78 [12]. Utilization of MCDA methods in chemical sciences is rather scarce, however there are  
79 some studies where they are used. For instance, TOPSIS and AHP have been used in  
80 chemicals selection (solvents and derivatisation agents) [2,13–15], whereas AHP, TOPSIS  
81 and PROMETHEE have been used for chemical processes selection (analytical procedures,  
82 chemical processes, and process conditions) [16–23]. The basic concept of TOPSIS is  
83 selection of alternative, which have the shortest distance from the positive ideal solution in a  
84 geometrical sense. This tool assumes that each attribute has a monotonically increasing or  
85 decreasing utility. Therefore its algorithm provides to allocate the ideal and negative ideal  
86 solutions, what finally leads to obtain the ranking of alternatives and choice of the best option.  
87 It should be highlighted that there is a great deal of variation in the experimental conditions  
88 used for determination of CPs after derivatisation. Thus, aspects such as the type of sample,  
89 the concentration levels of CPs, or even if the analytical method of choice involves  
90 simultaneous or sequential derivatisation and extraction steps, can influence to a large extent  
91 the experimental conditions required to perform derivatisation reactions.

92 The mixture of N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) and chlorotrimethylsilane  
93 (TMCS) (99:1) has been used in several works for derivatisation of CPs. For instance,  
94 BSTFA:TMCS was used to derivatise 50 phenolic compounds (including 14 CPs) present in  
95 wastewater [24]. The sample preparation procedure was based on solid-phase extraction and  
96 derivatisation was performed with 100  $\mu\text{L}$  of BSTFA:TMCS at 60  $^{\circ}\text{C}$  for 2 h. In another  
97 study, 50  $\mu\text{L}$  of CPs solution was derivatised with 50  $\mu\text{L}$  of this mixture in 15 s at room  
98 temperature [25]. This study was aimed at the optimisation of electrospray ionization in mass  
99 spectrometry and sample preparation methods were not involved. Another study showed that  
100 BSTFA:TMCS derivatisation mixture can be preferentially applied in more polar solvents like



101 acetone than in dichloromethane or hexane due to the slower reaction rates in nonpolar  
102 solvents that in fact are commonly used for analytical extractions [26].

103 Acetic anhydride is one of the most commonly applied derivatisation agents to derivatise CPs.  
104 It has been used to simultaneously derivatise and extract CPs by dispersive liquid-liquid  
105 microextraction [27]. Thus, 50  $\mu\text{L}$  of acetic anhydride was added to the sample together with  
106 a mixture of 0.5 mL of acetone (disperser solvent) and 10  $\mu\text{L}$  of chlorobenzene (extractant  
107 solvent). The simultaneous extraction/derivatisation procedure was performed in a short time  
108 (<3 min) and presumably at room temperature [27]. Acetic anhydride was also used as  
109 derivatising agent in a simultaneous ultrasound assisted dispersive liquid-liquid  
110 microextraction/aqueous acetylation under basic conditions derivatisation procedure to the  
111 simultaneous determination of CPs and chloroanisoles in wine samples. The optimised  
112 procedure involved a volume of 65  $\mu\text{L}$  of acetic anhydride per sample together with 180  $\mu\text{L}$   
113 of tetrachloroethene (extractant solvent) at 60  $^{\circ}\text{C}$  [28]. In another procedure described for  
114 determination of cork-taint compounds by GC-MS, 200  $\mu\text{L}$  of acetic anhydride was applied  
115 for derivatisation of CPs under basic conditions (pH 11) and, subsequently, extraction of  
116 acetylated analytes was performed by dispersive liquid-liquid microextraction [29]. Acetic  
117 anhydride was also used to derivatise phenolic compounds in water samples directly. A  
118 volume of 400  $\mu\text{L}$  of derivatisation agent, 55  $^{\circ}\text{C}$  of reaction temperature and 20 min were  
119 established as optimal conditions [30].

120 As regards BSTFA, the fourth choice in the ranking, it is said that poor resolution is obtained  
121 if excess of reagent is not removed [31]. In case of our experiments no excess of BSTFA was  
122 removed, so it may potentially deteriorate its performance in terms of peak areas and overall  
123 chromatogram quality. BSTFA has been used for derivatisation of CPs present in urine  
124 samples at 80  $^{\circ}\text{C}$  for 1 h after enzymatic hydrolysis and solid-phase extraction [32]. Another  
125 procedure involved the application of BSTFA for the simultaneous derivatisation (silylation)



126 and dispersive liquid-liquid microextraction with a derivatisation/extraction time of ~5 min at  
127 the room temperature [33].

128 All above-mentioned examples show that derivatisation reactions are applied in a variety of  
129 ways in combination with different sample preparation techniques. What is more, it is hard to  
130 select one optimal set of conditions of performing derivatisation reaction. The aim of the  
131 study is to perform a comprehensive assessment of derivatisation agents that are applied for  
132 CPs determination. Based on different groups of criteria, namely derivatisation reaction  
133 effectiveness, quality of chromatogram and greenness of the agents themselves, it is aimed to  
134 create derivatisation agents rankings. This study represents the first work aimed at the  
135 selection of derivatisation agents for CPs determination from several alternatives through a  
136 more holistic approach. The selection procedure is not sample preparation type specific.

137

## 138 **2. Materials and Methods**

### 139 **2.1. Chemicals**

140 The analytical standards were purchased from Sigma Aldrich (Germany): 2,4-dichlorophenol  
141 (2,4-DCP), 2,6-dichlorophenol (2,6-DCP), 2,4,6-trichlorophenol (2,4,6- TCP), 2,3,4-  
142 trichlorophenol (2,3,4-TCP), 2,4,5-trichlorophenol (2,4,5-TCP), 2,3,4,5-tetrachlorophenol  
143 (2,3,4,5-TeCP), 2,3,4,6-tetrachlorophenol (2,3,4,6-TeCP), pentachlorophenol (PCP) as well  
144 heptane (anhydrous, 99%). Acetic anhydride was purchased from Sigma-Aldrich (Germany).  
145 A stock standard solution of CPs was prepared in heptane with concentration level of 1  $\mu\text{g}$   
146  $\text{mL}^{-1}$  for each of analytes.

147 All derivatisation agents - acetic anhydride, ethyl chloroformate, N-  
148 heptafluorobutyrylimidazole (HFBI), hexamethyldisilazane (HMDS),  
149 N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA), N,O-bis(trimethylsilyl)acetamide (BSA),  
150 chlorotrimethylsilane (TMCS) and BSTFA:TMCS (99:1) were purchased from Sigma-



151 Aldrich (Germany). Deuterated naphthalene (Sigma-Aldrich, Germany) was applied as  
152 internal standard. Internal standard was used mainly to compensate the stability of mass  
153 spectrometer operation.

154

## 155 ***2.2. Derivatisation of CPs***

156 A number of derivatisation agents typically used for CPs determination, namely acylating  
157 agents (acetic anhydride, ethyl chloroformate, N-heptafluorobutyrylimidazole (HFBI)) and  
158 silylating agents (hexamethyldisilazane (HMDS), N,O-bis(trimethylsilyl)trifluoroacetamide  
159 (BSTFA), N,O-bis(trimethylsilyl)acetamide (BSA), chlorotrimethylsilane (TMCS) and  
160 BSTFA:TMCS (99:1)), have been assessed in this work. All of these derivatisation agents are  
161 commonly applied in various sample preparation techniques before final determination of CPs  
162 and other phenolic compounds with gas chromatography.

163 The derivatisation procedure was as follows: 100  $\mu\text{L}$  of 1.0  $\mu\text{g mL}^{-1}$  working solution of eight  
164 (8) CPs in heptane was placed in the glass chromatographic vial with 250  $\mu\text{L}$  glass insert.  
165 After that, 40  $\mu\text{L}$  of 2.0  $\mu\text{g mL}^{-1}$  solution of deuterated naphthalene in methanol as an internal  
166 standard (IS) was added. Such IS is selected intentionally, in order not to undergo  
167 derivatisation reaction, but to overcome the reproducibility of GC injections and stability of  
168 MS signal. Each derivatisation agent was added as purchased in the amount of 10  $\mu\text{L}$ . The  
169 solution was vortexed for 1 min and the reaction was carried out for 10 min at room  
170 temperature without any enhancement. After that, the mixture was immediately injected into  
171 the GC-MS system.

172

## 173 ***2.3. Chromatographic conditions***

174 The analysis of CPs derivatives was performed by using Agilent Technologies Gas  
175 Chromatograph 7890A coupled with Agilent Technologies Mass Spectrometer 5975C.



176 Separation of analytes took place on Agilent Technologies chromatographic column DB5-MS  
177 (30m, id: 0,25mm, film thickness: 0.25 $\mu$ m, 95% PDMS, 5% phenyl groups) with 2 m of fused  
178 silica pre-column. Helium 6.0 was used as carrier gas with a constant flow equal  
179 to 1 mL min<sup>-1</sup>. 1  $\mu$ L of sample was injected in a splitless mode. GC oven temperature program  
180 was as follows: 100 °C for 5 min, then an increase of 10 °Cmin<sup>-1</sup> to reach 280°C that was held  
181 for 10min. Transfer line temperature was set at 280°C. The temperature of ion source in mass  
182 spectrometer was set at 250 °C, while the temperature of quadrupole at 150 °C. CPs  
183 derivatives were analysed by GC-MS in SCAN mode.

184

#### 185 **2.4.TOPSIS**

186 TOPSIS is one of the expert systems included in the MCDA methods. It was developed by  
187 Hwang and Yoon in 1981 [34]. Its aim is ranking of available alternatives, or in other words,  
188 selecting the best option among all of them. TOPSIS mathematical model allows finding a  
189 winner by choosing the alternative that simultaneously has the shortest distance from the  
190 positive ideal solution and at the same time the farthest distance from the negative ideal  
191 solution.

192 General steps for all MCDA methods are presented elsewhere [35]. Initially, the main aim of  
193 the analysis should be defined. In the present case the evaluation concerns choosing the best  
194 derivatising agent for CPs determination. Then, criteria and alternatives are established.  
195 Criteria represent groups of parameters that are able to describe each available option  
196 (alternative) and concurrently make the assessment and arrangement possible. Bearing in  
197 mind sustainable development, criteria are divided into three main groups describing different  
198 points of view: greenness, derivatisation effectiveness and chromatographic quality. This idea  
199 is summarised in **Table 1**.



200 The properties and safety data for derivatisation agents were taken from material safety data  
201 sheets (MSDS) for the respective compounds. Detailed descriptions of greenness parameters  
202 are provided elsewhere [2]. Derivatisation effectiveness and chromatographic quality  
203 parameters were determined by performing chromatographic experiments (for 8 CPs).  
204 Alternatives are examples of derivatisation agents typically used in CPs determination, as  
205 described in section 2.2.

206 To apply one of the MCDA methods, all of the factors describing possible options must be  
207 numerical or easily transformable into calculable units [21]. According to this requirement,  
208 hazard (H) and precautionary (P) statements as well as signal word and special hazards arising  
209 from the substance or mixture/hazardous decomposition products were transformed into  
210 numerical values. Hazard and precautionary statements were transformed to penalty points  
211 based on 10 point scale, as described previously [2]. Therefore, values for signal wording  
212 information have been determined in accordance with the pattern: “none” – 0 points,  
213 “warning” - 1 point, “danger” – 4 points [2]. This approach was also used in transformation of  
214 “special hazards arising from the substance or mixture/hazardous decomposition products” in  
215 combination with the analytical eco-scale approach [36]. Thus, points for signal wording were  
216 multiplied by the number of labelling pictograms. Additionally, compounds marked with a (+)  
217 indication (hydrogen fluoride and hydrogen cyanides), were given extra 10 points due to  
218 hazard properties associated with lethal effects [2]. If there are more than one hazardous  
219 compound formed during fire or decomposition, then their points are summed up.

220 Next step of evaluation using MCDA method was giving a proper weight of each criterion.  
221 The choice of the best solution was carried out in four stages. First, a separate analysis  
222 according to three points of view, namely greenness, derivatisation effectiveness, and  
223 chromatogram quality was conducted. Then ranking by all criteria was performed. Weighting



224 of greenness criteria was based on an approach proposed in previous research [2]. Given  
225 values of weight are presented in **Table 2**.

226 In case of derivatisation effectiveness, responses ratio for analytes and internal standard, as  
227 well as relative standard deviations (RSD) for every of 8 analytes were measured. Their  
228 weights (for each CPs) were characterised as having the same importance. The weights for  
229 assessment according to all CPs' chromatographic quality, including retention time of last  
230 eluting compound and peaks' symmetry described by tailing factor and overall chromatogram  
231 quality, were established and are presented in the **Table 3**.

232 The last step was application of TOPSIS. In general, the input data are the matrix consisting  
233 of  $n$  alternatives which are described by  $m$  criteria. The algorithm of TOPSIS can be described  
234 in several steps as follows:

235 1. Construction of normalised decision matrix

$$236 \quad r_{ij} = x_{ij} \div \sqrt{\sum x_{ij}^2}, \quad i = 1, 2, \dots, m \text{ and } j = 1, 2, \dots, n \quad (1)$$

237 Where  $x_{ij}$  and  $r_{ij}$  are original and normalised scores in decision matrix, respectively.

238 2. Construction of the weighted normalised decision matrix

$$239 \quad v_{ij} = r_{ij} \times w_j, \quad i = 1, 2, \dots, m \text{ and } j = 1, 2, \dots, n \quad (2)$$

240 Where  $w_j$  is the weight of the criterion  $j$  and  $\sum_{j=1}^n w_j = 1$

241 3. Determination of positive ideal ( $A^*$ ) and negative ideal ( $A^-$ ) solutions

$$242 \quad A^* = \{(max_i v_{ij} | j \in C_b), (min_i v_{ij} | j \in C_c)\} = \{v_i^* | j = 1, 2, \dots, m\} \quad (3)$$

$$243 \quad A^- = \{(min_i v_{ij} | j \in C_b), (max_i v_{ij} | j \in C_c)\} = \{v_j^* | j = 1, 2, \dots, m\} \quad (4)$$

244 4. Calculation of the separation measures for each alternative

$$245 \quad S_i^* = \sqrt{\sum_{j=1}^m (v_{ij} - v_j^*)^2} \quad j = 1, 2, \dots, m \quad (5)$$

246 
$$S_i^- = \sqrt{\sum_{j=1}^m (v_{ij} - v_j^-)^2} \quad j = 1, 2, \dots, m \quad (6)$$

247 5. Calculation of the relative closeness to the ideal solution

248 
$$C_i^* = \frac{S_i^-}{S_i^* + S_i^-}, \quad i = 1, 2, \dots, m \quad \text{and} \quad 0 < C_i^* < 1 \quad (7)$$

249 6. Arrangement of scenarios in order of closest to ideal to furthest from ideal - creation  
250 of a ranking

251 The alternative with  $C_i^*$  closest to 1 is the best preference among the possible options.

252 Above, only basic information about TOPSIS algorithm is presented. For more details please  
253 refer to the articles describing its fundamentals. All the calculations involving TOPSIS  
254 application for CPs derivatisation agents assessment included in this study were performed in  
255 Excel program (Microsoft 2010).

256

### 257 3. Results and Discussion

258 The chemical structures of selected CPs is shown in **Figure 1**, whereas acyl and silyl  
259 derivatives formed by reaction of CPs with the above mentioned derivatisation agents are  
260 shown in **Figure 2**. The application of derivatisation agents (alternatives) that show minimal  
261 environment, health and safety issues and give rise to a quantitative conversion of CPs in a  
262 reduced reaction time and without additional energy consumption are clearly the preferable  
263 solution. Rankings of the 8 alternative derivatisation agents were performed according to  
264 different groups of criteria. Initially, no derivatisation option was considered as an alternative  
265 but no chromatographic peaks were obtained for CPs in given chromatographic conditions.

266 As it is preselection of derivatisation agents, we do not aim to work in optimised  
267 derivatisation reaction conditions but in constant conditions for every agent. It is not feasible  
268 to select derivatisation agents' optimal reaction conditions before selection of the agent itself.

269 The optimisation of derivatisation reaction conditions is one of the next steps in procedure  
270 development. In fact, as shown in the introduction, sometimes optimised derivatisation  
271 conditions differ strongly, even for single given agent and analyte(s).

272

### 273 ***3.1.Ranking by chromatographic quality***

274 The first ranking was performed with chromatogram quality criteria being input data.  
275 Retention time of last eluting analyte - PCP was a measure of chromatographic run time,  
276 symmetry factor of 2,3,4,6-TeCP was selected to represent tailing of the derivatised CPs. To  
277 avoid excess of criteria this peak was selected as all of them give very similar results. Last  
278 criterion is strictly arbitrary and reflects the easiness of analyst to read the chromatogram. In  
279 other words, chromatogram with many artificial peaks was assessed as being low quality.  
280 Here, arbitrary five point scale was used.

281 **Table 4** shows ranking results within above-described criteria. The best alternative within  
282 these criteria was the mixture of BSTFA:TMCS (99:1). This alternative was characterised by  
283 best performance in terms of peak symmetry, and its chromatogram contained no many  
284 artificial peaks, with score 4 out of 5. The retention time of PCP with this alternative was  
285 moderate (17.5 min), as in case of all other silylating agents. The second rank was occupied  
286 by acetic anhydride with an easy to interpret chromatogram (4 points) and good symmetry of  
287 peaks. The retention time of PCP was 16.9 min, what was the second best result, being HFBI  
288 characterised by a shorter chromatographic run time (PCP retention time of 14.4 min). In fact,  
289 HFBI occupied the third rank position with very good symmetry of peaks and moderate  
290 easiness (3) of chromatogram reading. The values of similarities to ideal solution of three first  
291 alternatives did not differ significantly. This means that three best derivatisation agents  
292 perform rather similarly, within these criteria. The next ranks were obtained by other  
293 silylating agents. In general, their chromatograms were easy to be interpreted but the peaks



294 were strongly tailing. Last place was occupied by ethyl chloroformate, as PCP had the longest  
295 retention time (18.5 min), peaks were not symmetric and the chromatogram was rather hard to  
296 be interpreted (2 out of 5 points).

297

### 298 ***3.2.Ranking by derivatisation effectiveness***

299 The ranking of derivatisation effectiveness was performed considering two types of criteria.  
300 The first group of criteria were the ratios of peak areas for every analyte to internal standard,  
301 what reflects the reaction efficiency and the possibility to obtain good sensitivity. The second  
302 group of criteria was relative standard deviations ( $n = 3$ ) of ratios of peak areas of analytes  
303 and internal standard of all CPs. This group of criteria reflects repeatability of derivatisation  
304 reaction and the possibility to obtain precise results.

305 **Table 4** presents the results for above mentioned criteria. The first rank for these criteria  
306 ranking was obtained by acetic anhydride. It is characterised by large peak areas (the best for  
307 4 out of 8 CPs) and good precision (the best for only 1 analyte). The second rank was for  
308 BSTFA:TMCS (99:1) mixture and the reason for obtaining high rank was excellent precision  
309 (the best for 6 out of 8 analytes) and good performance for peak areas. The next positions in  
310 the ranking were obtained by other silylating agents. The lowest ranks were obtained by ethyl  
311 chloroformate and HFBI. HFBI was characterised by poor precision (the poorest for 4 out of 8  
312 analytes) and poor peak areas (the poorest for 3 out of 8 analytes). Similarly, ethyl  
313 chloroformate performance was poor in terms of precision (the poorest for 3 out of 8 analytes)  
314 and weak performance in terms of peak areas.

315

### 316 ***3.3.Ranking by greenness***

317 **Table 4** presents the results of ranking by greenness criteria. The weights to criteria were  
318 assigned according to derivatisation agents selection guide [2], with the difference that the



319 criterion of carcinogenicity was not included in the assessment as all the agents are classified  
320 as not carcinogenic. As a result, 0.05 of total weight originally assigned to carcinogenicity  
321 criterion was transferred to “precautionary statements” weight, which was therefore 0.25  
322 instead of 0.2. The mixture of BSTFA:TMCS (99:1) was treated in this ranking as a  
323 compound with mixed properties – 0.99 of BSTFA properties and 0.01 of TMCS properties.  
324 HFBI was first rank, mainly because it had neither hazard nor precautionary statements. The  
325 next ranks were obtained by silylating agents. The last ranks were obtained by acetic  
326 anhydride, HMDS and ethyl chloroformate. These derivatisation agents are labelled with  
327 many hazard statements and they cause problems with handling what is expressed by many  
328 precautionary labels. To our best knowledge, no other studies deal with assessment of  
329 derivatisation agents in terms of their greenness for a particular group of analytes.

330

### 331 ***3.4. Comprehensive ranking***

332 It is clear that consideration of different assessment criteria results in completely different  
333 rankings. Therefore, it is beneficial to perform ranking with all criteria at the same time. As  
334 the main goal of derivatisation agent selection is to obtain good analytical performance and  
335 greenness we investigate how the results change for variable weights with no dominant group  
336 of criteria. **Figure 3** shows the ranking results for such weights applied. BSTFA:TMCS (99:1)  
337 is the first rank for different combinations of weights for derivatisation efficiency and  
338 chromatogram quality if the weight for greenness does not exceed 40 %. At this value of  
339 weight for greenness criteria no matter what are the weights for two other groups of criteria  
340 HFBI is the first rank.

341 The most often mentioned advantage of silylation agents over methylation and acetylation  
342 ones is that they produce derivatives of higher masses, which is especially important in case  
343 of analytes of low molecular weight. In this way the risk of losses by evaporation during



344 sample preparation is minimised, which is likely to be observed in case of methyl esters or  
345 acetates of low molecular weight analytes. In addition, in case of silyl derivatives,  
346 characteristic fragmentation pattern is observed, which facilitates the identification and also  
347 characteristic ions for SIM may be easily selected. Silylation agents, especially BSTFA, are  
348 also recognised as those reacting with analytes fast and quantitatively under mild conditions  
349 [26]. Additionally, it has been also emphasized in some studies that byproducts of the reaction  
350 of analytes with BSTFA/TMCS and excess of this agent elute early in the chromatogram (far  
351 from derivatised analytes), which simplifies the evaluation of obtained results [37]. This has  
352 been also observed in our study – considering chromatogram quality BSTFA/TMCS has been  
353 ranked as the best alternative. Some authors also indicate that alkylation and acylation  
354 reagents (in contrast to silylation ones) are not applicable to all phenols relevant in  
355 environmental analysis [38]. On the other hand, BSTFA is rather expensive, which is  
356 probably the reason why acetic anhydride is applied for chlorophenols determination in water  
357 in majority of reported studies. Interestingly, in EPA methods for such a purpose,  
358 pentafluorobenzyl bromide is advised.

359

360

#### 361 **4. Conclusions**

362 The selection of derivatisation agent is seldom taken into consideration during procedure  
363 development. The presented study shows a comprehensive method for the selection of  
364 derivatisation agent for CPs for further optimization. The rankings give strongly different  
365 results if different ranking criteria are considered. Thus, derivatisation agents that stand out  
366 from the rest of alternatives within one ranking are poorly assessed when different criteria are  
367 considered. Therefore, a comprehensive assessment of derivatisation agents considering many  
368 criteria is strongly recommended. Regarding derivatisation agents applied to CPs



369 determination, the best peak areas and precisions were reached by acetic anhydride, the best  
370 symmetry of peaks and overall chromatogram quality was obtained with BSTFA:TMCS  
371 mixture, while the greenest alternative was HFBI. If all criteria are considered together  
372 BSTFA:TMCS mixture is the best alternative.

373 Application of TOPSIS allows considering many criteria during selection process and is easy  
374 to be applied algorithm. It allows users to pick criteria that are relevant to the optimisation  
375 process and by application of weights can assign relative importance to criteria. This makes  
376 the presented approach very flexible.

377

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383

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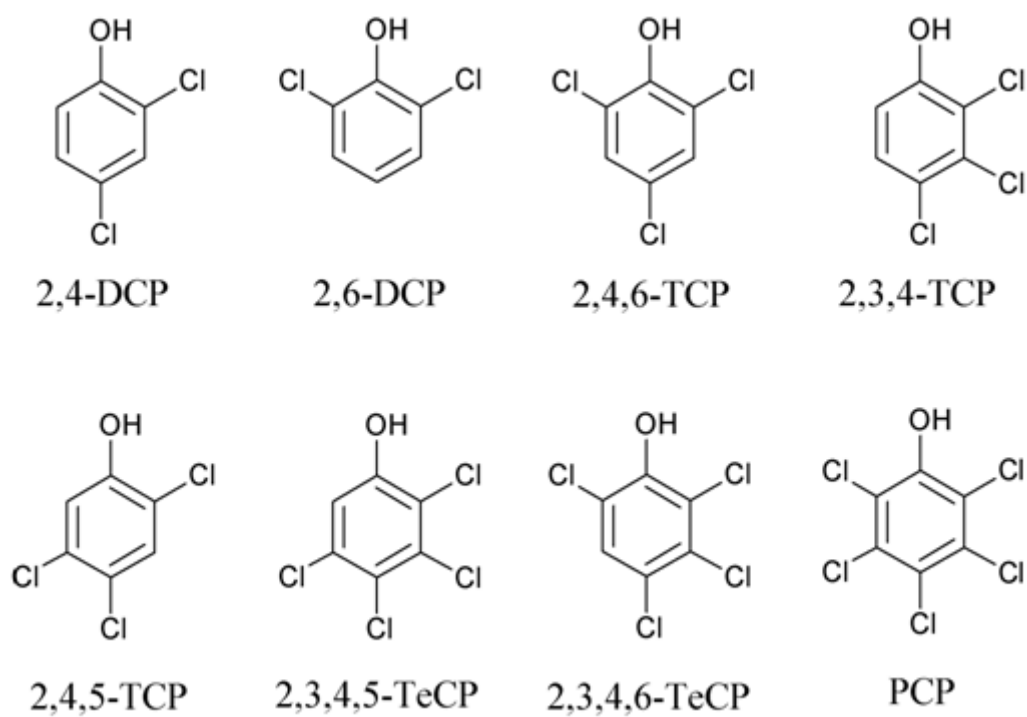
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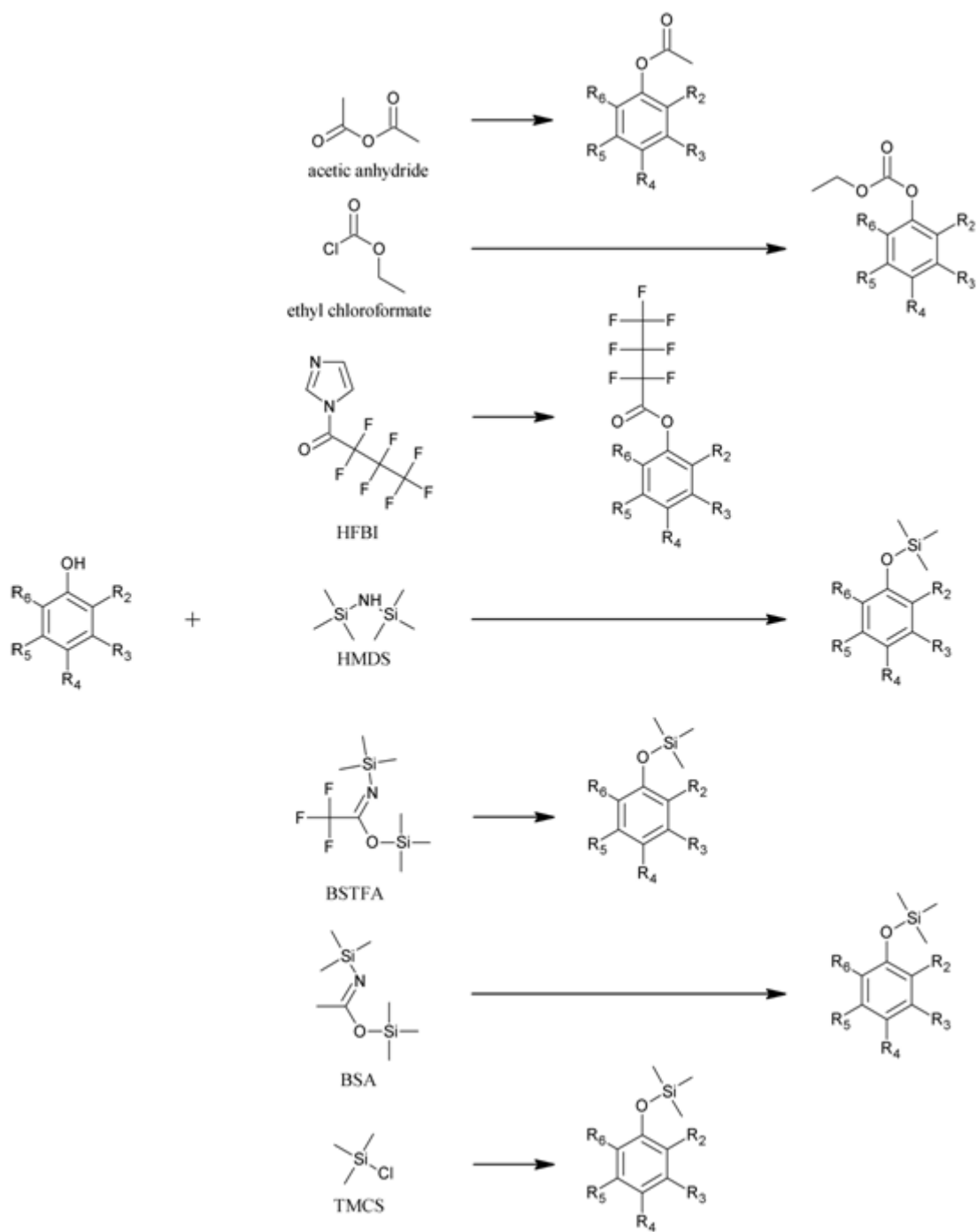
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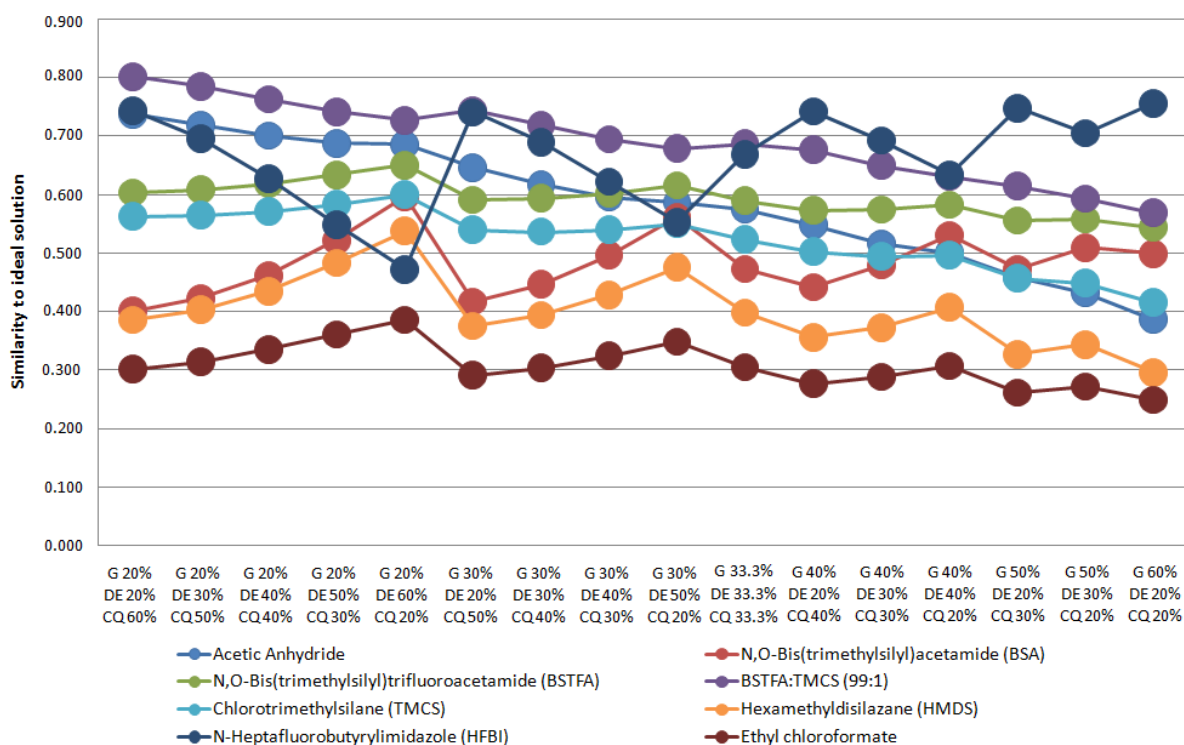
**Figures with captions**



**Figure 1.** Chemical structures of the eight CPs.



**Figure 2.** Derivatisation products obtained by reaction of CPs (R<sub>i</sub>=H, Cl) with acetic anhydride, ethyl chloroformate, HFBI, HMDS, BSTFA, BSA and TMCS.



**Figure 3.** The results of rankings for changing weights of criteria. G- Greenness, DE – Derivatisation efficiency, CQ – chromatogram quality.

**Table 1**

Criteria for TOPSIS analysis and its classification.

Greenness parameters	Derivatisation effectiveness	Chromatographic quality
	parameters	parameters
<ul style="list-style-type: none"> <li>Boiling point</li> <li>Flash point</li> <li>Vapour pressure</li> <li>log <math>K_{ow}</math></li> <li>log <math>K_{oc}</math></li> <li>log BCF</li> <li>Total removal wastewater treatment (%)</li> <li>Persistence time (h)</li> </ul>	<ul style="list-style-type: none"> <li>Responses ratio</li> <li>RSD</li> </ul>	<ul style="list-style-type: none"> <li>Retention time of last eluting compound</li> <li>Symmetry of all peaks</li> <li>Easiness to obtain information from chromatogram – number of artificial peaks within range of elution of analytes</li> </ul>

- 
- Hazard statements (H)
  - Precautionary statements  
(P)
  - Signal word
  - Special hazards arising  
from the substance or  
mixture/Hazardous  
decomposition products
-



**Table 2**

Weighting of criteria in case of green approach [2].

<b>Criterion</b>	<b>Weight</b>
Boiling point	0.025
Flash point	0.025
Vapour pressure	0.025
logK <sub>ow</sub>	0.025
logK <sub>oc</sub>	0.025
logBCF	0.025
Total removal by wastewater treatment (%)	0.025
Persistence time	0.025
Hazard statements (H)	0.25
Precautionary statements (P)	0.25
Signal Word	0.2
Special hazards arising from the substance or mixture/Hazardous decomposition products	0.1

**Table 3**

Weighting of criteria for comprehensive ranking of derivatization agents.

Chromatogram quality		Derivatisation effectiveness		Greenness	
Criteria	Weight	Criteria	Weight	Criteria	Weight
Retention time of last eluting compound	0.13(3)	Responses ratio		Boiling point	0.005
Tailing factor for 2,3,4,6-TTCP	0.13(3)	2,6-DCP		Flash point	0.005
Overall chromatogram quality	0.13(3)	2,4-DCP		Vapour pressure	0.005
		2,4,6-TCP	0.025	logKow	0.005
		2,4,5-TCP		logKoc	0.005
		2,3,4-TCP	logBCF	0.005	
		2,3,4,6-TTCP	Total removal by wastewater treatment (%)	0.005	
		2,3,4,5-TTCP	Persistence time	0.005	
		PCP	Hazard statements (H)	0.05	
		RSD	Precautionary statements (P)	0.05	
		2,6-DCP	Signal Word	0.04	
		2,4-DCP	Special hazards arising from the substance or mixture/Hazardous decomposition products	0.02	
		2,4,6-TCP	0.025		
		2,4,5-TCP			
		2,3,4-TCP			
		2,3,4,6-TTCP			
		2,3,4,5-TTCP			
		PCP			

**Table 4**

Ranking results according to different criteria.

Ranking for chromatogram quality criteria		Ranking for derivatisation effectiveness criteria		Ranking for greenness criteria	
Derivatisation agent	Similarity to ideal solution	Derivatisation agent	Similarit y to ideal solution	Derivatisation agent	Similarit y to ideal solution
		Acetic			
BSTFA:TMCS (99:1)	0.855	Anhydride	0.812	HFBI	0.793
		BSTFA:TMC			
Acetic Anhydride	0.832	S (99:1)	0.757	BSTFA	0.530
				BSTFA:TMC	
HFBI	0.773	BSA	0.724	S (99:1)	0.529
BSTFA	0.608	BSTFA	0.696	BSA	0.510
TMCS	0.573	TMCS	0.655	TMCS	0.367
				Acetic	
BSA	0.382	HMDS	0.643	Anhydride	0.310
		Ethyl			
HMDS	0.382	chloroformate	0.430	HMDS	0.238
				Ethyl	
Ethyl chloroformate	0.300	HFBI	0.316	chloroformate	0.230