

Selection of Derivatisation Agents for Chlorophenols Determination with Multicriteria Decision Analysis

Marta Bystrzanowska^a, Renata Marcinkowska^a, Francisco Pena-Pereira^b, Marek
Tobiszewski^{a*}

^a*Department of Analytical Chemistry, Faculty of Chemistry, Gdańsk University of Technology
(GUT), 11/12 G. Narutowicza St., 80-233 Gdańsk, Poland.*

^b*Department of Analytical and Food Chemistry, Faculty of Chemistry, University of Vigo,
Campus As Lagoas - Marcosende s/n, 36310 Vigo, Spain*

* corresponding author: marek.tobiszewski@pg.edu.pl; marektobiszewski@wp.pl

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 μL of BSTFA:TMCS at 60 $^{\circ}\text{C}$ for 2 h. In another
97 study, 50 μL of CPs solution was derivatised with 50 μL 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 μL of acetic anhydride was added to the sample together with

106 a mixture of 0.5 mL of acetone (disperser solvent) and 10 μL 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 μL of acetic anhydride per sample together with 180 μL

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 μL 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 μL 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 μg
146 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 μL 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 μL glass insert.
165 After that, 40 μL 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 μL . 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 μ 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⁻¹. 1 μ 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⁻¹ 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

378 **ACKNOWLEDGEMENTS**

379 F. Pena-Pereira thanks Xunta de Galicia for financial support as a post-doctoral researcher of
380 the I2C program.

381 The authors would like to express their sincere gratitude to prof. Bożena Zabiegała from
382 Gdańsk University of Technology for scientific consultations.

383

384 **References**

385 [1] P. Anastas, N. Eghbali, Green chemistry: Principles and practice, Chem. Soc. Rev. 39
386 (2010) 301–312.

387 [2] M. Tobiszewski, J. Namieśnik, F. Pena-Pereira, A derivatisation agent selection guide,
388 Green Chem. 19 (2017) 5911–5922.

389 [3] T. Ge, J. Han, Y. Qi, X. Gu, L. Ma, C. Zhang, et al., The toxic effects of chlorophenols
390 and associated mechanisms in fish, Aquat. Toxicol. 184 (2017) 78–93.

391 [4] A.O. Olaniran, E.O. Igbinsosa, Chlorophenols and other related derivatives of
392 environmental concern: Properties, distribution and microbial degradation processes,
393 Chemosphere. 83 (2011) 1297–1306.



- 394 [5] M. Czaplicka, Sources and transformations of chlorophenols in the natural
395 environment, *Sci. Total Environ.* 322 (2004) 21–39.
- 396 [6] Agency for Toxic Substances & Disease Registry (ATSDR), Priority List of
397 Hazardous Substances, (2013). <http://www.atsdr.cdc.gov/SPL/>.
- 398 [7] P. De Morais, T. Stoichev, M.C.P. Basto, M.T.S.D. Vasconcelos, Extraction and
399 preconcentration techniques for chromatographic determination of chlorophenols in
400 environmental and food samples, *Talanta.* 89 (2012) 1–11.
- 401 [8] F. Orata, Derivatization Reactions and Reagents for Gas Chromatography Analysis, in:
402 M. Ali Mohd (Ed.), *Adv. Gas Chromatogr. - Prog. Agric. Biomed. Ind. Appl.*, InTech,
403 2007.
- 404 [9] V.G. Zaikin, J.M. Halket, Derivatization in mass spectrometry — 2 . Acylation, *Eur. J.*
405 *Mass Spectrom.* 9 (2003) 421–434.
- 406 [10] J.M. Halket, V.G. Zaikin, Derivatization in mass spectrometry — 1 . Silylation, *Eur. J.*
407 *Mass Spectrom.* 9 (2003) 1–21.
- 408 [11] J. Figueira, S. Greco, M. Ehrgott, Multiple criteria decision analysis: State of the art
409 surveys, Springer-Verlag, New York, USA, 2005.
- 410 [12] A. Mardani, A. Jusoh, K.M.D. Nor, Z. Khalifah, N. Zakwan, A. Valipour, Multiple
411 criteria decision-making techniques and their applications - A review of the literature
412 from 2000 to 2014, *Econ. Res. Istraz.* 28 (2015) 516–571.
- 413 [13] M. Tobiszewski, S. Tsakovski, V. Simeonov, J. Namiesnik, F. Pena-Pereira, A solvent
414 selection guide based on chemometrics and multicriteria decision analysis, *Green*
415 *Chem.* 17 (2015) 4773–4785.
- 416 [14] P. Bigus, J. Namieśnik, M. Tobiszewski, Application of multicriteria decision analysis
417 in solvent type optimization for chlorophenols determination with a dispersive liquid-
418 liquid microextraction, *J. Chromatogr. A.* 1446 (2016) 21–26.



- 419 [15] S. Perez-Vega, S. Peter, I. Salmeron-Ochoa, A. Nieva-De La Hidalga, P.N. Sharratt,
420 Analytical hierarchy processes (AHP) for the selection of solvents in early stages of
421 pharmaceutical process development, *Process Saf. Environ. Prot.* 89 (2011) 261–267.
- 422 [16] J. Serna, E.N. Díaz Martínez, P.C. Narváez Rincón, M. Camargo, D. Gálvez, Á.
423 Orjuela, Multi-criteria decision analysis for the selection of sustainable chemical
424 process routes during early design stages, *Chem. Eng. Res. Des.* 113 (2016) 28–49.
- 425 [17] C. Li, X. Zhang, S. Zhang, K. Suzuki, Environmentally conscious design of chemical
426 processes and products: Multi-optimization method, *Chem. Eng. Res. Des.* 87 (2009)
427 233–243.
- 428 [18] M. Tobiszewski, A. Orłowski, Multicriteria decision analysis in ranking of analytical
429 procedures for aldrin determination in water, *J. Chromatogr. A.* 1387 (2015) 116–122.
- 430 [19] D. Xu, L. Lv, J. Ren, W. Shen, S. Wei, L. Dong, Life cycle sustainability assessment
431 of chemical processes: A vector-based three-dimensional algorithm coupled with AHP,
432 *Ind. Eng. Chem. Res.* 56 (2017) 11216–11227.
- 433 [20] R. Jędrkiewicz, A. Orłowski, J. Namieśnik, M. Tobiszewski, Green analytical
434 chemistry introduction to chloropropanols determination at no economic and analytical
435 performance costs?, *Talanta.* 147 (2016) 282–288.
- 436 [21] R. Jędrkiewicz, S. Tsakovski, A. Lavenu, J. Namieśnik, M. Tobiszewski,
437 Simultaneous grouping and ranking with combination of SOM and TOPSIS for
438 selection of preferable analytical procedure for furan determination in food, *Talanta.*
439 178 (2018) 928–933.
- 440 [22] M. Cinelli, S.R. Coles, M.N. Nadagouda, J. Błaszczyszki, R. Słowiński, R.S. Varma,
441 et al., Robustness analysis of a green chemistry-based model for the classification of
442 silver nanoparticles synthesis processes, *J. Clean. Prod.* 162 (2017) 938–948.
- 443 [23] P. Bigus, J. Namieśnik, M. Tobiszewski, Implementation of multicriteria decision



- 444 analysis in design of experiment for dispersive liquid-liquid microextraction
445 optimization for chlorophenols determination, *J. Chromatogr. A.* 1553 (2018) 25–31.
- 446 [24] W. Zhong, D. Wang, X. Xu, B. Wang, Q. Luo, S. Senthil Kumaran, et al., A gas
447 chromatography/mass spectrometry method for the simultaneous analysis of 50 phenols
448 in wastewater using deconvolution technology, *Chinese Sci. Bull.* 56 (2011) 275–284.
- 449 [25] R.-Y. Hsu, J.-H. Liao, H.-W. Tien, G.-R. Her, Gas chromatography electrospray
450 ionization mass spectrometry analysis of trimethylsilyl derivatives, *J. Mass Spectrom.*
451 51 (2016) 883–888.
- 452 [26] D. Li, J. Park, J.-R. Oh, Silyl derivatization of alkylphenols, chlorophenols, and
453 bisphenol a for simultaneous GC/MS determination, *Anal. Chem.* 73 (2001) 3089–
454 3095.
- 455 [27] N. Fattahi, Y. Assadi, M.R. Milani Hosseini, E.Z. Jahromi, Determination of
456 chlorophenols in water samples using simultaneous dispersive liquid-liquid
457 microextraction and derivatization followed by gas chromatography-electron-capture
458 detection, *J. Chromatogr. A.* 1157 (2007) 23–29.
- 459 [28] C. Pizarro, C. Sáenz-González, N. Pérez-del-Notario, J.M. González-Sáiz,
460 Development of an ultrasound-assisted emulsification-microextraction method for the
461 determination of the main compounds causing cork taint in wines, *J. Chromatogr. A.*
462 1229 (2012) 63–71.
- 463 [29] N. Campillo, P. Viñas, J.I. Cacho, R. Peñalver, M. Hernández-Córdoba, Evaluation of
464 dispersive liquid-liquid microextraction for the simultaneous determination of
465 chlorophenols and haloanisoles in wines and cork stoppers using gas chromatography-
466 mass spectrometry, *J. Chromatogr. A.* 1217 (2010) 7323–7330.
- 467 [30] Y.J. Yu, S. Zhong, G.Y. Su, H.L. Liu, X.L. Dai, R.J. Wang, et al., Trace analysis of
468 phenolic compounds in water by in situ acetylation coupled with purge and trap-



- 469 GC/MS, *Anal. Methods*. 4 (2012) 2156–2161.
- 470 [31] C. Basheer, H.K. Lee, Analysis of endocrine disrupting alkylphenols, chlorophenols
471 and bisphenol-A using hollow fiber-protected liquid-phase microextraction coupled
472 with injection port-derivatization gas chromatography-mass spectrometry, *J.*
473 *Chromatogr. A*. 1057 (2004) 163–169.
- 474 [32] L. Schmidt, T. Göen, Simultaneous determination of the full chlorophenol spectrum in
475 human urine using gas chromatography with tandem mass spectrometry, *Anal. Chim.*
476 *Acta*. 965 (2017) 123–130.
- 477 [33] M. Saraji, H. Ghambari, Suitability of dispersive liquid-liquid microextraction for the
478 in situ silylation of chlorophenols in water samples before gas chromatography with
479 mass spectrometry, *J. Sep. Sci.* 38 (2015) 3552–3559.
- 480 [34] C.L. Hwang, K.P. Yoon, *Multiple Attribute Decision Making: Methods and*
481 *Applications*, Springer-Verlag, New York, USA, 1981.
- 482 [35] M. Bystrzanowska, M. Tobiszewski, How can analysts use multicriteria decision
483 analysis?, *TrAC - Trends Anal. Chem.* 105 (2018) 98–105.
- 484 [36] A. Gałuszka, Z.M. Migaszewski, P. Konieczka, J. Namieśnik, Analytical Eco-Scale
485 for assessing the greenness of analytical procedures, *TrAC Trends Anal. Chem.* 37
486 (2012) 61–72.
- 487 [37] Á. Kovács, A. Kende, M. Mörtl, G. Volk, T. Rikker, K. Torkos, Determination of
488 phenols and chlorophenols as trimethylsilyl derivatives using gas chromatography–
489 mass spectrometry, *J. Chromatogr. A*. 1194 (2008) 139–142.
- 490 [38] Á. Kovács, M. Mörtl, A. Kende, Development and optimization of a method for the
491 analysis of phenols and chlorophenols from aqueous samples by gas chromatography–
492 mass spectrometry, after solid-phase extraction and trimethylsilylation, *Microchem. J.*
493 99 (2011) 125–131.
- 494



Figures with captions

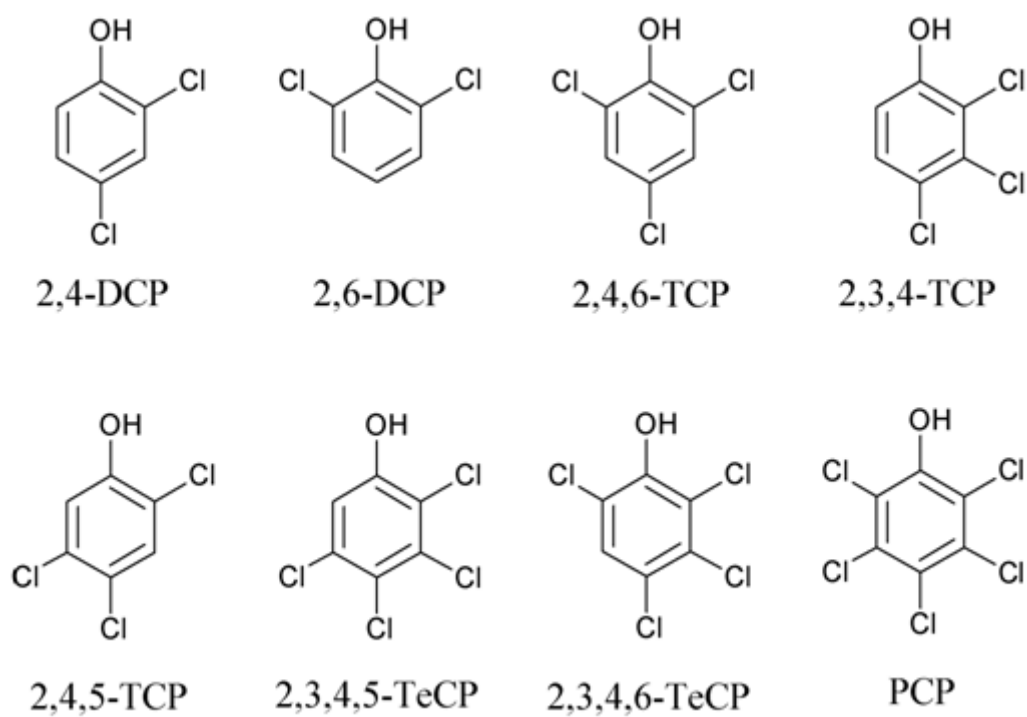


Figure 1. Chemical structures of the eight CPs.

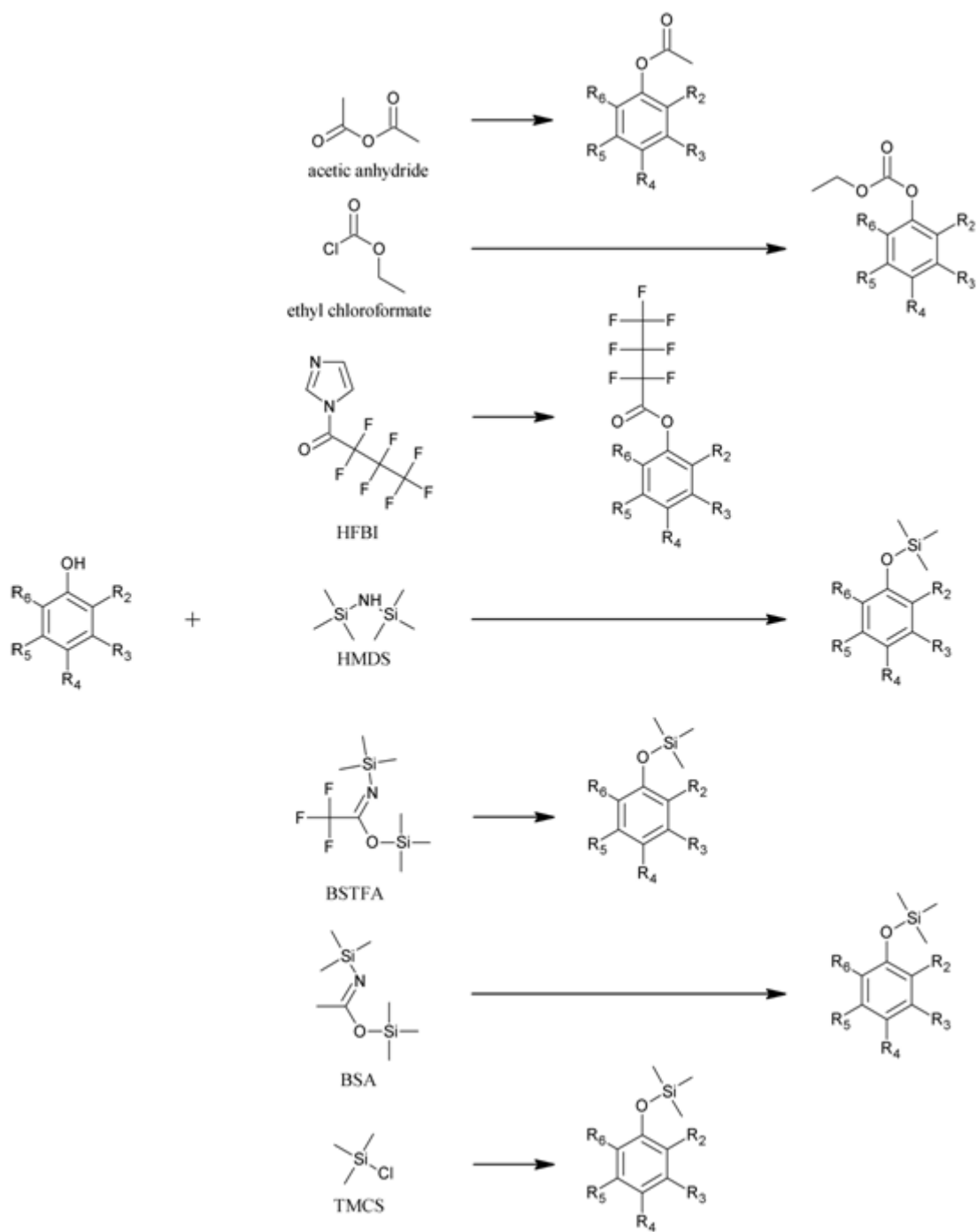


Figure 2. Derivatization products obtained by reaction of CPs (R_i=H, Cl) with acetic anhydride, ethyl chloroformate, HFBI, HMDS, BSTFA, BSA and TMCS.

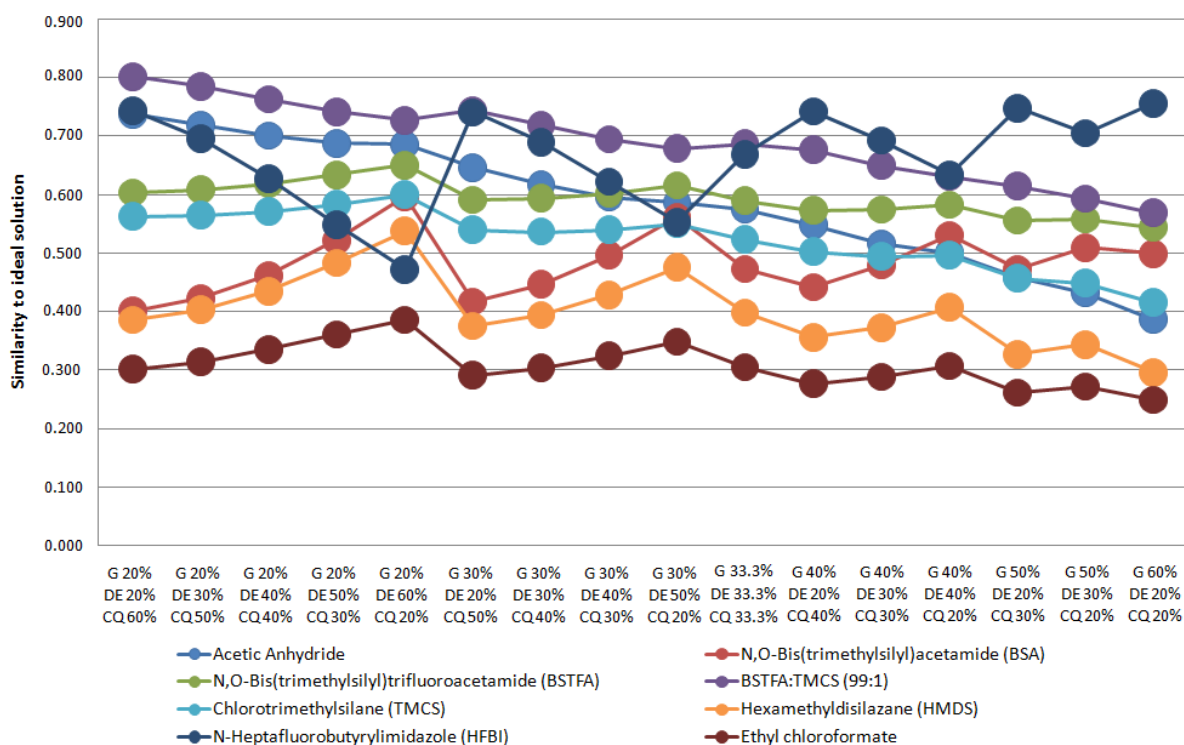


Figure 3. The results of rankings for changing weights of criteria. G- Greenness, DE – Derivatisation efficiency, CQ – chromatogram quality.

Table 1

Criteria for TOPSIS analysis and its classification.

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

-
- 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].

Criterion	Weight
Boiling point	0.025
Flash point	0.025
Vapour pressure	0.025
logK _{ow}	0.025
logK _{oc}	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