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Metal-Organic Framework-based Magnetic Dispersive micro-Solid-Phase Extraction for the Gas Chromatography–Mass Spectrometry determination of polycyclic aromatic compounds in water samples

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1 **Metal-Organic Framework-based Magnetic Dispersive micro-Solid-Phase Extraction for the Gas**
2 **Chromatography–Mass Spectrometry determination of polycyclic aromatic compounds in water**
3 **samples**

4

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15

16 **Abstract**

17 A magnetic hybrid material based on the use of the mixed-ligand Metal-Organic Framework (MOF) PUM198 is proposed
18 for the magnetic dispersive micro solid-phase extraction (MD- μ SPE) of the 16 polycyclic aromatic hydrocarbons (PAHs)
19 included in the US-EPA priority pollutants list. PUM198 is a thermally robust MOF characterized by a doubly
20 interpenetrated microporous framework in which Zn²⁺ ions and carboxylate groups define 2D planes that are pillared by a
21 bis-pyridine-bis amide ligand containing a biphenyl scaffold. PUM198 revealed to be ideal to adsorb PAHs efficiently
22 through non-covalent interactions. A Plackett-Burman design followed by a Central Composite Design and the multicriteria
23 method of the desirability functions were applied to find the optimal conditions for the extraction of the investigated PAHs,
24 resulting in a reduced solvent consumption, i.e., 50 μ L of solvent *per* extraction for 5 mL of sample, approximately 3–20
25 times lower than those reported in previous studies, thus satisfying the principles of green analytical chemistry. Method
26 validation proved the reliability of the method for the determination of PAHs at trace level, obtaining detection limits in the
27 6.7–27 ng/L range, good precision with *RSD*_s% lower than 19% and recovery rates in the 99 (\pm 13)–126 (\pm 8)% range near

28 the quantitation limit. Finally, the applicability of the method was demonstrated by analyzing underground water samples
29 taken from contaminated sites

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32 **Keywords**

33 polycyclic aromatic hydrocarbon, metal-organic framework, pillared MOF, magnetic dispersive micro solid-phase
34 extraction, design of experiments, gas chromatography–mass spectrometry

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52

53 **1. Introduction**

54 The existence of life and the sustenance of many ecosystems strictly depends on water quality. In addition to its biological
55 aspects, water plays a key role for agriculture and husbandry, as well as for human life, having also strong socio-economic
56 implications [1,2]. The occurrence of polycyclic aromatic hydrocarbons (PAHs) in water is a matter of concern. Indeed,
57 these ubiquitous environmental contaminants have been recognized either as certainly or potentially carcinogenic by the
58 International Agency for Research on Cancer, therefore the exposure to contaminated water poses a risk to the human health
59 and wildlife [3,4]. PAHs can be introduced in the environment from both natural and anthropogenic sources [2,5]. Evidence
60 suggests that anthropogenic PAHs reach water bodies mainly through run-offs from urban areas, direct discharge and
61 deposition from the atmosphere [6,7]. The health and environmental concerns related to this class of compounds make their
62 quantitation and monitoring in water of paramount importance. For these reasons, the US Environmental Protection Agency
63 (US-EPA) included 16 PAHs in the priority pollutants list [8].

64 The main analytical challenge related to the quantitation of contaminants in environmental matrices is related to their low
65 concentration level. In addition, the increasing attention to the environmental impact of analytical procedures has posed new
66 challenges in the development of more sustainable analytical methodologies. Within this frame of reference,
67 miniaturization, reduction of sample size, and the consumption of small amounts of organic solvents are demanded to meet
68 the requirements of green analytical chemistry. In this context, a proper sample treatment is required both to pre-concentrate
69 the analytes and to remove potential interfering compounds for achieving high sensitivity and selectivity [9,10]. Among
70 extraction techniques, dispersive micro solid-phase extraction (D- μ SPE) has received increasing attention due to its
71 efficiency, cost effectiveness and speed of execution [11,12]. The main steps involved in this miniaturized sample
72 preparation technique include: i) the dispersion of the sorbent into the sample solution, ii) sorbent recovery, iii) the
73 dispersion of the recovered sorbent into a solvent for analyte desorption, iv) extract collection and vii) analysis [12].

74 In 1999, Šafaříková and Šafařík offered a straightforward solution to the major disadvantage of D- μ SPE, i.e., the low
75 recovery of the sorbent after the adsorption step [11], by reporting the first application of a magnetic sorbent for sample
76 preparation in analytical chemistry [13,14]. Since then, a variety of nanomaterial-based magnetic sorbents have been
77 developed, including molecularly imprinted polymers, ionic liquids, carbon nanotubes, graphene oxide, and silica [12,15].
78 In this context, the combination of the unique characteristics of nanomaterials –namely high surface area and tunable
79 affinity towards target analytes– with the ease of recovery offered by magnetic nanoparticles, such as iron oxide
80 nanoparticles (IONPs), allows for the development of analytical methods based on magnetic dispersive micro solid-phase
81 extraction (MD- μ SPE) with improved selectivity, sensitivity, and enrichment capabilities.

82 Metal-Organic Frameworks are crystalline porous materials made of metallic nodes (i.e., a simple metal ion or a
83 polymetallic aggregate) linked by polytopic organic ligands [16–18]. Their ultimate structure depends on the geometry of
84 the building blocks according to the principles of the reticular chemistry [19,20]. Characteristics such as large surface area,
85 high porosity, and thermal stability make MOFs suitable for gas storage, heterogeneous catalysis, as well as for sample
86 preparation and sensing [21]. More recently, the combination of MOF porosity and nets flexibility has been extensively
87 exploited through the crystalline sponge method to host small molecules into their pores [22], even in a very large amount
88 with a post-synthetic protocol [23,24]. Based on the aforementioned considerations, it is not surprising that popular MOFs,
89 such as HKUST [25,26], UiO66 [27,28], MIL101(Cr) [29] and ZIF-8 [30], have been successfully used in different μ SPE
90 applications. To achieve high sorption capacity, it is mandatory to maximize the analyte-sorbent interactions: this can be
91 done, for example, by the introduction of suitable functional groups [27]. One of the most successful ways to obtain
92 responsive MOFs is the pillaring-strategy, which involves the use of mixed-ligand frameworks, where layers are pillared by
93 a ditopic ligand (pillar) [24,31,32]. The rational design of the framework exploits the characteristics of the two different
94 ligands, making possible the insertion of different functional groups as well as the modulation of the framework flexibility
95 [33].

96 Magnetic MOFs can be easily obtained *via* several approaches, including direct magnetization and either *in situ* IONPs or
97 MOF growth, thus making them promising materials for the MD- μ SPE of both organic and inorganic compounds of
98 environmental, clinical, and food concern [34].

99 In the framework of a research activity dealing with the development of novel materials for miniaturized sample preparation
100 techniques, [35,36] a hybrid magnetic sorbent obtained by the direct magnetization of a Zn-containing mixed-ligand MOF
101 deriving from terephthalic acid and a bis-pyridine-bis-amide ligand with amino-functionalized IONPs was developed for the
102 MD- μ SPE of the 16 priority pollutants PAHs from water samples. The MD- μ SPE procedure was optimized by using an
103 experimental design to identify the optimal setting of the most critical factors by running a reduced number of experiments.
104 In this context, our focus was on the treatment of a reduced volume of sample and the consumption of low amounts of
105 solvent. Finally, the MD- μ SPE–GC–MS method was successfully validated and applied the determination of PAHs in
106 underground water samples taken from a contaminated site.

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110 2. Materials and Methods

111 2.1. Chemicals

112 Acetonitrile (> 99.9% purity), acetone (> 99.5% purity), FeCl₂·4H₂O, n-hexane, toluene, Zn(NO₃)₂·6H₂O (all > 99% purity),
113 (3-aminopropyl)triethoxysilane (APTES), terephthalic acid (both > 98% purity), FeCl₃ (> 97% purity), HCl (> 37% in H₂O),
114 NH₄OH (33% in H₂O) were purchased from Sigma-Aldrich (Milan, Italy). N, N'-dimethylformamide (DMF, 99.8% purity)
115 was from VWR International (Milan, Italy). Methylene chloride (> 99.9% purity) and methanol (> 99.8% purity) were
116 purchased from Honeywell International Inc. (Morristown, USA). Cyclohexane (> 99.8% purity) was from Carlo Erba
117 Reagents (Milan, Italy), whereas isopropanol (> 99.98% purity) was purchased from Fisher Chemicals (Milan, Italy).

118 PAH-Mix 16 (EPA 550, EPA 610) containing naphthalene (N), acenaphthylene (Acy), acenaphthene (Ace), fluorene (F),
119 phenanthrene (P), anthracene (Ant), fluoranthene (Fl), pyrene (Pyr), benz[a]anthracene (BaAnt), chrysene (Chr),
120 benzo[b]fluoranthene (BbFl), benzo[k]fluoranthene (BkFl), benz[a]pyrene (BaPyr), indeno[1,2,3-c,d]pyrene (IPyr),
121 dibenz[a,h]anthracene (DBahAnt), benzo[g,h,i]perylene (BghiPer) (all 100 mg/L in acetonitrile), and PAH-DX-Mix 16
122 containing naphthalene-d₈ (N-d₈), acenaphthylene-d₈ (Acy-d₈), acenaphthene-d₁₀ (Ace-d₁₀), fluorene-d₁₀ (F-d₁₀),
123 phenanthrene-d₁₀ (P-d₁₀), anthracene-d₁₀ (Ant-d₁₀), fluoranthene-d₁₂ (Fl-d₁₂), pyrene (Pyr-d₁₂), benz[a]anthracene-d₁₂
124 (BaAnt-d₁₂), chrysene-d₁₂ (Chr-d₁₂), benzo[b]fluoranthene-d₁₂ (BbFl-d₁₂), benzo[k]fluoranthene-d₁₂ (BkFl-d₁₂),
125 benzo[a]pyrene-d₁₂ (BaPyr-d₁₂), indeno[1,2,3-c,d]pyrene-d₁₂ (IPyr-d₁₂), dibenz[a,h]anthracene-d₁₄ (DBahAnt-d₁₄),
126 benzo[g,h,i]perylene-d₁₂ (BghiPer-d₁₂) (all 10 mg/L in acetonitrile) to be used as internal standards (ISs) were purchased
127 from NEOCHEMA GmbH (Bodenheim, Germany).

128 All the listed chemicals were used without further purification.

129 2.2. Magnetic sorbent preparation and characterization

130 2.2.1. IONPs synthesis and silanization

131 IONPs were prepared by the coprecipitation protocol [37] with some modifications. Briefly, by operating under nitrogen
132 atmosphere at the constant temperature of 85 °C, FeCl₂·4H₂O (1.00 g, 5.0 mmol), FeCl₃ (1.56 g, 9.62 mmol) and 12 mL of
133 an aqueous solution of HCl 2 mol/L were vigorously stirred until complete dissolution. Thereafter, 10 mL of an aqueous
134 solution of NH₄OH (33%) were added dropwise and the mixture was stirred for 1 h. The reaction mixture was cooled at
135 room temperature and the product was collected by magnetic decantation. IONPs were washed with ultrapure water until
136 neutrality, then they were washed two times with 25 mL of methanol and dried under a nitrogen flow overnight.

137 Silanization was carried out by following the procedure reported by Esmailzadeh [38] with minor modifications. IONPs
138 (0.100 g) were dispersed by stirring at room temperature for 45 min in 15 mL of anhydrous toluene under nitrogen
139 atmosphere. Thereafter, 150 μ L of APTES were added and the solution was stirred at 120 $^{\circ}$ C for 18 h under nitrogen
140 atmosphere. The reaction mixture was cooled at room temperature and the product was collected by magnetic decantation.
141 Silanized IONPs (IONPs@NH₂) were washed two times with 25 mL of n-hexane, two times with 25 mL of acetone, two
142 times with 25 mL of methanol, and dried under a nitrogen flow overnight.

143 2.2.2. PUM198 synthesis

144 PUM198 was prepared by following the procedure reported by Balestri et al. [39]. Briefly, terephthalic acid (66 mg, 0.44
145 mmol), the bis-pyridine-bis amide ligand [40] (80 mg, 0.20 mmol), Zn(NO₃)₂·6H₂O (120 mg, 0.40 mmol), and 41 mL of
146 DMF were introduced in a 70 mL glass tube closed with a screw cap. The solution was maintained at 80 $^{\circ}$ C for 4 days
147 without stirring and then slowly cooled at room temperature. Yellow crystals were collected by vacuum filtration, washed
148 with DMF, and stored under DMF until use.

149 2.2.3. PUM198 magnetization

150 The magnetization of PUM198 was carried out by a direct magnetization approach by following the procedure proposed by
151 Hu et al. [41] with minor modifications. PUM198 crystals (20 mg) were first dried on a vacuum filter and dispersed in 3.5
152 mL of DMF together with IONPs@NH₂ (6.5 mg). The mixture was stirred vigorously at 120 $^{\circ}$ C for 12 h and cooled down
153 at room temperature. The magnetic sorbent was recovered by magnetic decantation and washed two times with 5 mL of
154 DMF.

155 Prior the use, the magnetic MOF was activated by a solvent exchange procedure. In brief, the sorbent was dispersed in
156 acetone for 24 h at room temperature by gentle shaking and recovered by magnetic decantation. The same procedure was
157 repeated with methylene chloride, then the sorbent was kept under vacuum at 50 $^{\circ}$ C overnight.

158 2.2.4. Characterization

159 Characterization was carried out by Attenuated Total Reflectance–Fourier Transform–Infrared (ATR–FT–IR) spectroscopy
160 in the mid infrared region (450–4000 cm⁻¹) using a Perkin Elmer Spectrum Two FT–IR Spectrometer (Milan, Italy). Powder
161 X-Ray Diffraction (PXRD) analyses were performed in Bragg-Brentano geometry using a Cu-K α radiation on a Rigaku
162 Smartlab XE equipped with a 2D Hypix3000 solid-state detector.

163 A Quanta FEG 250 (Thermo Fisher Scientific) Environmental Scanning Electron Microscope (ESEM) equipped with a
164 Bruker XFlash 6 | 30 (Billerica, Massachusetts) detector was used for the morphological investigation of the magnetic
165 sorbent and for the Energy Dispersive X-Ray analysis (EDX).

166 The magnetic properties of the sorbent and bare IONPs were determined by a Vibrating Sample Magnetometer (VSM)
167 model 7400 from Lake Shore (Westerville, USA). The maximum applied field was 1.8 T.

168

169 2.3. Optimization of the MD- μ SPE procedure

170 The MD- μ SPE procedure was carried out by means of an Argolab DU-32 ultrasonication bath (Modena, Italy) by applying
171 an ultrasound frequency of 40 kHz. All the extraction experiments were carried out using aqueous working solutions at the
172 concentration of 500 ng/L of each PAH. After extraction, 50 μ L of extract were recovered and spiked with the IS solution so
173 that their final concentration was 10 μ g/L. The ratio between the analyte peak area and the IS peak area deriving from the
174 injection of 1 μ L of extract was used as the response variable.

175 2.3.1. Selection of the elution solvent

176 Acetonitrile, isopropanol, cyclohexane, and a mixture 10% *v/v* of isopropanol in cyclohexane were tested as elution
177 solvents. The extractions were carried out under the following operating conditions: sample volume: 3 mL; sorbent amount:
178 10 mg; extraction time: 10 min; solvent volume: 130 μ L; elution time: 10 min. The ultrasound power was set at 72 W and
179 the temperature was kept at ambient conditions. The experiments were independently replicated three times. The extractive
180 capability of each solvent was evaluated in terms of number of extracted analytes, signal intensity and repeatability. One-
181 way analysis of variance (ANOVA) was used to measure statistically significant differences ($\alpha = 0.05$). Normality and
182 homoscedasticity assumptions were verified by applying Shapiro-Wilk's test and Bartlett's test (both $\alpha = 0.05$). The effect
183 size was estimated in terms of Cohen's η^2 [42]. Solvent-to-solvent multiple comparisons were performed by carrying out a
184 Bonferroni corrected Student's *t*-test (overall $\alpha = 0.05$).

185 2.3.2. Design of Experiments

186 2.3.2.1. Screening

187 The experimentation for the screening stage was planned according to a Plackett-Burman Design (PBD). The $N = 12$
188 experimental runs were performed in random order. Seven factors ($k = 7$) were investigated at two levels (-1 and +1):
189 sorbent amount (3–12 mg, *A*), sample volume (2–5 mL, *B*), solvent volume (70–200 μ L, *C*), extraction time (5–15 min, *D*),
190 elution time (5–15 min, *E*), ultrasonication power (48–96 W, *F*), and temperature (ice bath–ambient condition, *G*). The
191 design was saturated with four dummy variables. Data were fitted with a first-order model as follows:

192

$$y = b_0 + \sum b_i x_i + e$$

193 The coefficients related to the dummy variables b_d were used for the estimation of the pure experimental variance. The
194 significance of each regression coefficient was evaluated by comparing its absolute value with the respective semiamplitude
195 of the 95% confidence interval.

196 2.3.2.1. Optimization

197 Three main factors were investigated within their respective experimental domain as follows: sample volume (1–5 mL, X_1),
198 solvent volume (50–150 μ L, X_2), sorbent amount (2–14 mg, X_3). The experiments were planned according to a Box-Wilson
199 Central Composite Design (CCD) and each factor was studied at three levels (-1, 0, and +1). The experimental plan
200 accounted for $N = 20$ runs, including $n_0 = 6$ independent replicated measurements in the center of the experimental domain
201 for the estimation of the pure experimental variance. Experimental data were fitted with a second-order model as follows:

$$202 \quad y = b_0 + \sum b_i x_i + \sum b_{ij} x_i x_j + \sum b_{ii} x_i^2 + e$$

203 The significance of each regression coefficient was evaluated by comparing its absolute value with the respective
204 semiamplitude of the 95% confidence interval. The adequacy of each model was evaluated in terms of i) explained variance
205 (R_{adj}^2), ii) predictive capability in leave-one-out cross-validation (Q^2), and iii) validity by carrying out a lack-of-fit test ($\alpha =$
206 0.01).

207 Multicriteria optimization was carried out by means of the Derringer's desirability function method [43]. The desirability d_i
208 was defined for each analyte as:

$$209 \quad d_i = \begin{cases} 0 & \text{if } y_i < L_i \\ \frac{y_i - L_i}{U_i - L_i} & \text{otherwise} \end{cases}$$

210 where L_i is the upper limit of the 95% confidence interval of the minimum predicted response within the experimental
211 domain and U_i is the maximum predicted response within the experimental domain. The global desirability was computed
212 as the geometric mean of the single desirability values. The maximum global desirability value was found with a derivative-
213 free search algorithm.

214

215 2.4. MD- μ SPE procedure

216 5.4 mg of sorbent (5.4 ± 0.1 mg; $n = 33$) were added to 5 mL of aqueous sample spiked with 10 μ L of IS solution (final
217 concentration: 200 ng/L) and the mixture was ultrasonicated for 5 min. The sorbent was magnetically recovered, and the
218 supernatant was discarded. Thereafter, the analytes were eluted with 50 μ L of acetonitrile by ultrasonication for 15 min. The

219 ultrasonication power was set at 48 W and the ultrasonication was carried out adding ice in the ultrasonication bath. Before
220 each ultrasonication step, the sample was vortexed for 10 s to ensure the homogeneous dispersion of the sorbent.
221 The sorbent was magnetically separated, and the extract was transferred into a clear glass 2 mL vial equipped with a 300 μ L
222 glass insert. One microliter of extract was introduced in the GC injection port by means of a PAL COMBI-xt autosampler
223 (CTC Analytics AG, Zwingen, Switzerland) equipped with a 10 μ L syringe.

224

225 2.5. GC–MS analysis

226 A HP 6890 Series Plus gas chromatograph hyphenated with an MSD 5937 single quadrupole mass spectrometer (both by
227 Agilent Technologies, Milan, Italy) was used for the analyses.

228 An Rxi-5Sil MS capillary column (30 m length \times 0.25 mm i.d., 0.25 μ m film thickness; Restek, Bellafonte, USA) and
229 temperature programming (70 $^{\circ}$ C, held for 0.50 min, 15 $^{\circ}$ C/min to 290 $^{\circ}$ C, held for 4.00 min; runtime: 19.17 min) were used
230 for the chromatographic separation (constant flow mode: 1.0 mL/min). The carrier gas was helium. The split/splitless inlet,
231 equipped with a 5190-2293 ultra-inert liner (Agilent Technologies), was held at 300 $^{\circ}$ C and the injection was carried out in
232 pulsed splitless mode (pressure pulse: 20.0 psi until 0.3 min; purge flow: 1.2 mL/min at 1.20 min). The transfer line
233 temperature was 220 $^{\circ}$ C.

234 The mass spectrometer was equipped with an electron ionization ion source (EI–MS; 70 eV) maintained at 150 $^{\circ}$ C and mass
235 spectra were acquired in selected ion monitoring (SIM) mode. The following operating conditions were used: electron
236 multiplier voltage: 1153 V; dwell time: 30 ms; solvent delay: 3.80 min. Prior the analyses, 1 μ L of a solution containing
237 both PAHs and perdeuterated PAHs at the concentration of 1 mg/L in acetonitrile was injected and a full-scan
238 chromatogram was recorded (mass range: 45–350 m/z) in order to properly select the ions to be used for time-scheduled
239 SIM mode (Table S1).

240

241 2.6. Method validation and enrichment capability

242 The MD- μ SPE–GC–MS method was validated according to the EURACHEM guidelines [44] using drinking water as a
243 blank matrix by operating under the optimized conditions.

244 Limits of detection (LODs) and limits of quantitation (LOQs) were evaluated by submitting to the whole analytical method
245 10 aliquots of fortified blank matrix (30 ng/L for each analyte) in order to estimate the standard deviation s_0 . LODs and
246 LOQs, expressed in the signal domain, were calculated as follows:

247
$$LOD = y_0 + 2t_{(\alpha, m-1)} \frac{s_0}{\sqrt{n}}$$

248
$$LOQ = y_0 + 10 \frac{s_0}{\sqrt{n}}$$

249 where y_0 is the average signal of the unspiked procedural blank, t is the one-sided Student's t -value at the 5% significance
250 level and for $m - 1$ degrees of freedom, and n is the number of replicates *per* sample ($n = 2$) that will be averaged when
251 reporting the results. The corresponding concentrations were calculated according to the calibration curve equations by
252 projecting the obtained values on the x axis.

253 The calibration functions were evaluated in the LOQ–600 ng/L range ($k = 9$ concentration levels, $n = 2$ independent
254 replicated measurements *per* level) for each analyte. Student's t -test was carried out to assess the significance of the
255 intercept ($\alpha = 0.05$). Mandel's fitting test was used to assess the linearity of the calibration functions across the working
256 range, whereas the validity of the regression models was estimated in terms of lack-of-fit (both at $\alpha = 0.01$).

257 Trueness and precision were evaluated at 60, 250 and 550 ng/L concentration levels. Repeatability and intermediate
258 precision were estimated by carrying out a set of independent duplicated measurements for each concentration level each
259 day for 5 days. The measurements were performed by a different operator and by using freshly prepared working solutions
260 each day. ANOVA ($\alpha = 0.05$) was carried out to evaluate the variability under intermediate precision conditions. Both
261 repeatability and intermediate precision were expressed as relative standard deviations ($RSD\%$). Trueness was expressed in
262 terms of spike-recovery rate ($RR\%$) as follows:

263
$$RR\% = \frac{x'}{x_{\text{spike}}} \times 100$$

264 where x' is the concentration calculated *via* the calibration curve equation and x_{spike} is the nominal spiked concentration of
265 the analyte in the blank matrix. $n = 10$ independent determinations *per* concentration level were carried out.

266 Extraction yield was calculated from the ratio between the experimental and theoretical peak areas for each aromatic
267 hydrocarbon: accordingly, the theoretical peak areas were evaluated by spiking each analyte directly into the extraction
268 solvent used for the desorption step. Enrichment factors (EFs) were also calculated to estimate the enrichment capability of
269 the composite material and the ones of the bare IONPs. The experiments were carried out by working under the optimized
270 conditions by submitting to the MD- μ SPE procedure solutions at the concentration of 500 ng/L. EFs were calculated as the
271 ratio between the peak area for each analyte in the extract and the peak area for each analyte obtained by submitting to
272 analysis a solution at the concentration of 50 μ g/L. Since the measurements ($n = 3$) were carried out at different
273 concentration levels, the responses were corrected by using the proper response factor [6].

274 2.7. Analysis of real samples

275 The analytical method was used for the quantitation of PAHs in 19 underground water samples collected in the province of
276 Parma (Emilia-Romagna, Italy), in the neighboring of a company devoted to the production of tar and other chemicals. All
277 the samples were stored in amber glass vials sealed with PTFE septa at 4 °C until the analysis. Each sample was analyzed in
278 duplicate.

279 2.8. Software

280 Multiple linear regression and multicriteria optimization were carried out by running using in-house written MATLAB
281 R2019a (Mathworks, Natick, Massachusetts, USA) scripts. The HP ChemStation (Agilent Technologies) software was used
282 for signal acquisition and for the handling of GC–MS data.

283

284 3. Results and discussion

285 3.1. Synthesis and characterization of the magnetic PUM198

286 PUM198 is a microporous pillared MOF resulting from the self-assembly of $\text{Zn}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, terephthalic acid, and a bis-
287 pyridine-bis amide ligand containing a biphenylene scaffold [39]. Although non specific interactions with the MOF can be
288 established, especially when considering high concentration levels, the presence of differently extended aromatic ligands
289 can promote interaction between the framework and target analytes via non-covalent interactions, i.e., π - π stacking and
290 London dispersion forces, thus increasing the adsorption yield.

291 PUM198 is characterized by a doubly interpenetrated framework, where the py-containing ligands (L1) connect 2D planes
292 containing the terephthalate and the Zn^{2+} ions, as can be seen in Figure 1. In the SBUs of formula $[\text{Zn}_2(\kappa^1\text{-COO})_2(\mu\text{-}$
293 $\text{COO})_2(\text{L1})_4]$ two carboxylates bridge the two Zn^{2+} ions, while the other two behave as monodentate ligands. Microporous
294 channels of $5.6 \text{ \AA} \times 17.4 \text{ \AA}$ run along the c-axis direction, where several DMF molecules can be found. After removal of the
295 solvent electron density, a void volume corresponding to 28% of unit cell was calculated (2125 \AA^3 , calculated by Contact
296 Surface Function of Mercury [45], Figure S1). The framework results rather thermally stable, as evidenced by TGA
297 analysis, with decomposition occurring at 400 °C. The presence in the framework of the aromatic rings contained in the two
298 organic linkers creates an ideal environment for host-guest interactions between the framework and the PAH adsorbed
299 molecules.

300 For the fabrication of the MD- μ SPE device, a post-synthetic modification of PUM198 was then required. The material was
301 assembled by a multi-step procedure, based on direct magnetization of the MOF with amino-functionalized IONPs. The

302 synthetic protocol considers the initial synthesis of bare IONPs followed by their functionalization with amino groups and,
303 lastly, the grafting of the obtained IONPs@NH₂ onto PUM198.

304 The successfulness of the assembly was confirmed by ATR-FT-IR spectroscopy and PXRD analysis: the spectra and traces
305 corresponding to the different intermediates are reported in Figure 2. Bare IONPs showed a broad weak absorption band
306 around 3400 cm⁻¹ and a mild one around 550 cm⁻¹. These signals are ascribed to the O-H and Fe-O stretching vibrations,
307 typical of Fe₃O₄ systems [38]. The absorption bands around 990 cm⁻¹ and 1220 cm⁻¹ in the IONPs@NH₂ spectrum
308 confirmed the successful functionalization of IONPs with APTES, since they are related to the Si-O-Fe and Si-O-Si
309 vibrations [46], respectively. The band at 1660 cm⁻¹ in the spectrum of PUM198 can be related with the presence of
310 monodentate κ¹-COO⁻ groups in the framework. In addition, the band at 1670 cm⁻¹ could be related to the stretching of the
311 amidic C=O of L1 [40]. The spectrum of IONPs/PUM198 showed the main bands present in the PUM198 and IONPs
312 spectra. The attenuation of the band at 1660 cm⁻¹ could be indicative of the involvement of the κ¹-COO⁻ groups of the
313 framework in grafting the IONPs@NH₂ on the surface of coarse PUM198 crystals: this spectral evidence is in agreement
314 with the ESEM micrographs (Figure S2). A similar result, but involving free carboxylic groups was observed by Hu et al.
315 [41], who grafted APTES-coated magnetite on MOF-5 crystals. The absorption bands around 990 cm⁻¹ (related to the Si-O-
316 Fe vibration) was not visible in the spectrum related to the magnetic sorbent, but its diffraction trace showed a broad band
317 around $2\theta \approx 23^\circ$, present also in the trace of IONPs@NH₂, most likely ascribable to the amorphous nature of the APTES
318 coating. In addition, the presence of Si in the sorbent, as well as the one of other elements related to IONPs and PUM198
319 (Fe, Zn, O, and C), was confirmed by EDX (Figure S3).

320 Comparison between the PXRD traces of pristine PUM198 and magnetized IONPs/PUM198 indicates retention of the
321 starting framework, with the intense signal at $2\theta \approx 36^\circ$ assuring the functionalization of the MOF crystals with magnetic
322 coating.

323 The magnetic measurements gave clear indication about the successful synthesis of the sorbent (Figure S4). At room
324 temperature bare IONPs showed an evident magnetic response with a specific magnetization value of 39 A×m²/kg at 1.8 T
325 (Figure S4a); IONPs/PUM198 displayed a similar magnetic response with magnetization reaching 12 A×m²/kg at 1.8 T
326 (Figure S4b). In the latter case, the specific magnetization was calculated considering the total mass of the specimen
327 analyzed with VSM, while renormalizing magnetization only to the weight fraction of IONPs a value of 40 A×m²/kg at 1.8
328 T was obtained, which well compares with the bare IONPs value. Both the graphs in Figure S4 show that the magnetic
329 response was dominated by the superparamagnetic contribution of the smaller IONPs, while a minor fraction of larger
330 magnetic aggregates gave rise to a small hysteresis (insets in Figures S4a and S4b).

331 3.2. Optimization of the MD- μ SPE procedure

332 3.2.1. Selection of the elution solvent

333 The solvent plays a crucial role in all the sample preparation techniques that involve an elution step. Several factors should
334 be taken into consideration both to provide a high extraction efficiency and to ensure a reliable chromatographic behavior of
335 the analytes. In the present study the effect of isopropanol, cyclohexane, and acetonitrile was evaluated for the elution of the
336 target analytes. The results are summarized in Figure 3.

337 One-way ANOVA highlighted statistically significant differences in the average response for all the analytes ($p < 0.05$;
338 Cohen's $\eta^2 \geq 0.77$). Despite cyclohexane being nonpolar as the analytes, it showed weak extractive capabilities, providing
339 poor GC-MS signals, whereas high molecular weight PAHs were not recovered. This behavior could be ascribed to the
340 residual water on the sorbent which prevented the cyclohexane to properly wet its surface: in the case of high molecular
341 weight PAHs, being more lipophilic [47], they could have preferably remained adsorbed rather than released into the
342 residual water for water/cyclohexane partitioning. A similar explanation was pointed out by Arcoleo et al. when methylene
343 chloride was used in the development of a microextraction by packed sorbent (MEPS) procedure for the extraction of PAHs
344 from polar samples [6]. Furthermore, this behavior could also be ascribed to the impossibility of cyclohexane in establishing
345 interactions with the framework other than London dispersion forces, whereas acetonitrile and isopropanol can interact *via*
346 hydrogen bonding with carboxylic and amide groups. In fact, the extractive capacity of cyclohexane could be improved in
347 terms of number of extracted analytes by adding 10% *v/v* of isopropanol. Nevertheless, the addition of isopropanol provided
348 poor repeatability ($RSD\% > 24\%$) and did not significantly improve ($p > 0.05$ Bonferroni corrected) the extraction ability
349 towards the analytes which were extracted with cyclohexane alone. The best results were achieved with isopropanol and
350 acetonitrile: acetonitrile showed greater or not statistically significantly different performances in terms of extraction
351 capability when compared with isopropanol ($p > 0.05$ Bonferroni corrected). As for the repeatability, the most promising
352 results were obtained with acetonitrile, with $RSD\%$ lower than 13%, whereas isopropanol provided $RSD\%$ up to 26%. The
353 poor repeatability achieved by using isopropanol might be related to its viscosity, which could obstruct the diffusion of the
354 analytes towards the organic phase. For the reasons stated above, acetonitrile was selected as the elution solvent and used
355 for further experimentation.

356 3.2.2. Design of Experiments

357 3.2.2.1. Screening

358 Since there are a multitude of factors that can potentially affect the effectiveness of the MD- μ SPE procedure [48], a
359 preliminary screening step is crucial. Screening designs allows for i) the elimination of the poorly influent factors ii) the

360 adjustment of the experimental domain of the important ones by carrying out a reduced number of experiments. In the
361 present work, the following factors were studied according to a PBD experimental plan: sorbent amount, sample volume,
362 solvent volume, extraction time, elution time, ultrasonication power, and temperature.

363 The experimental domains were set according to preliminary experiments (data not shown) and previous studies [47,49,50].
364 To guarantee a good balance between the time required for the sample preparation and analysis time, extraction and elution
365 times greater than 15 min were not considered (see section 2.5). Temperature was studied as a categorical variable as “ice
366 bath” and “ambient condition”, since the ultrasonication process inevitably increases the temperature of the water bath
367 without the possibility of a fine control. Ionic strength was not investigated, since our previous study [36] highlighted that
368 high concentration of sodium ions could hinder the interaction between the sorbent and the analytes by establishing π -cation
369 interactions with the MOF lattice, resulting in a decrease of the performance.

370 In general, the results highlighted three different behaviors of the analytes: i) the response of low molecular weight PAHs
371 was positively influenced by the amount of sorbent used for the extraction; ii) the response of mid-molecular weight
372 analytes was positively influenced by the sample volume and negatively influenced by the solvent volume; iii) the response
373 of high molecular weight PAHs was negatively influenced by the sorbent and the solvent amounts, whereas it was positively
374 influenced by the amount of sample subjected to the extraction procedure. As an example, the coefficient plot of Ace, Pyr,
375 and BaPyr are reported in Figure S5.

376 The remaining investigated factor did not significantly impact the recovery of the analytes and were, therefore, fixed at a
377 reasonable value for the rest of the experimentation: i) extraction time had a negligible effect with a negative coefficient for
378 most of the analytes, therefore its value was fixed at 5 min; ii) elution time had a positive coefficients on the majority of the
379 analytes, therefore its value was fixed at 15 min; iii) the ultrasonication power was set at 48 W; iv) ice was added to the
380 ultrasonication bath to prevent the loss of low molecular weight PAHs and the evaporation of the elution solvent.

381 3.2.2.2. Optimization

382 The results of the PBD suggested that sample volume, solvent volume, and sorbent amount are the most critical factors
383 affecting modelled responses. Therefore, these factors were further investigated by carrying out the experiments of a CCD
384 for the estimation of the response surfaces. The experimental domains of the three factors were adjusted according to the
385 results obtained from the PBD.

386 Although more intense signals could be obtained by incrementing the amount of sample subjected to analysis, the
387 experimental domain was expanded towards smaller volumes (1 mL), whereas volumes greater than 5 mL were not
388 considered. This ensures low sample consumption, thus allowing the treatment of small sample volumes when its

389 availability is limited. The solvent volume had a negative influence on the signal intensity, suggesting that the partition
390 equilibrium is reached below 200 μL and that larger volumes dilutes the extract. The experimental domain was shifted
391 downwards: 50 μL were selected as the lower level, since a smaller volume was difficult to recover, whereas the upper level
392 was decreased at 150 μL . The experimental domain of the sorbent amount was extended both upwards (14 mg) and
393 downwards (2 mg) because low and high molecular weight PAHs showed opposite behaviors in the screening stage.
394 Amounts smaller than 2 mg were not considered to avoid a large error in the mass measurement, whereas values higher than
395 14 mg were not considered to limit the amount of sorbent *per* extraction.

396 ANOVA was carried out on the logarithmically transformed responses [51]. All the models were significant and valid, thus
397 meaning that the error deriving from the model approximation is not significantly greater than the pure experimental error
398 ($p > 0.01$). The calculated models (Table 1) showed $R_{\text{adj}}^2 \geq 0.91$ and $Q^2 \geq 0.75$, demonstrating their adequacy in fitting and
399 their predictive capability in cross-validation. As an example, the contour plots related to Ace, Pyr, and BaPyr are reported
400 in Figure S6.

401 As far as only the main factors are considered, sample volume and solvent volume are almost always present with a positive
402 and negative coefficient, respectively. This is in accordance with the findings of the screening stage and with the general
403 idea behind preconcentration processes that involves an elution step: the larger the sample volume and the smaller the eluent
404 volume, the greater the preconcentration factor. The main factor related to the sorbent mass had a positive influence on low
405 molecular weight PAHs and a negative influence on high molecular weight PAHs. Quadratic terms related to the sample
406 volume and sorbent amount are also present with a negative coefficient, suggesting that the response increases until certain
407 values and then it increases less rapidly and/or reaches a plateau. This could be related to the saturation of the sorption sites.
408 Interaction terms involving the sorbent mass are also present.

409 The response functions were then combined in a single response using the Derringer's method of the desirability functions.
410 The maximum global desirability value $D = 0.90$ (single desirability values $d_i \geq 0.71$) was achieved with the extraction of 5
411 mL of sample by using 5.4 mg of sorbent and 50 μL of acetonitrile. This means that a good compromise in the experimental
412 setting of the investigated factors have been reached. The optimal experimental conditions were valid, since lack-of-fit was
413 not significant and the models performed well not only in fitting, but also in cross-validation. In addition, the optimal values
414 of the investigated factors are more than feasible, allowing for the simultaneous extraction of all the target analytes ensuring
415 a low consumption of sample, solvent, and sorbent.

416

417

418 3.3. Validation of the MD- μ SPE-GC-MS method

419 The developed analytical method was validated by operating under optimized conditions. LODs, LOQs, calibration curve
420 equations, and EFs are summarized in Table 2. In order to evaluate the performances of the magnetic MOF accounting for
421 both stages of the extraction process, namely the adsorption and desorption stages, extraction yields were also calculated
422 (Table S2). The lowest extraction yields were obtained for the low molecular weight compounds, thus suggesting an easier
423 escape of these pollutants from the channels of the MOF as a consequence of the reduced dimension. Taking into account
424 that the optimal extraction conditions proved that a sample volume of 5000 μ L and a sample extract of 50 μ L had to be
425 used, the same results were obtained for the EFs (Figure S7) with the highest enrichment capabilities observed for the mid-
426 molecular weight PAHs. The low molecular weight analytes showed the lowest EFs, whereas for the high molecular weight
427 PAHs an intermediate situation was observed. This could be ascribed to the different steric hindrance. As already stated,
428 low molecular weight compounds could easily diffuse inside and outside MOF pores, thus being less retained. The high
429 molecular weight PAHs showed EFs 20–30% lower than those achieved for mid-molecular weight compounds: this
430 behavior suggests that the high molecular weight PAHs could have been sorbed also on the PUM198 surface rather than
431 diffusing inside MOF cavities due to their high steric hindrance. Mid-molecular weight PAHs could benefit from both
432 interaction mechanisms, and showed, therefore, the highest EFs. This is in accordance with the LODs and the LOQs that
433 were derived through the validation process. Lastly, the EFs for the IONPs/PUM198 were compared with the ones of bare
434 IONPs: an average improvement of 11 standard deviations [52] was observed, proving the successful IONPs
435 functionalization.

436 The analytical method exhibited LODs in the 6.7–27 ng/L range, adequate with the detection of all the 16 analytes at trace
437 levels. The calibration models were statistically significant ($p < 0.05$), and linearity was verified according to the Mandel's
438 fitting test in the LOQ–600 ng/L range for all the PAHs. All the calibration models were not affected by significant lack-of-
439 fit, meaning that the approximation error could be explained in terms of pure experimental variance.

440 The results of the precision study showed $RSDs_{\%}$ for repeatability within 16% (level 1: 60 ng/L), 18% (level 2: 250 ng/L),
441 and 17% (level 3: 550 ng/L). Satisfactory results were achieved also by working under intermediate precision conditions,
442 with $RSDs_{\%}$ within 19% (level 1: 60 ng/L), 26% (level 2: 250 ng/L), and 24% (level 3: 550 ng/L). ANOVA did not
443 highlight the presence of statistically significant differences ($p > 0.05$) among the results obtained under intermediate
444 precision conditions. Acceptable trueness, expressed in terms of average spike-recovery rate (\pm semiamplitude of the 95%
445 confidence interval), was achieved across all the linear range: 99 (± 13)–126 (± 8)% (level 1: 60 ng/L), 80 (± 5)–115 (± 7)%
446 (level 2: 250 ng/L), and 88 (± 14)–99 (± 9)% (level 3: 550 ng/L). All the achieved results are reported in Table S3.

447 The performances of the developed analytical method were compared with other MD- μ SPE-based methods reported in the
448 literature. Several parameters were taken into consideration: i.e., sorbent material, analytical technique, sorbent amount,
449 sample volume, solvent volume, estimate of the time *per* sample (calculated as the sum between the time required for the
450 adsorption and the time required for the elution), number of analytes, and LODs. As shown in Table 3, the developed MD-
451 μ SPE-GC-MS provided LODs lower or comparable with those achieved in previously published studies. This finding is
452 remarkable, especially considering that that the proposed methodology is able to produce a noticeable preconcentration by
453 using reduced volume of sample without the need of any solvent exchange procedure. Another key point concerns the
454 consumption of a small amount of extraction solvent, only 50 μ L *per* extraction, approximately 3-20 times lower than that
455 used in previous studies [27,48,49,51,55–60] according to the principles of green analytical chemistry. Finally, a good
456 sample throughput can be forecasted, being the time required for the extraction procedure compatible with the analysis time.

457

458 3.4. Analysis of real water samples

459 Finally, the method was applied for the determination of PAHs in 19 underground water samples taken in the neighboring
460 of a contaminated site in the province of Parma. As shown in Table 4, 6 samples out of 19 were characterized by PAH
461 pollution. As an example, the waterfall plot (Figure S8) shows the gas chromatograms of the sample A1, a procedural blank
462 and a fortified blank.

463 As shown in Table 4, various PAHs were determined in all the investigated samples. A2 and A5 samples were massively
464 contaminated samples, showing the highest \sum^{16} PAH concentrations: 830 (± 30) and 197 (± 5) μ g/L, respectively, with Ace
465 being the most abundant analyte (81 and 64% of the total, respectively). Except for the samples A1 and A6, the low
466 molecular weight analytes were the most abundant compounds, whereas among the high molecular weight PAHs, only IPyr,
467 was detected in sample A6. Finally, for confirmation purposes, the analytical results were compared with those obtained
468 using the EPA8272 method properly extended for the detection of high molecular weight PAHs. The results obtained *via* the
469 MD- μ SPE-GC-MS method were comparable with the ones obtained *via* the independent SPME-GC-MS method, thus
470 demonstrating the reliability of the method presented in this study,

471

472 4. Conclusions

473 A reliable MD- μ SPE-GC-MS based on the post-synthetically modified MOF PUM198 is proposed for the extraction and
474 determination of the 16 US-EPA priority PAHs from water samples. PUM198 proved to be a suitable material for the

475 enrichment of PAHs due to its porosity and structure with the aromatic ligands creating an ideal environment for host-guest
476 interactions between the framework and the analytes of interest. The method exhibited quantitation limits in the low ng/L
477 range, good precision and trueness across all the linear range, ensuring accurate results also at the LOQ level. In accordance
478 with the principles of green analytical chemistry, the key points of the proposed methodology rely on both the reduced
479 solvent consumption and the low amount of sample required for the extraction procedure, approximatively 3–20 times lower
480 than those reported in other studies, thus suggesting the applicability of the method also for the treatment of samples of
481 limited availability. Finally, the good balance between the time required for sample preparation and analysis time allows for
482 good sample throughput, making the method suitable for routine applications.

483

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488

489 **Authorship Contribution Statement**

490 **Fabio Fornari:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing - Original
491 Draft, Visualization

492 **Federica Bianchi:** Conceptualization, Methodology, Resources, Writing - Review & Editing, Funding acquisition,
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497 **Paolo Pio Mazzeo:** Formal analysis, Investigation, Writing - Review & Editing

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500 **Declaration of Competing Interest**

501 The authors declare that they have no known competing financial interests or personal relationships that could have
502 appeared to influence the work reported in this paper.

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663 **Figure captions**

664 **Figure 1:** Schematic representation of the synthetic protocol of PUM198. In the framework, the organic linkers are reported
665 in grey while metallic SBUs are reported in colored polyhedral style. Spacefill representation of the nets is superimposed to
666 clarify the formation of channels running along the crystallographic a-axis. Hydrogen atoms are omitted for the sake of
667 clarity.

668

669 **Figure 2:** ATR–FT–IR spectra (top) and PXRD traces (bottom) of IONPs, IONPs@NH₂, PUM198, and IONPs/PUM198.
670 ATR–FT–IR signals are reported as normalized transmittance (%; normalized to the maximum). PXRD signals are reported
671 as normalized intensity (normalized between the maximum and the minimum). Each spectrum was shifted upwards or
672 downwards for comparison purposes.

673

674 **Figure 3:** Effect of different solvents on analyte extraction. Results are plotted as mean (\pm standard deviation). ACN:
675 acetonitrile; iPrOH: isopropanol; Cy: cyclohexane.

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