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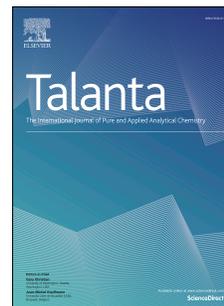
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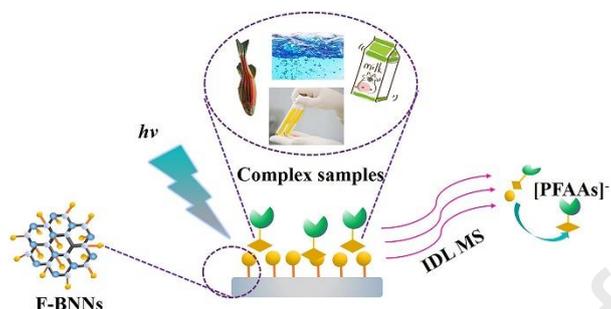
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Credit Author Statement

Yanfang Zhao: conceptualization, methodology, formal analysis, and original draft preparation; Huizhi Li: methodology, data analysis, and software preparation; Guiju Xu: investigation, experiment of sample pretreatment, and methodology; Rabah Boukherroub: writing- review & editing; Xiang Yu: project administration, validation, and review; Xiangfeng Chen: conceptualization, draft review, and language editing.

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Graphical abstract



Fluorinated hexagonal boron nitride nanosheets (F-BNNs) was first used as an inorganic matrix for matrix-assisted laser desorption and ionization mass spectrometry (MALDI MS) analysis of perfluoroalkyl acids (PFAAs) in complex samples in negative reflector mode.

1 **Fluorinated Boron Nitride Nanosheets as an Inorganic**
2 **Matrix for the MALDI Mass Spectrometry Analysis of**
3 **Perfluoroalkyl Acids**

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6

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15

16 **Abstract**

17 We report, for the first time, the application of fluorinated hexagonal boron nitride
18 nanosheets (F-BNNs) as an effective inorganic matrix for matrix-assisted laser
19 desorption and ionization mass spectrometry (MALDI-MS) analysis of perfluoroalkyl
20 acids (PFAAs). Fluoride modification of F-BNNs increases both enrichment ability and
21 ionization efficiency. The method was validated using environmental water, milk,
22 human serum samples, and zebrafish imaging that has been previously exposed to
23 PFAAs. The method provided in this work holds considerable promise in term of rapid
24 analysis, sample requirement, and practicability.

25 **Keywords:** Fluorinated hexagonal boron nitride nanosheets; Inorganic matrix;
26 Perfluoroalkyl acids; Fluorine–fluorine interactions; MALDI-MS; Imaging

27

28 **1. Introduction**

29 Matrix-assisted laser desorption and ionization mass spectrometry (MALDI-
30 MS) has been developed into a convenient and sensitive strategy for analyzing
31 various molecules in complex samples [1,2]. Organic matrices, including sinapic
32 acid (SA), 2,5-dihydroxybenzoic acid (DHB) and α -cyano-4-hydroxycinnamic
33 acid (CHCA), are usually employed by MALDI-MS [3,4]. However, these
34 matrices commonly produce high background noise in the low molecular weight
35 range ($m/z < 600$), which may limit their application for the detection of various
36 small molecules [5-7].

37 To overcome these limitations, extensive efforts have been devoted to the
38 development of various organic molecules, such as 3,4-dimethoxycinnamic acid
39 (DMCA) [8], 3-aminophthalhydrazide (3-APH) [9], and 2,3,4,5-tetrakis (3',4'-
40 dihydroxylphenyl) thiophene (DHPT) [10], for use as MALDI-MS matrices.
41 Nanomaterials, including carbon materials [11-13], silicon-based materials
42 [14,15], metal-containing nanomaterials [16,17], and covalent organic
43 frameworks [18,19] have been successfully applied as inorganic matrices to
44 enhance the signal-to-noise ratio of MALDI-MS and expand its application.

45 Specifically, boron nitride nanosheets (BNNs) have demonstrated great
46 potential as a MALDI matrix, owing to its similarity to graphene, namely its
47 atomic arrangement and electron configuration [20]. It is well-established that
48 the shape/size of nanomaterials may affect the spectroscopic signal [21,22].
49 Therefore, the large nanosheets of boron nitride, featuring a high density of active
50 sites, are favorable in enhancing its performance in MALDI-MS analysis.
51 Moreover, both the large specific surface area (SSA) and polarity of the B–N
52 bond enable BNNs to easily adsorb other molecules *via* weak interactions [23,24].
53 The proton transporter with a structure comprising B–H six-membered rings is
54 expected to help in ionizing analytes during the MALDI process. Fluorinated
55 hexagonal boron nitride nanosheets (F-BNNs) are an important derivative of
56 BNNs [25,26]. Unlike BNNs, the F atoms provide much opportunities to adsorb
57 and enrich other fluorinated compounds via fluorine–fluorine interactions [27].

58 It is noteworthy that fluoride modification can significantly reduce the
59 agglomeration of BNNs, providing them with good dispersibility in water to
60 assist the LDI process.

61 Perfluoroalkyl acids (PFAAs) are a class of synthetic organic pollutants with
62 carbon skeletons whose hydrogen atoms are replaced by fluorine atoms [28,29].
63 PFAAs are widely applied in industrial manufacturing and consumer goods due
64 to their special properties originating from their fluorine atoms. PFAAs screening
65 is significantly important to the studies of environmental development and public
66 health [30]. To date, high-performance liquid chromatography coupled with
67 tandem mass spectrometry (HPLC-MS/MS) is the primary method in detecting
68 PFAAs in complex samples [31,32]. However, such methods require
69 complicated, and laborious sample preparation procedures.

70 In this study, porous F-BNNs substrate was prepared and employed as an
71 efficient platform to improve the MALDI-MS analysis of PFAAs, for the first
72 time. We demonstrated that F-BNNs exhibit better MALDI-MS performance in
73 negative-ion mode than traditional organic matrices and carbon-based materials.
74 Furthermore, high sensitivity and good reproducibility were achieved when the
75 F-BNNs were used as an adsorbent of PFAAs and MALDI-MS matrix. Notably,
76 the method allowed successful detection of PFAAs in environmental water, milk,
77 and human serum samples. Moreover, MALDI-MS imaging (MSI) using the F-
78 BNNs matrix revealed the distribution of PFAAs in zebrafish after their exposure
79 to these chemicals. These results demonstrate that F-BNNs is an effective matrix
80 for MALDI-MS analysis of PFAAs in complex environmental and biological
81 samples. Fig. 1 illustrates the synthesis of the F-BNNs and its application.

82 **2. Experimental**

83 *2.1 Chemicals*

84 PFAAs included perfluorobutanoic acid (PFBA), perfluorobutanesulfonic acid
85 (PFBS), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA),
86 perfluorohexanesulfonate (PFHxS), perfluorooctanoic acid (PFOA),
87 perfluorononanoic acid (PFNA), perfluorooctanoic sulfonic acid (PFOS),

88 perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnA). The
89 details of chemicals and other reagents are provided in the Supporting
90 Information.

91 *2.2 Preparation of F-BNNs matrix*

92 The BNNs were synthesized using a modified literature method [33]. The
93 BNNs were then fluorinated *via* a one-step process employing ammonium
94 fluoride [34]. The chemicals, characterization methods, and detailed synthetic
95 procedures are described in the Supporting Information.

96 *2.3 Sample preparation*

97 The details of sample preparation procedure are described in the Supporting
98 Information.

99 *2.4 MALDI-MS analysis*

100 A Bruker rapiflex TOF mass spectrometer (Bruker, Bremen, Germany) was
101 employed to conduct MALDI experiments. Sample measurements were recorded
102 in negative reflector mode within a mass range of m/z 200–600. All the mass
103 spectra were acquired using flexControl software (version 3.4) provided by the
104 manufacturer. The obtained MS data were analysed by Flex Analysis 4.0, and
105 MSI results were analysed by Scils 2018b software (Bruker, Bremen, Germany).
106 The other instrumental parameters are described in the Supporting Information.

107 **3. Results and discussion**

108 *3.1 Characterization of F-BNNs*

109 Scanning electron microscopy (SEM) image of the F-BNNs (Fig. 2a) showed
110 a 2D layered structure with extensive wrinkles, which was further confirmed by
111 transmission electron microscopy (TEM) (Fig. 2b) imaging. X-ray photoelectron
112 spectroscopy (XPS) (Fig. 2c) was carried out to identify the related elements and
113 chemical composition of the F-BNNs. The B 1s, N 1s, and O 1s were observed
114 at binding energies of 190.5, 397.9, and 532.1 eV, respectively. As expected, a
115 peak at 686.9 eV corresponding to F 1s was evidenced for the F-BNNs, but not
116 for the un-modified BNNs. In addition, C 1s peaks were observed in both the
117 BNN and F-BNNs XPS spectra, which may be ascribed to the carbon coating

118 employed during XPS test procedure. The F 1s fine spectrum (Fig. 2d) of the F-
119 BNNs indicated their successfully modification with fluoride. The B 1s fine
120 spectrum in the F-BNNs (Fig. 2e) is deconvoluted into three peaks corresponding
121 to B–N, B–F, and B–O bonds at 190.3, 191.0, and 192.0 eV, respectively. The
122 binding energies of the B–F and B–N bonds are in good agreement with a
123 previous study on F-BNNs obtained *via* a hydrothermal reaction method [34].
124 Notably, the presence of B–F bond signal in the B 1s XPS spectrum further
125 confirmed the successful fluorine-functionalization [35]. The N 1s fine spectrum
126 of the F-BNNs (Fig. 2f) exhibited a main peak at 397.9 eV due to N–B bonds,
127 and a peak at around 398.7 eV ascribed to N–F bonds. The BNNs and F-BNNs
128 were subsequently evaluated by X-ray diffraction (XRD) (Fig. 2g). The XRD
129 pattern of BNNs possessed a wide diffraction peak at 25.3° and another peak at
130 42.5° assigned the (002) and (100) planes of BNNs, respectively. The ordered in-
131 plane characteristics of the BNNs were clearly altered by fluorine-
132 functionalization [36]; for instance, the disappearance of the (100) diffraction
133 peak at 42.5° in the F-BNNs pattern obviously indicated that fluorine-
134 functionalization caused a collapse of the crystal structure of BNNs. The FTIR
135 spectra of BNNs and F-BNNs (Fig. 2h) displayed a strong band at 1379.2 cm^{-1}
136 ascribed to B–N stretching. Moreover, the sharp band at 804.1 cm^{-1} was assigned
137 to the B–N–B out-of-plane bending mode [37]. Additionally, a B–F vibrational
138 feature was reflected by the presence of two weak peaks at around 1265.2 and
139 1075.2 cm^{-1} , respectively. The F-BNNs' SSA was determined to be $798.1\text{ m}^2/\text{g}$
140 (Fig. 2i), and the pore size was 3.5 nm (Fig. 2i insert). The optical properties of
141 F-BNNs were assessed during UV-vis absorption spectrophotometry. A strong
142 and wide (300 to 700 nm) optical absorption was observed (Fig. S1); this feature
143 is beneficial for its application as an inorganic matrix to absorb efficiently the
144 incoming laser energy and then transfer it to target molecules to achieve their
145 desorption/ionization and analysis by MALDI-MS [18].

146 *3.2 Comparative study of the desorption/ionization of PFAAs*

147 F-BNNs exhibited a clean background (Fig. S2) in low-mass region. The
148 performance of the F-BNNs as a MALDI matrix was compared to that of other
149 traditional organic matrices and graphene-based materials, including CHCA,
150 DHB, BNNs, graphene oxide (GO), and graphene sheets (GS). As shown in Fig.
151 3a, ten deprotonated $[M-H]^-$ ions of PFAAs were detected using the F-BNNs
152 matrix. The m/z peaks at 213.03, 299.10, 313.05, 363.06, 399.11, 413.07, 463.08,
153 499.13, 512.94, and 563.09 were assigned to $[PFBA-H]^-$, $[PFBS-H]^-$, $[PFHxA-$
154 $H]^-$, $[PFHpA-H]^-$, $[PFHxS-H]^-$, $[PFOA-H]^-$, $[PFNA-H]^-$, $[PFOS-H]^-$, $[PFDA-$
155 $H]^-$, $[PFUnA-H]^-$ species, respectively. In contrast, the BNNs (Fig. 3b), CHCA
156 (Fig. 3c), DHB (Fig. 3d), GO (Fig. 3e), and GS (Fig. 3f) matrices only detected
157 seven, five, four, three, and three analytes, respectively. Moreover, the relative
158 mass peak intensities of the analytes detected with the F-BNNs matrix were
159 higher than those recorded using the other matrices. These results demonstrate
160 that the F-BNNs effectively increased the desorption/ionization efficiencies of
161 small molecules.

162 *3.3 Salt tolerance and repeatability of F-BNNs as a MALDI matrix*

163 The salt tolerance experiments in supporting information were conducted for
164 the analysis of various aqueous solutions of PFHxS in presence of increasing
165 concentration of NaCl (0-500 mM). When NaCl concentration reached 500 mM,
166 the mass peak intensity of PFHxS decreased to 84.5% of the initial value (Fig.
167 4a), demonstrating the strong salt tolerance of F-BNNs as an inorganic matrix.
168 The relative standard deviations (RSDs) of shot-to-shot and spot-to-spot for
169 PFAAs were 6.72-11.3% and 7.33-12.6%, respectively (Table S1). Furthermore,
170 six batches of F-BNNs were prepared to study the reproducibility of the synthetic
171 method. As presented in Table S2, the batch-to-batch assay varied from 2.99%
172 to 13.4%, which clearly demonstrates the good reproducibility performance
173 owing to the uniform distribution of F-BNNs.

174 *3.4 Possible interaction mechanism between F-BNNs and PFAAs*

175 The electronic transition mechanism provided a significant influence in
176 desorption/ionization of PFAAs. Upon laser light adsorption, electrons were

177 emitted from F-BNNs, followed by their subsequent interaction with PFAAs to
178 produce $[M-H]^-$ [38]. The superior performance of the F-BNNs can be attributed
179 to its unique structural characteristics and the possible ionization mechanism,
180 which can be summarized as follows: (i) The fluorine atoms of the F-BNNs
181 provide a great affinity for PFAAs based on fluorine–fluorine interactions [35].
182 The F-BNNs could, therefore, effectively adsorb numerous fluorinated analytes
183 *via* fluorine affinity. (ii) The fluorine atoms of the F-BNNs also enhance the
184 affinity for analytes by providing sites for hydrophobic interactions and hydrogen
185 bonding, thus improving the ionization efficiencies of the target molecules [39].
186 (iii) Fluoride modification can improve the dispersibility of the F-BNNs in water;
187 homogeneous F-BNNs can offer satisfactory reproducibility [40].

188 *3.5 Method validation and analysis of PFAAs in real samples*

189 To evaluate the ability of the F-BNNs as an effective adsorbent and matrix for
190 MALDI-MS, it was applied for PFAAs detection in water (Table S3). The limit
191 of detection (LOD) of PFAAs was determined by spotting of a series of diluted
192 standard solution which were enriched by F-BNNs on a stainless MALDI target
193 plate until corresponding to signal-to-noise (S/N) ratio of three was obtained.
194 Linearity of the proposed method was evaluated for PFAAs mixed standard
195 solutions with a series of concentrations ($0.3\text{--}500\ \mu\text{g L}^{-1}$). MALDI-MS analysis
196 was performed according to the parameters described in the section of 2.3 and
197 Supporting Information. The limit of detection (LOD, signal to noise, $S/N=3$) of
198 the matrix for the PFAAs analytes was $0.08\text{--}0.2\ \mu\text{g L}^{-1}$, the linear range was 0.3--
199 $500\ \mu\text{g L}^{-1}$, and the correlation coefficient (r) was between 0.9841 and 0.9955.
200 Compared to blank water (Fig. S3a), ten PFAAs were clearly detected in the
201 spectrum after spiking the water with $5\ \mu\text{g L}^{-1}$ of PFAAs (Fig. S3b). The
202 reproducibility study was performed by parallel analysis of RSDs of the shot-to-
203 shots and sample-to-sample RSDs. The reproducibility RSD of the shot-to-shot
204 was 7.56–14.6%, and sample-to-sample RSD was 5.35–12.5%. The method was
205 then used to investigate PFAAs detection in wastewater; specifically, PFOS (0.33
206 $\mu\text{g L}^{-1}$) was found in leather wastewater (Fig. S3c), PFBS ($0.22\ \mu\text{g L}^{-1}$) was

207 detected in dyeing wastewater, and PFHxS was measured in both leather (0.13
208 $\mu\text{g L}^{-1}$) and dyeing (0.12 $\mu\text{g L}^{-1}$) wastewater (Fig. S3d).

209 In addition, the method was used to investigate the analytes in milk (Table S4).
210 The LODs of PFAAs were 0.15–1.5 $\mu\text{g L}^{-1}$, the linear dynamic range was 0.2–
211 500 $\mu\text{g L}^{-1}$, and the r ranged from 0.9878 to 0.9975. The reproducibility RSD of
212 the shot-to-shot was 6.39–14.5%, and sample-to-sample RSD was 6.38–14.7%
213 was obtained. The mass spectrum obtained without the F-BNNs matrix (Fig. S4a)
214 showed no PFAAs in the milk samples, unless they were purposely spiked
215 samples. In contrast, all ten PFAAs were successfully detected in the presence of
216 the F-BNNs matrix (Fig. S4b), proving that the FBNNs can effectively serve as
217 an enrichment and ionization matrix for the MALDI-MS detection of PFAAs in
218 milk samples.

219 To further study the performance of the F-BNNs matrix in quantitative
220 analysis, PFAAs in human serum samples were determined by using the
221 developed method. The spectra collected before (Fig. 4b) and after (Fig. 4c)
222 PFAAs (5 $\mu\text{g L}^{-1}$) enrichment were compared, with the peaks of six PFAAs being
223 clearly observed in the latter. The PFAAs linear detection range was from 2 to
224 500 $\mu\text{g L}^{-1}$, and the r was between 0.9788 and 0.9963 (Table S5). The LODs was
225 0.14–1.50 $\mu\text{g L}^{-1}$. The reproducibility RSDs toward shot-to-shot was 8.32–
226 13.6%, and sample-to-sample RSDs was between 7.62% and 13.5%.

227 The F-BNNs showed a homogeneous substance (Fig. S5), and were used as a
228 matrix for MALDI-MSI analysis of zebrafish exposed to PFAAs, where the
229 spatial distribution of the PFAAs was clearly revealed (Fig. 4d). The PFAAs
230 primarily accumulated around the eyes, liver, sexual organs, anus, and end of sex
231 organ. The distribution of PFAAs in the eyes may be due to the eyes being
232 exposed to the outside environment. Meanwhile, the PFAAs in the liver could be
233 detected because the liver, as a detoxification organ, easily transports and
234 metabolizes exogenous pollutants. Furthermore, some of the perfluorinated
235 compounds were metabolized by the body and entered the anus and reproductive
236 organs. The results showed that F-BNNs can be used as a matrix for MALDI-

237 MSI, which could provide spatial distribution information in zebrafish exposed
238 to PFAAs. The distribution of target exposed at the same concentration for fish
239 could not be detected with conventional organic substrate.

240 **4. Conclusion**

241 In summary, F-BNNs matrix was successfully applied in MALDI-MS and MSI
242 analysis of PFAAs in complex samples. Compared with both organic (CHCA, DHB)
243 and inorganic (GO, GS and pure BNNs) matrices, the F-BNNs showed minimal
244 background interference and high sensitivity. F-BNNs matrix exhibited good salt
245 tolerance and high reproducibility. Fluoride modification facilitated extraction and
246 ionization efficiency. The detailed mechanism by which the F-BNNs assisted
247 desorption/ionization process needs to be further studied. It is expected that this work
248 can serve as a foundation for the F-BNNs-assisted MALDI-MS detection of other
249 perfluorinated molecules in complex environmental and biological samples.

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- 390

391

Figure Captions

392 **Fig. 1:** Scheme illustrating the synthesis of F-BNNs and the analysis of PFAAs in complex samples
393 by MALDI MS and MSI using the F-BNNs as an adsorbent and matrix.

394

395 **Fig. 2:** (a) SEM and (b) TEM images of F-BNNs; (c) survey XPS spectrum and high-resolution
396 spectra of the (d) F 1s, (e) B 1s, and (f) N 1s spectra of F-BNNs; (g) XRD patterns and (h) FT-IR
397 spectra of BNNs and F-BNNs; (i) N₂ adsorption (green line)-desorption (red line) isotherm of F-
398 BNNs, and its pore size distribution (inset).

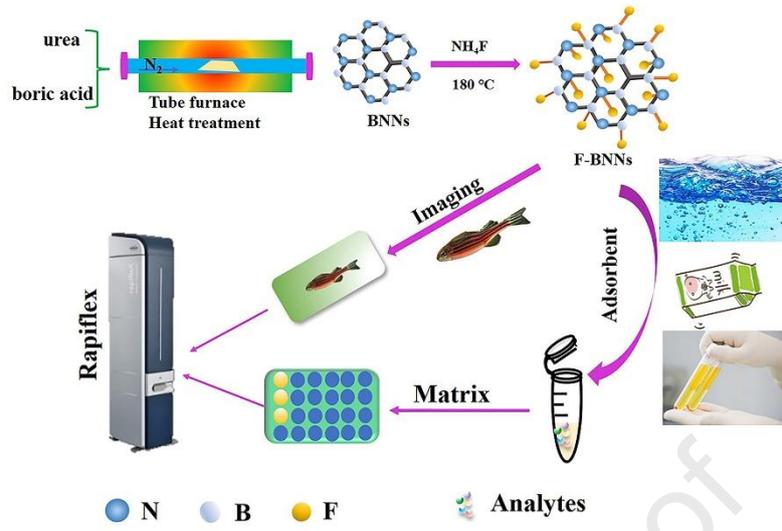
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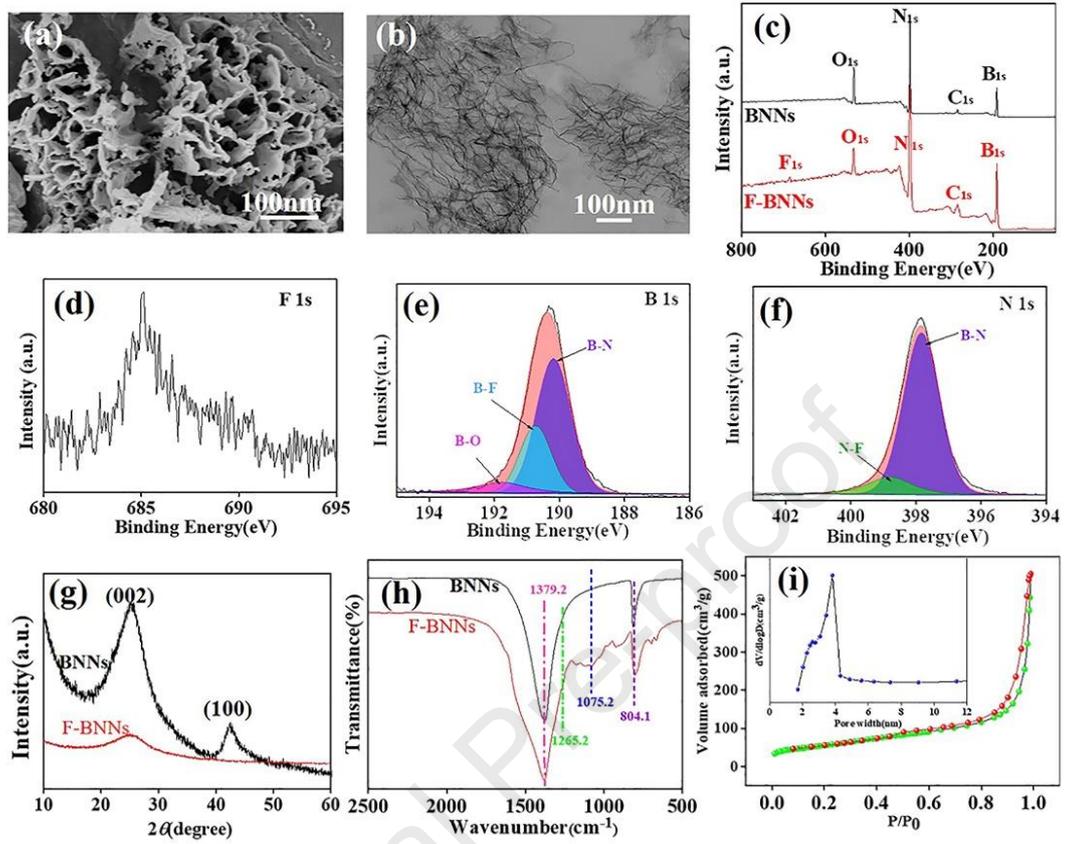
400 **Fig. 3:** Mass spectra of PFAAs obtained using (a) F-BNNs, (b) BNNs, (c) CHCA, (d) DHB, (e) GO,
401 (f) GS matrices. Each analyte concentration was set at 10 µg L⁻¹.

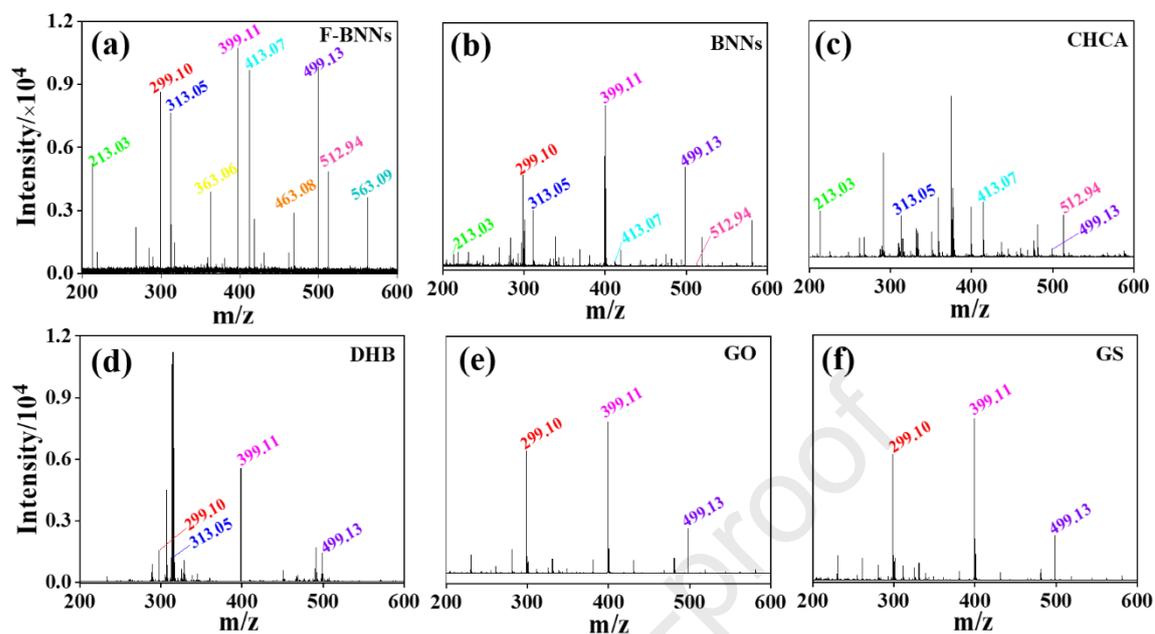
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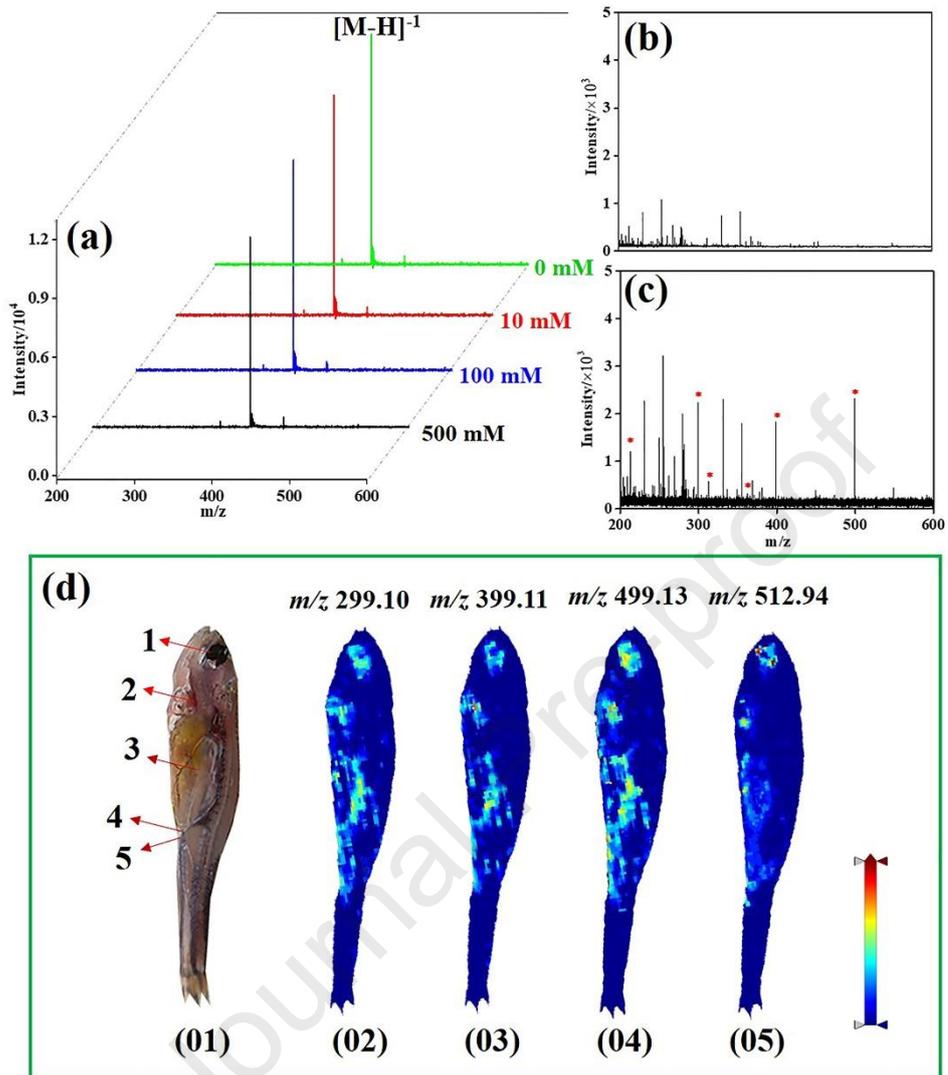
403 **Fig. 4:** Salt tolerance of F-BNNs matrix (a). Mass spectra of blank human serum sample with F-
404 BNNs as enrichment and ionization material without (b), and with (c) spiked with PFAAs. MALDI-
405 MSI analysis of PFAA distribution in zebrafish using the F-BNN matrix; 1-Eyes, 2-Liver, 3-Sexual
406 organs, 4-Anus, 5-End of sex organ; (01) Fish model, Different PFAA molecules of (02) m/z 299.10,
407 (03) m/z 399.11, (04) m/z 499.13, and (05) m/z. 512.94 distribution in zebrafish.

408









Highlights

- F-BNNs was used as absorbent and inorganic matrix for MALDI-MS analysis of PFAAs in water, milk, and human serum samples.
- Mass imaging of PFAAs in zebrafish was explored using F-BNNs.
- The possible ionization mechanism of F-BNNs as matrix was discussed.

Declaration of competing interest

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

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