analytical chemistry

Review

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Advances in Solid Phase Microextraction and Perspective on Future Directions

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CONTENTS

Solid phase microextraction (SPME) is a versatile, nonexhaustive sample preparation tool that has been demonstrated to be well-suited for facile and effective analysis of a broad range of compounds in a plethora of studies. A growing number of reports describing diverse SPME workflows for novel investigations in a variety of fields, such as flavor and fragrance investigations, environmental studies, and diverse bioanalytical applications, among others, corroborate the applicability of this microextraction tool in the analytical sciences. Several reviews compiling the most significant applications of SPME in specific areas, including analysis of wine volatiles, *in vivo* analysis of pollutants, on-site analysis of soils, analysis of water samples, food analysis, *in vitro* and *in vivo* metabolomics studies, pharmaceutical and biomedical analysis, among others, have been recently published by different authors.[1−8] In addition to the diverse types of applications of SPME, the different features offered by this microextraction technology in comparison to exhaustive extraction techniques have been a matter of consideration in several reviews. Boyaci et al., for instance, discussed the main advantages and limitations of SPME over

Special Issue: Fundamental and Applied Reviews in Analytical Chemistry 2018

Published: November 8, 2017

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

traditional sample preparation methodologies, while Souza-Silva et al. presented a comprehensive overview of the considerations and challenges associated with the use of SPME for analysis of different complex matrixes.[9−12] Various publications reviewing the most relevant developments in SPME extraction phases, coating preparation procedures, geometries, and experimental setups have also been recently reported.[13−18] In addition, novel coupling approaches combining the simplicity of SPME for simple and effective sample cleanup and the capabilities of mass spectrometry (MS) instrumentation stand-out to showcase the potential of SPME-MS toward the streamlining of analytical workflows in the near future.[19,20] Undoubtedly, SPME is a constantly evolving analytical technology with great potential to fulfill the needs of novel analytical applications in various fields of study.

This review presents the most recent and innovative work published on SPME, mostly focused on original studies reported from 2014 to date. The main sections of this review are comprised of an introduction to the main principles of SPME supported by recent fundamental studies involving computational modeling; an overview of novel developments in SPME coating materials and geometries; a summary of the most significant, recently published applications of SPME in food, environmental, and bioanalytical studies; and finally, a section describing anticipated future research directions and developments in SPME, including current progress on the direct coupling of multiple configurations of SPME to mass spectrometry, which certainly demonstrates the flexibility of SPME for hyphenation with new technologies.

FUNDAMENTALS

Exhaustive Extraction versus Microextraction. Extraction is the most common strategy in analytical sample preparation procedures to isolate, clean up, and preconcentrate analytes of interest from a given matrix so as to enable their compatibility with analytical separation and/or detection instrumentation.[21] In extraction techniques, the extraction phase (extractant) comes into contact with the sample matrix, and analytes are transported between the two phases. Traditional sample preparation protocols usually entail the exhaustive extraction of analytes from the matrix, which is generally achieved by partitioning the analytes of interest into suitable liquid solvents or solid sorbents. In exhaustive techniques, such as liquid−liquid extraction (LLE) or solid-phase extraction (SPE), the phase ratio of extractant to sample is significantly higher than in microextraction approaches, and geometries are more restrictive to ensure the efficient quantitative transfer of analytes. The purpose of exhaustive extraction in traditional techniques is to achieve high sensitivity and enable the use of straightforward calibration methods validated by the recovery of spikes. However, the major drawback of this approach is that the spikes frequently do not follow the behavior of native analytes in complex matrixes.

Since the introduction of the first practical format of microextraction in analytical sample preparation in 1990, microextraction methodology has substantially evolved, nowadays offering numerous successful sample preparation techniques.[15,22] In principle, microextraction can be defined as an extraction method in which the extractant (liquid or solid) has substantially smaller volume (typically <100 μL or <100 mg) compared to the sample (>1 mL); as such, at equilibrium, the extracted fraction of analyte is frequently negligible (or nonexhaustive).[23] It should be emphasized that despite its name, SPME technology is not a miniaturized version of SPE. Rather, it is typically an open bed, diffusion rate controlled extractive technology that offers efficient analyte enrichment from a range of sample matrixes by using appropriate device formats according to the application.[24,25] In other words, the mass transfer process that leads to the partitioning equilibria of compounds between a sample matrix and a coating-containing sorbent is the main principle of operation of SPME. Suppose an extractant (e) of volume V_e is exposed in a sample of volume V_s with an initial analyte concentration of C_s^0 for a period of time that is sufficient for equilibrium to be reached. The quantity extracted by the extractant can be determined by the following equation:[26]

$$n_e^{eq} = \frac{K_{es} V_e V_s}{K_{es} V_e + V_s} C_s^0 \tag{1}$$

where K_{es} ($= C_e^{eq}/C_s^{eq}$) is the partition coefficient or distribution coefficient utilized in SPME and defined by the ratio of the equilibrium concentration of analyte in the extractant (C_e^{eq}) to that in the sample matrix (C_s^{eq}).

In addition to the quantity of analyte extracted by the method, two parameters essential in the quantitative description of microextraction processes include the extraction efficiency of the method, namely, the recovery (R), and the enrichment factor (E), which can be both described as follows:

$$R(\%) = \frac{n_e^{eq}}{n_s^0} \times 100 \tag{2}$$

where n_s^0 is the initial quantity of analytes in the sample. Combining eq 1 and eq 2 and assuming that the extractant to sample volume ratio (V_e/V_s) is represented by φ,

$$R(\%) = \frac{K_{es}}{K_{es} + \varphi^{-1}} \times 100 \tag{3}$$

The enrichment factor (E) can be defined by

$$E = \frac{C_e^{eq}}{C_s^0} = \frac{n_e^{eq}}{n_s^0} \times \frac{V_s}{V_e} \tag{4}$$

By combining eq 3 and eq 4

$$E = \frac{R}{\varphi} \tag{5}$$

As follows from eq 3, recovery depends not only on the partition coefficient of an analyte but also on the phase ratio. Since the phase ratio (φ) in a typical microextraction experiment is very low, the recovery in a partition extraction is negligibly small as long as K_{es} is not large. While low recoveries are not a concern in many applications, owing to the advent of sensitive detectors, analyte recoveries can be further improved by increasing the volume of the sorbent coating (adsorbent weight, increase φ) or through the employment of coating chemistries of high partition coefficient K_{es}.[27] If analyte recovery is still insufficient for the chosen detector, or in cases where the goal is to exhaustively extract analytes of interest, multiple extractions of the same sample can also be performed.[28] In microextraction, especially for SPME applications that employ direct injection techniques, it is possible to inject the whole quantity of the extracted amount into the detection system. Even in cases where analyte recovery is small, microextraction techniques are able to provide good enrichment, close to K_{es}, while the concentration of analyte(s) in the matrix remains largely unchanged. In other words, SPME

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

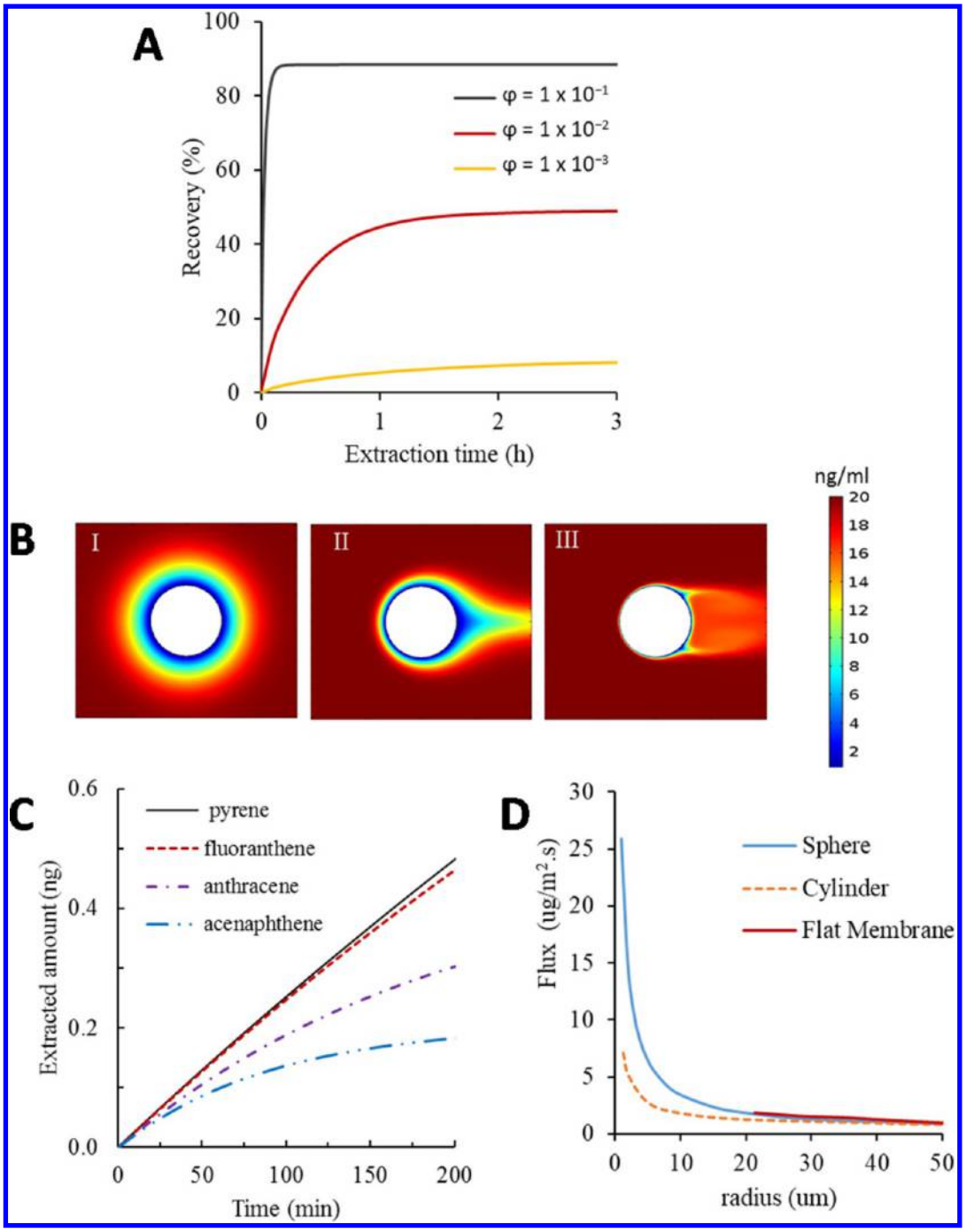

Figure 1. Effect of different parameters on kinetics of SPME. (A) Computational simulation results on the dependence of the extraction time profile on variations in the extractant to sample volume ratio (φ). Volume of the extractant, V_e, was assumed constant (0.6 μL) and sample volume, V_s, was varied from 6 to 600 μL. Extraction was considered under diffusion-only conditions with a partition coefficient (K_{es}) value of 100. (B) Surface concentration showing the effect of fluid flow on the diffusion boundary layer around the extractant, at 5 s of extraction. (I) A diffusion-only trial, with flow velocity of 0 cm s^{-1}, (II) with flow velocity of 0.2 cm s^{-1}, (III) with flow velocity of 10 cm s^{-1}. Initial analyte concentration was set as 20 ng mL^{-1} for all simulations, diffusivity (D_S) = 2 × 10^{-9} m^2 s^{-1}, and K = 1 × 10^{12} M^{-1} [Reproduced from Alam, M. N.; Ricardez-Sandoval, L.; Pawliszyn, *Ind. Eng. Chem. Res.* **2017**, *56* (13), 3679−3686 (ref 30). Copyright (2017) American Chemical Society].[30] (C) Extraction kinetics for polycyclic aromatic hydrocarbons (PAHs), obtained from a simulation using a computational model. D_S values are 7.66 × 10^{-6}, 6.84 × 10^{-6}, 6.59 × 10^{-6}, and 6.59 × 10^{-6} cm^2 s^{-1}; K values are 1 × 10^6 M^{-1}, 2 × 10^6 M^{-1}, 7 × 10^6 M^{-1}, and 10 × 10^6 M^{-1} for acenaphthene, anthracene, fluoranthene, and pyrene, respectively. Γ_{max}, which is the maximum surface concentration on the extraction phase, was set at 8 × 10^{-5} mol m^{-2}. Assumptions: concentrations of all analytes were 20.8 ng mL^{-1}, fluid linear velocity of 0.2 cm/s using a 75-μm Car/PDMS fiber. Γ_{max} and K values are assumed as 1 × 10^{-5}mol/m^2 and × 10^8 M^{-1}, respectively [Reproduced from Alam, M. N.; Ricardez-Sandoval, L.; Pawliszyn, *Ind. Eng. Chem. Res.* **2017**, *56* (13), 3679−3686 (ref 30). Copyright (2017) American Chemical Society].[30] (D) Effect of radius of different geometries of extractants on the mass transfer kinetics in the linear regime of extraction (in this example, the extraction time was 2 min). While the sample volume was fixed, the radius of the fiber (cylindrical) and particle (spherical) were decreased. For the flat membrane, a square membrane was considered whose size decreases by decreasing both dimensions (length and width). Since by decreasing the dimensions of the flat membrane similar kinetics as the spherical particle are provided, only results pertaining to larger flat membranes (>20 μm) are shown in the figure.

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

employs a small quantity of extraction phase to obtain a relatively higher concentration of analyte in the extraction phase while not significantly disturbing the concentration of analytes in the sample, unlike exhaustive extraction, where the concentration of analytes remaining in the sample after extraction is depleted (see eq 4 and eq 5).[24,25] Accordingly, high sensitivities can be achieved with SPME through the use of small ratios of extraction phase volume to sample volume and by directly injecting the entire extracted amount to the instrument. This is contrary to exhaustive techniques, where the enrichment factor is relatively low and becomes lower as the recovery increases, since the concentration in the sample matrix at equilibrium approaches "0" as the method approaches 100% recovery. In exhaustive techniques, increases in sensitivity can be achieved either through a reduction of the extract volume (in LLE) or through desorption with strong solvents (in SPE). In many cases, additional steps involving evaporation and reconstitution may be required as well.

Recently, the extraction kinetics of an analyte in an aqueous sample of different φ values was studied with a computational model. As shown in Figure 1A, exhaustive recovery can be achieved faster as compared to equilibrium extraction. At higher φ values, provided that either an appropriate extractant geometry (perculation through a highly porous bed in SPE) or procedure (dispersion of solvent via shaking or other methods in LE) is employed, a high interfacial contact area can be obtained, thus circumventing the transport of analytes from a far distance. In some microextraction techniques, where the geometry of the device results in a low contact area between the extraction phase and the sample matrix, the mass transfer of analytes might become the limitation in the extraction process. As a means to overcome this issue, dispersion of the extraction phase into the sample can be used to enhance the mass transfer rate. In addition, since the transport of analytes in microextraction approaches consists of diffusive and convective transport mechanisms, the extraction kinetics can be improved through the employment of appropriate agitation techniques in microextraction protocols. In addition to targeting convective transport as a pathway to increase analyte uptake, improvements to the diffusive transportation of analytes through a reduction in the dimension of the device can also enable enhanced quantification via SPME, as recently shown by Piri-Moghadham et al.[29] Further discussion regarding the effect of device geometry on the extraction kinetics will be provided in the next sections.

Calibration Models for Quantification with SPME. Different calibration approaches have been proposed to achieve quantitative results with SPME. Indeed, the type of application dictates the selection of a particular calibration method. The following section will briefly discuss calibration strategies specific to various SPME methods. Other traditional calibration techniques can be found in a previous review authored by Ouyang et al.[31,32]

Equilibrium Calibration. In SPME, equilibrium-based sampling is carried out by exposing the extractant to the sample for a well-defined period of time, until the concentrations of the analytes under study in the sample matrix and in the extractant reach equilibria. The extractant is then removed from the sample and subsequently submitted to desorption and/or instrumental analysis. In cases where only two phases, the sample matrix and the extractant, need to be considered, the amount of analyte extracted at equilibrium (n_e) can be described by eq 1. For *in vivo* or on-site applications,[11−13] where the sample volume is considerably larger that the volume of the extraction phase, $V_s \gg K_{es}V_e$, eq 1 can be written as

$$n^{eq} = K_{es}V_eC_s^0 \quad (6)$$

This equation describes two important features of SPME methodology. The first one is that the extraction phase can be exposed directly to various large volume matrixes, such as ambient air, water, production stream, etc., without necessitating the collection of a definite amount of sample. This distinct advantage of SPME, namely, the integration of the sampling and sample preparation steps, facilitates on-site analyses due to its simplified workflow. Second, if the K_{es} of a given analyte is known, then the concentration of said analyte can be determined by the amount extracted at equilibrium. This mode of quantification does not require any external calibration, which may slow down the analytical process and introduce additional errors. This feature of SPME is highly desirable for field analysis.

Boundary Layer in SPME and Diffusive (or Diffusion-Limited) Calibration. In order to properly select from the various calibration approaches afforded by SPME for a particular application, the processes governing the diffusion boundary layer must first be well-understood by the analyst. To this effect, in order to better elucidate these processes, Alam et al. employed computational simulations to study the effect of flow velocity on the diffusion layer.[30] Figure 1B shows the concentration profiles in the sample (2D) domain corresponding to the center of the cylindrical extractant at various fluid flow velocities. If no agitation is applied to the sample matrix, then a normally symmetrical diffusion layer is obtained (Figure 1B-I), as seen by the color differences. The diffusion layer around the extractant is distorted when convective flow is considered from left to right (Figure 1B-II). The flow compresses the diffusion layer around the upstream edge (entrance to the extractant) of the extractant, whereas an expansion in the diffusion layer can be observed at the back of the extractant. The average thickness of the diffusion layer is also shown to be dependent on the convection speed being employed, being considerably thinner at faster flow rates in relation to slower flow rates (Figure 1B-III). As clearly indicated in Figure 1B, the best agitation method to be employed in SPME is a vortex type of agitation, where the respective movement of the sampling device versus sample frequently changes its direction, thus enabling the equalization of the mass transfer rates of both sides of the device.

A graph depicting the shape of typical extraction kinetics curves for different classes of compounds in SPME is illustrated in Figure 1C .[30] As can be seen, first, a linear uptake zone can be observed, followed by a curvilinear or kinetic zone, before equilibrium is reached. As shown in Figure 1C, the extracted amounts for all four analytes used in this example were very similar until 25 min of extraction time had elapsed. Since the diffusion coefficients of the selected compounds in water are very close to each other, the extracted amounts are similar at the diffusion-controlled initial stage. During this initial stage, the effect of equilibrium constants (or partition coefficients for liquid coatings, K_{es} or log P) is negligible on the kinetics. This initial independence of K on the extraction rate introduces an interesting feature of SPME, enabling calibrations based on the diffusion coefficient values of analytes, which are similar for small molecules, and can be conveniently calculated.[7]

In cases where analyte quantification via SPME is to be carried out in the pre-equilibrium regime, a calibration model must be employed. The basis of most models to date consider the diffusion of analytes according to Fick's law of diffusion.[33,34]

DOI: 10.1021/acs.analchem.7b04502
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Fick's first law describes transport of a chemical within a phase as a flux, F, which is a function of the diffusion coefficient, D, cross-sectional area, A_e, and a concentration gradient, dC/dx, perpendicular to A_e:

$$F = -DA_e\frac{dC}{dx} \tag{7}$$

The diffusion coefficient (cm^2/s), termed as an intraphase mass transfer coefficient, k_i (cm/s), can be substituted into eq 7 to provide a more intuitive way to express flux:

$$F_i = k_i A_e \Delta C \tag{8}$$

where ΔC is the concentration difference between bulk phase i and the interface between the sample and extractant. Thus, the flux from the sample to the sample-side interface can be expressed as

$$F_s = k_s A_e (C_s^{bulk} - C_s^{interface}) \tag{9}$$

where k_s is the mass transfer coefficient for the sample-side boundary layer, A_e is the area of the extraction phase, C_s^{bulk} is the concentration in the sample, and $C_s^{interface}$ is the concentration at the interface of the sample side. Similarly, the flux between the extractant-side interface and the bulk of the extractant can be expressed as

$$F_e = k_e A_e (C_e^{interface} - C_e^{bulk}) \tag{10}$$

where k_e is the mass transfer coefficient for the extractant-side boundary layer, $C_e^{interface}$ is the concentration at the sampler side of the interface, and C_e^{bulk} is the concentration in the bulk of the extraction phase. The concentrations at the interface ($C_s^{interface}$ and $C_e^{interface}$) can be eliminated by assuming continuity of fluxes

$$F_s = F_e (\equiv F) \tag{11}$$

and sorption equilibrium at the interface:

$$C_e^{interface} = K_{es} C_s^{interface} \tag{12}$$

Combining eqs 10−12 yields a relationship between the contaminant flux (F), the concentration in the extractant, and the sample concentration:

$$F = V_e\frac{dC_e}{dt} = k_0 A_e\left(C_s - \frac{C_e}{K_{es}}\right) \tag{13}$$

where the overall mass transfer coefficient (k_0) is given by

$$\frac{1}{k_0} = \frac{1}{k_s} + \frac{1}{k_e K_{es}} \tag{14}$$

Equation 14 shows that the overall resistance ($1/k_0$) equals the sum of resistances of the sample boundary layer ($1/k_s$), and the extraction phase boundary layer ($1/(k_e K_{es})$).

In the early stages of uptake, when C_e/K_{es} is very small compared to C_s, and the elimination rate from the extractant is relatively insignificant (assuming C_e equals zero at time zero), the change in concentration in the extractant could then be considered to be due only to uptake:

$$V_e\frac{dC_e}{dt} = k_0 A_e C_s \tag{15}$$

and, once integrated and rearranged:

$$N_e = k_0 A_e C_s t \tag{16}$$

This relationship shows that under a linear uptake regime, the mass of analyte in the extractant is linearly related to its concentration in the sample phase. If we assume that mass transfer is controlled by the sample boundary layer ($k_0 = k_s$) and given that k_s can be expressed in terms of sample diffusivity and boundary layer thickness ($k_s = D_s/\delta$), then

$$N_e = \frac{D_s A_e}{\delta_s} C_s t \tag{17}$$

or

$$C_s = \frac{N_e \delta_s}{D_s A_e t} \tag{18}$$

Equation 18 expresses the relationship between an extracted amount of analyte and its sample concentration for extraction via a flat membrane-type extractant. Koziel et al.[35] proposed the following eq 19 for SPME devices consisted of a cylindrical fiber geometry (also known as the interface model):

$$C_s = \frac{N_e \ln\left(\frac{b+\delta_s}{b}\right)}{2\pi D_s L t} \tag{19}$$

where L and b are considered as the fiber length and outside diameters of the fiber, respectively. The values of the diffusion coefficient can be found in the literature or calculated.[36] The boundary layer thickness, δ_s, can also be estimated if properties such as the kinematic viscosity of the matrix, sample media linear velocity, analyte diffusion coefficient, and the extraction device dimensions are known.[35]

However, the effective thickness of the boundary layer in eq 19 is an average estimate that does not account for changes with respect to the formation of wakes behind the extraction phase in cases where unidirectional fluid flow is employed.[37−39] In such cases, employment of this method will introduce large errors in calculations, since the diffusion layer thickness is not uniform around the fiber and is dependent on the physical dimensions of the fiber coating, sample flow conditions, and the physicochemical properties of the analytes under study.[40] Chen et al.[34] proposed another diffusion-based calibration model, which considers an actual swirl flow around the SPME fiber (also known as the cross-flow model):

$$C_s = \frac{N_e b}{E R e^m S c^{1/3} A_e D_s t} \tag{20}$$

The constants E and m are dependent on the Reynolds number and are available in the literature.[41]

While the models (eqs 19 and 20) discussed so far do not require a calibrant, the diffusion coefficients of the compounds in the sample matrix as well as the physical properties of the sample under investigation must be known for such methods to be employed, which might limit their applicability. During the initial linear extraction regime, it can be assumed that the constants D_s, A_e, and δ_s do not vary during sampling; as such, these three parameters can be coupled to provide a single parameter, R_s ($R_s = D_s A_e/\delta_s$), termed the "sampling rate".[42] If the sampling rate, R_s, remains constant throughout the duration of sampling, the relationship between the concentration of the target analyte in the sample matrix and the extracted amount of analyte can be expressed by

$$C_s = \frac{N_e}{R_s t} \tag{21}$$

DOI: 10.1021/acs.analchem.7b04502
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where the sampling rate (m^3/s) is dependent on the target compound and on the geometry of the extractant.[42] In order to guarantee the accuracy of experimental field results, R_s should be determined through calibration studies undertaken under controlled environmental conditions similar to field conditions. Employment of this method circumvents the need for distribution coefficient determinations or the loading of deuterated standards prior to sampling, which greatly simplifies the experimental operation.

A significant constraint of diffusion-based calibration techniques is that the flow velocity or agitation of the sample matrix must be controlled so as to maintain a fixed diffusion layer thickness or sampling rate.[36] Sometimes, additional equipment such as a hand-held drill can be used to control sample convection. However, the diffusion layer thickness, δ_s, can be artificially fixed by retracting the extractant a known distance, Z, into a housing (a narrow tube or needle) in such a way that no convective flow occurs within the tube (in the Z region). Therefore, by replacing δ_s with Z, eq 18 yields eq 22:[26]

$$C_s = \frac{N_e Z}{D_s A_e t} \tag{22}$$

The fiber-retracted-in needle sampler allows for the sampler to be used in unsteady fluid velocity conditions.[43] During deployment of this device, the extraction phase is retracted into the needle at a certain distance to create an artificial static domain in which the analytes are assumed to be transported only by diffusion. Indeed, accurate TWA concentrations have been reported for both air and water samples with the use of the retracted SPME device.[44]

Kinetic Calibration. In order to obtain an equation that describes the full extraction time profile (similar to Figure 1C), Ai solved for eq 13 at steady state diffusion conditions in both the sample matrix and the extractant, resulting in the following nonlinear equation:[45]

$$n = [1 - \exp(-a_e t)]\frac{K_{es} V_e V_s}{K_{es} V_e + V_s} C_s^0 \tag{23}$$

where n is the amount of analyte extracted at time t, t is the extraction time, and a_e is the extraction rate constant that describes how fast equilibrium can be attained, which is dependent on the volumes of the extractant, headspace, and sample; mass transfer and partition coefficients; and the surface area of the extractant. Equation 23 expresses the relationship between the amount of analyte extracted on the SPME extractant, n, and the initial concentration of the analyte in the sample matrix C_s^0 as a function of extraction time t. By combining eq 1 and eq 23, the following equation can be used to obtain a full extraction time profile:[45]

$$\frac{n}{n^{eq}} = 1 - \exp(-a_e t) \tag{24}$$

On the basis of this mathematical expression to describe analyte absorption in SPME, and as a means to calibrate and account for variations during the extraction process, preloading of an internal standard on the extractant prior to the deployment of the device for sampling was introduced by Chen and Pawliszyn as kinetic calibration.[46] In this calibration approach, the following equation, derived from eq 13, is proposed to describe the internal standard desorption from the extractant:

$$q = [1 - \exp(-a_d t)]\frac{V_s}{K_{es} V_e + V_s} q_0 \tag{25}$$

where q_0 and q are the amount of standard loaded before deployment of the extractant and after extraction time t has elapsed, respectively, and a_d is the desorption rate constant (s^{-1}). If the extractant-to-sample phase ratio is significantly low or $K_{es} V_e \ll V_s$, the desorption of standard from an SPME fiber can be described by the following equation:

$$q = q_0[1 - \exp(-a_d t)] \tag{26}$$

Experimentally determined q and q_0 at a known sampling time will provide the value of the desorption rate constant. Here, it is assumed that the desorption and extraction processes are isotropic in nature for SPME sampling.[47,48] Therefore, the a_d value obtained from eq 26 can be used in eq 24 along with the value of extracted amount at the particular time (n) to estimate the extracted amount at equilibrium, n_e. Then, the n_e value can be used to estimate the initial concentrations of target analytes in the sample, C_s^0, from eq 6. This principle, namely, the principle of kinetic calibration, was later termed the in-fiber standardization technique.[49] Equation 23 describes the typical extraction time profile of a compound in SPME sampling. When extraction time goes to infinity, meaning that adsorption equilibrium is reached, the exponential term of eq 23 vanishes and becomes eq 1. Therefore, the standard loaded calibration technique can also be used at equilibrium conditions, which might be useful for applications where an internal standard can be loaded into the sample matrix.[50]

Effect of Device Geometries on Mass Transfer Kinetics. As already emphasized, the device geometry can also affect the mass transfer kinetics in SPME. To better understand this phenomenon, an assessment of the effect of three basic geometries of SPME devices, namely, fiber, thin film, and spherical particle, on equilibration time was conducted. Parameters such as size and geometry of the probes were taken into account throughout the comparison. The radial variation of extractants of different shaped devices was studied, and the corresponding overall mass flux for a no-stirred sample system was calculated. As already highlighted in previously published experimental work,[29] the equilibration time of the SPME device was demonstrated to be directly related to its radius. This experimental system was simulated in order to attain a more in-depth understanding of the mechanism behind the obtained experimental observations. As can be seen in Figure 1D, an inverse relation was observed between the extractant size and the mass flux, which is in agreement with the trends obtained in the aforementioned experiment. Owing to the mass-transfer limitation of SPME processes, a higher flux of analytes provides shorter equilibration times. Since a decrease in the size of the extractant would correspondingly decrease the mass transfer limitation, faster equilibrium is expected for devices with smaller dimensions. In the case of SPME devices with a particle-shaped support, it is expected that the fastest increase in flux would be exhibited with a reduction in the particle radius due to the three-dimensional variation of the size of a sphere with respect to its radius. On the other hand, the fixed length of the cylindrical fiber geometry is responsible for a lower flux with respect to a decrease in the fiber radius. As shown in Figure 1D, the flux would be independent of geometry for extractants of dimensions larger than approximately 30 μm. In addition, the results in Figure 1D indicate that the fastest way to perform any extraction, including microextraction, is to use the smallest possible

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

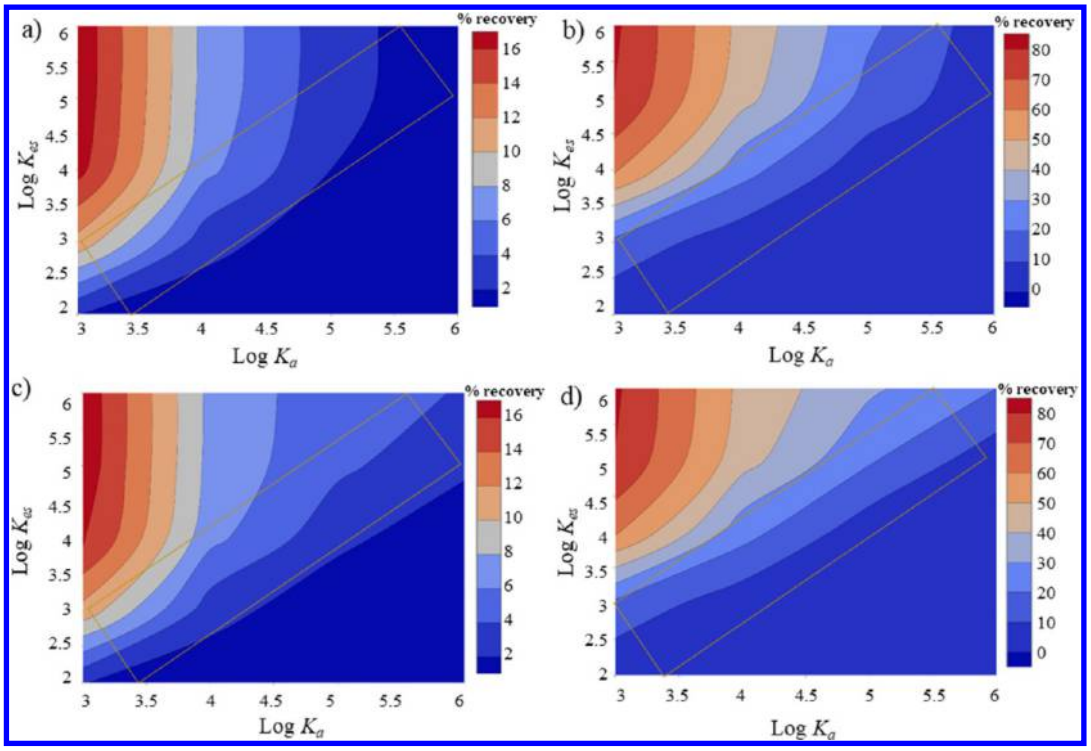

Figure 2. Effect of coating-sample distribution constant (K_{es}) on analyte recovery for varying analyte-matrix binding constants (K_a) at two different extreme cases; assuming forward binding rate constant, k_r, changes with changing the K_a at a short extraction time of 5 min (a) and at 500 min (b). In another case, the k_r was assumed to be fixed at 1 s^{-1}. (c) 5 min extraction time and (d) 50 min. Initial concentration of the matrix components was kept constant at 30 ng L^{-1}.

coated spherical particles. While the amounts of extracted analyte by a small particle is generally low in comparison to a traditional fiber, a large number of these particles can be used during single extractions so as to increase the sensitivity of the method. Previously, the inability to sufficiently collect such particles required for desorption was a hindrance to method development; however, this issue has been since addressed by employing magnetic collection, as will be described in the section corresponding to shapes of support. Development of other collection approaches that facilitate the use of small particles will likely follow.

Balanced Analyte Coverage. Rapid improvements in coating materials alongside the diverse device geometries offered by SPME allow for application of this technology toward analysis of complex samples, such as in applications involving *in vivo* analysis and determinations in food matrixes, applications which were previously difficult to implement by directly exposing traditional devices to complex sample matrixes. However, the recent advent of matrix-compatible SPME coatings (which are discussed further on in this review), where materials such as polydimethylsiloxane (PDMS),[51,52] polytetrafluoroethylene amorphous fluoroplastics (PTFE AF),[53] or polyacrylonitrile (PAN) are used as SPME coating,[54,55] has demonstrated that in addition to limiting matrix effects, SPME is capable of providing balanced coverage of analytes with a broad range of properties from complex sample matrixes. Recently, mathematical models were used to investigate a distinct feature of SPME, namely, how binding matrix components help to achieve balanced coverage in analyses carried out by single SPME devices in complex matrixes.

The computational simulation results pertaining to the recoveries of analytes with a wide range of K_{es} values and analyte-matrix binding constants K_a at three different extraction times have been plotted as color maps in Figure 2. In general, recoveries increased as K_{es} was increased for analytes characterized by lower K_a values. This is true for all extraction time regimes. Results from the a 5 min extraction simulation showed that the recoveries of analytes characterized by log K_a values of more than 4.5 were less than 2%, caused by their low free concentrations due to binding; however, the recoveries of lower log K_a compounds were shown to be significantly higher, owing to their lower binding affinity for matrix components, despite the fact that their affinities for the extraction phase are lower than those of compounds characterized by high log K_a values. As extraction time is increased, the recoveries of analytes with higher K_a values increase correspondingly, while the recoveries of lower log K_a analytes remain constant after extraction equilibria are reached for these compounds. Therefore, analytes characterized by very low binding constants can be rapidly extracted from complex matrixes in accordance to their affinity for the coating (K_{es}), while high binding constant analytes can be extracted in sufficient quantities for detection through employment of longer extraction times. Owing to the low recoveries of hydrophobic analytes within a reasonable extraction time due to the presence of binding matrix components, which limit their availability for extraction, hydrophilic analytes are not displaced by hydrophobic analytes during extraction. This interplay between K_{es} and K_a values during the extraction process results in the balanced coverage feature of SPME for analysis of complex matrixes. Expected analyte coverage percentages provided by general purpose coatings of a hydrophobic nature are shown in the rectangular boxes in Figure 2. Results shown on the two extreme corners of the plots, where the recovery is extremely high or low, are correspondingly only

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

Table 1. Summary of Various Examples of Coating Chemistries, Their Applications, and Performances

coating material	coating thickness (μm)	coating method	analytes	matrix	instrumentation	LOD (ng L^{-1})	ref
polypyrrole/CNT/TiO_2	55	electropolymerization	BTEX	tap water, mineral water, river water	GC-FID	0.01−0.04	58
MWCNT@IL/PANI	40	electrodeposition	benzoic acid esters	perfume samples	GC-FID	1.5−6.1	59
IL/CNT	30	electrodeposition	carbamate pesticides	apple and lettuce samples	GC-FID	15.2−27.2	60
glycine functionalized multiwall CNTs		sol−gel	venlafaxine and o-desmethylvenlafaxine	biological and water samples	HPLC-PAD	30−70	61
CNTs/flower-shaped zinc oxide		sol−gel	tramadol	urine samples	GC-FID	30	62
g-C_3N_4		sonication	uric acid	human urine	GC-MS	10	63
g-CN and graphene	100	sol−gel	PAHs	cosmetics	GC-MS	1−2	64
g-C_3N_4	140	silicon glue	acrylamide	potato chips	GC-FID	18	65
boron nitride		sol−gel	PAHs	environmental samples	GC-MS/MS	0.15−0.39	66
ZIF-8		layer-by-layer deposition	*n*-alkanes	petroleum based fuel and biological samples	GC-FID, GC-MS	0.46−1.06	67
ZIF-90	20	solvothermal deposition	polar phenolic endocrine disruptors	soil and water	GC-FID	28.9−196	68
ZIF-67	60	silicon sealant glue adhesion	organochlorine pesticides	vegetable samples	GC-μECD	0.09−0.45 ng g^{-1}	69
MOF-199/GO hybrid composites	40	chemical bonding	organochlorine pesticides	river water, soil, water convolvulus and longan	GC-ECD	2.3−6.9	70
IRMOF-3@ILs/PDMS	25	in situ growth	PAHs	water sample	GC-MS	12.0−15.4	71
Bio-MOF-1		in situ hydrothermal growth	PAHs	river and wastewater	GC-FID	20−5570	72
MOF/PANI	40	electrodeposition	chlorobenzenes	Persian Gulf, river and drinking water	GC-MS	0.1−0.2	73
MOA-MIL-53	10	silicon sealant glue adhesion	substituted chlorobenzenes	river and tap water	GC-ECD	0.1−60	74
tri metal center MOF	11−26	silicon sealant glue adhesion	BTEX	pond and river water	GC-MS	0.13−0.88	75
PCN-222		hydrothermal growth on SSF	nitrated PAHs	environmental water, PM2.5, and soil samples	GC-MS	0.1−20	76
MIP	300	in-tube polymeriation	sarcosine	urine samples	GC-FID, GC/MS	0.37 mg L^{-1}	77
PAF-48/gel	60	sol−gel process	styrene	food contact materials	GC-FID	0.003−0.060 μg kg^{-1}	78
PAF/IL	30	epoxy resin glue	organochlorine pesticides	juice and milk samples	GC-ECD	11−29	79
COF-SCU1	40	epoxy resin glue	volatile organic compounds	indoor air sample	GC-MS	0.03−0.15	80
COF-PDA	15	chemical immobilization	pyrethroids	vegetables and fruits	GC-ECD	11−23	81
SNW-1		covalent immobilization	phenols	honey sample	GC-MS	0.06−0.2	82
DNA aptamer	60−65	covalent immobilization	Thrombin	Human plasma	LC-MS/MS	0.3 nM	83
thiol functionalized aptamer		covalent immobilization	antibiotic residues	milk	HPLC-DAD	0.262−0.293	84
PIL/polymeric	500	in-situ polymerization	endocrine disrupting chemicals	human urine and environmental water	HPLC-DAD	11−65	85
PIL	12−54	spin coating	acrylamide	coffee and coffee powder	GC-MS	100−1000	86
IL/polyacrylate/NH_2/oligo dT20	98−125	chemical bonding	mRNA	RNA	RT-qPCR	5.0	87
phenylboronic acid functionalized CNTs		dipping	carbohydrates	biological fluids and biotissues	GC-MS		88

possible for coatings or matrix components containing specific high affinity sites. Additionally, coating chemistries typically employed in SPME of organic compounds (even polar coatings) have higher affinity toward hydrophobic analytes, which show higher binding affinity toward binding matrix components as compared to hydrophilic analytes. The high binding nature of hydrophobic analytes results in lower free concentrations of these compounds in the sample matrix, which in turn restricts their recoveries. Since the values of the desorption rate constant, k_r, are unknown for most of these analytes,[56] in Figure 2C,D, we have assumed that the desorption is fast, with k_r = 1, for all studied values of K_a. Here, equilibrium for these compounds is reached faster in comparison to cases where desorption from the matrix controls the extraction. In this case, hydrophobic analytes achieved equilibration at 50 min of extraction, whereas some hydrophobic analytes were still in their linear regime of extraction even after 500 min of extraction had elapsed. Such a finding would indicate that in cases where analytes are bound very strongly or irreversibly with matrix components, the amounts of such compounds that can be extracted via SPME might be too low to detect.

As described in the discussion presented above, application of new approaches of numerical modeling can facilitate a better understanding of the impact of mass transfer and partitioning of

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

analytes in multiphase systems on experimental results. Alternatively, by knowing parameters such as coating affinity constants, analyte diffusion coefficients, linear velocities, device dimensions, among others, it is possible to estimate mass transfer parameters and analyte partitioning among different phases, even in living systems. Such approaches can then be used not only toward in-silico optimization of extraction conditions but also to obtain valuable information related to various biological applications; for instance, to better elucidate mechanisms of drug delivery and distribution in living systems.

COATINGS

In SPME, the chemistry of the selected coating greatly defines the applicability of the technique for a study of interest. It is the extraction phase that determines the affinity that an analyte present in a given media (either sample or desorption media) displays for the extraction device. Since the introduction of SPME, a broad range of coating materials have been employed in the analysis of multiple analytes present in diverse matrixes. A summary of the most recent and interesting developments in terms of coating chemistries is presented in Table 1.[57] As further implementation of SPME in new applications strongly depends on the availability of compatible extraction phases, reviewing the most recent developments in terms of SPME coating materials can shed light on future directions to be followed. As well-known among SPME users, commercially available coating chemistries for GC applications include PDMS, polydimethylsiloxane/divinylbenzene (PDMS/DVB), Carboxen/polydimethylsiloxane (Car/PDMS), DVB/Car/PDMS, polyacrylate (PA), and CARBOWAX polyethylene glycol (PEG). On the other hand, for LC studies, only C18 coated fibers are commercially available to date. Despite the successful utilization of the aforementioned coating chemistries in both novel and routine-based applications, the limitations of such coating materials in relation to operation temperature, selectivity, robustness, carryover, swelling in solvents, and cost-affordability, have motivated researchers to explore alternative SPME coating chemistries. Indeed, new advancements in material chemistry have enabled the introduction of various sorbents with morphologies and physical-chemical properties well-suited for various SPME applications. Some examples of alternative coating materials include carbon nanotubes, graphitic carbon nitride, boron nitride, metal organic frameworks, and porous aromatic frameworks. In some instances, these materials are able to provide improved wettability, high surface area, easy surface modification, inherent functional groups, increased chemical interactions, and tunable pore sizes. As such, SPME coatings based on such materials may provide better mass transfer processes and higher enrichment factors as compared to currently available commercial coatings for a variety of applications. Other materials such as polymeric coatings, ionic liquids, aptamers, molecular imprinted polymers, conductive polymers, and metal oxides provide specific interactions (such as ionic interactions, Van der Waals forces, $\pi-\pi$ interactions, dipole−dipole interactions, hydrogen bonding, Lewis acid−base phenomenon), which can induce selectivity toward different classes of compounds. In this section, the most recent developments in alternative SPME coating materials will be discussed.

Carbon Nanotubes (CNTs). Carbon nanotubes are allotropes of carbon, having a two-dimensional structure with unique structural and chemical properties. They have high thermal, chemical, and mechanical stability, high surface area, and excellent adsorption capacity. Owing to the carbon backbone provided by this configuration, CNTs are highly hydrophobic and mostly applied for the extraction of hydrophobic analytes. As well, CNTs can be oxidized to incorporate functional groups, which increase their solubility and chemical reactivity to introduce desired moieties that facilitate the extraction of more polar compounds. Pristine CNTs and functionalized CNTs can extract analytes through hydrogen bonding, $\pi-\pi$ stacking interactions, as well as electrostatic and hydrophobic interactions. The $\pi-\pi$ electron donor−acceptor relation of highly polarized graphene sheets of CNTs and aromatic molecules containing a benzene ring has been exploited for extraction of PAHs, biological compounds, pharmaceutical, phthalates, antioxidants, pesticides, parabens, etc., whereas the extraction of metal ions, cationic species, and the adherence of polar compounds by hydrogen bonding and electrostatic interactions are attributed to the functional groups present on the surface of CNTs and the net negative charge that is found present in such configurations due to a highly delocalized electron cloud.[89] In recent papers, CNTs have been combined with a polypyrrole/titanium oxide composite for the extraction of benzene, toluene, ethylbenzene, and xylene (BTEX) in headspace (HS) mode from water samples.[58] In these investigations, CNTs were immobilized by electrochemical polymerization, with the resulting fibers exhibiting a porous surface structure, reproducible preparation, high sensitivity, long lifetime, high thermal stability, and strong adhesion of the coating to the steel wire due to unique properties provided by the conducting polymer, which was comprised of CNTs and TiO_2 particles.[58] A polyaniline/multiwall carbon nanotube (PANI/MWCNT) composite was also explored for the extraction of benzaldehyde from pharmaceutical formulations[90] and for the extraction of thymol and carvacrol from medicinal plants and honey.[91] In both cases, the composite was deposited on a platinized stainless steel by electrophoretic deposition, then used in direct immersion (DI) mode for determination of thymol and carvacrol on HPLC-UV and in HS mode for determination of benzaldehyde on GC-FID. The electrophoretic deposition of platinum increased the stability of the coating on the surface of the fiber and increased extraction efficiency. The extraction efficiency of the developed fibers was found to be superior to four (PDMS, PDMS/DVB, Car/PDMS and DVB/Car/PDMS) commercial fibers only for extraction of thymol and carvacrol. The developed fibers were stable up to 80 cycles in DI and 300 cycles in HS mode. In other work, aiming to increase extraction ability and provide multiple functional groups for anchorage on fiber, analogues of aniline were used as a new coating material. *O*-Toluidine and *O*-phenlenediamine, which exhibit redoxelectrochromic behavior and high thermostability, were used to coat CNTs via electrodeposition.[92] The developed nanofiber was employed in HS-SPME for determination of PAHs in water samples. A CNTs -silicon dioxide (CNTs-SiO_2) nanohybrid composite was hydrothermally synthesized in the presence of glucose for the detection of organophosphorus pesticides via GC-corona discharge-ion mobility spectrometry (GC-CD-IMS).[93] The developed composite was deposited via electro-spinning on a stainless steel needle using poly(vinyl alcohol) (PVA), a high molecular weight polymer, as a glue. It is important to highlight that, due to the materials selected in this workflow, the coating methodology is one step toward the development of nontoxic coating manufacturing process. Besides, the coatings were stable up to 120 cycles when used for extraction of organophosphorus pesticides from wastewater, river water, pear, grape, and eggplant. Tang et al.[94] made a coating composite by

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

grafting hydroxyl terminated polydimethyldiphenylsiloxane (PDMDPS) on multiwalled CNTs. These composites were immobilized on a stationary phase via sol−gel for extraction of polar aromatic analytes. COOH functionalized MWCNT were modified by thionyl chloride and reacted with PDMDPS. Hydrophobic interactions were provided by MWCNT, while the hydroxyl terminated PDMPDS provided hydrophilic interactions for analytes to adsorb on the developed composite fiber. The PDMPDS/MWCNT composite yielded a better extraction performance compared to four commercial fibers, namely, Car/PDMS, DVB/Car/PDMS, PDMS/DVB, and PA fibers. Unlike the works described above, Song and collaborators explored the layer-by-layer approach[95] for the deposition of MWCNTs on polystyrene particles via electrostatic interaction. Particles were coated with polydimethyl diallyl amine (PDDA) and polystyrene sulfonates (PSS) until the surface of the particles was positively charged, which allowed the particles to hold the MWCNTs in place with the electrostatic charge. This composite was then immobilized on the support by gluing. The developed coatings provided high enrichment factors (EFs), high thermal stability, and low limits of detection (LODs) for phthalate acid esters. In another work, a polyimidazolium ionic liquid functionalized MWCNT was coated on an electrodeposited polyaniline film supported by a stainless-steel fiber for extraction of benzene derivatives from water samples in HS mode. The polyionic liquid coating aided in the increased dispersion of MWCNT in water and organic solvents by preventing chain aggregation and provided better enrichment for benzene derivatives due to the porous nature of PANI and the $\pi-\pi$ stacking of the PIL/MWCNT composite.[96] Recently, Abbasian et al. employed a similar approach for determination of methamphetamines from urine samples.[97] However, coatings were synthesized via sol−gel and utilized in HS mode to detect this analyte at trace levels. In another application, 1-(3-aminopropyl)-3-methylimidazolium bromide was used as an $-NH_2$ terminated ionic liquid to functionalize it over −COOH terminated MWCNT by chemical reduction; the composite was then immobilized by electrodeposition on a PANI-modified stainless steel wire and used for extraction of benzoic acid esters from perfume samples.[59] The coatings were stable up to 330 °C and provided high selectivity for benzoic acid esters when employed for HS-SPME-GC analysis. Wu et al.[60] used a poly(3,4-ethylenedioxythiophene)-ionic liquid polymer functionalized MWCNT composite to fabricate SPME fibers by electrodeposition. To enhance the stability and durability of the resulting coatings, their outer surface was coated with nafion by dipping the outer surface in this solution. These coatings provided higher sensitivity for carbamate pesticide extraction from aqueous samples due to their increased hydrophobicity and $\pi-\pi$ interactions. The increased stability of the fibers, resulting from the applied nafion coating, enabled DI extraction of carbamate pesticides from fruit and vegetable samples.[60] Another study from same group utilized an MWCNT-ionic liquid-reduced graphene composite made through self-assembly process to yield a three-dimensional porous material.[98] This material was coelectrodeposited on a PANI modified stainless steel wire by cyclic voltammetry. The developed fiber maintained thermal stability up to 300 °C and provided high EFs for selected alcohols (C_8-C_{12}) in HS mode even after 200 extractions. Hollow fiber SPME (HF-SPME) methods were also developed by utilizing MWCNTs. Functionalized MWCNTs were modified with glycine[61] and ethylene diamine[99] and deposited in a hollow fiber via sol−gel. The developed fibers were employed for extraction of venlafaxine and o-desmethylvenlafaxine in human urine and real water as well as naproxen from water samples. Abbasain et al.[62] fashioned a composite of functionalized CNTs with flower shaped zinc oxide and deposited it in a polypropylene hollow fiber via sol−gel for detection of tramadol on GC-FID. The developed HF-SPME method provided good linearity at a wide range of concentrations, and low LODs with higher precision when compared with other methods published in the relevant literature for detection of tramadol. The good extraction efficiency of the developed fiber was attributed to strong hydrogen bonds among MWCNTs−OH, ZnO−OH, −OH of PEG, and the free silanol groups as well as to the interactions with the −OH and the $-N(CH_3)_2$ moieties of TMD, in addition to van der Waals interactions with the methyl groups of MTMOS and Tramadol, which increased overall adsorption of tramadol onto the hollow fiber.

Graphitic Carbon Nitride and Boron Nitride Nanotubes/Sheets. Graphitic carbon nitride (g-CN) is an analogue of graphene and a promising new material in the class of carbon materials. The g-CN family of carbon compounds exists in the g-C_3N_4 form mainly, and is composed of carbon and nitrogen atoms. The g-CN analogue demonstrates unique stability, including chemical resistance to various solvents and thermal endurance. These materials possess an electron-rich graphitic structure and free terminal amino groups (NH_2, NH), which bestow g-CN with the ability to absorb electron-deficient compounds through $\pi-\pi$ conjugation, net electron transfer, chelation, hydrogen bonding, electrostatic and hydrophobic interactions, redox, and acid−base reactions. The diverse physicochemical properties of g-CN were utilized for extraction of organic compounds by mobilizing g-CN on an SPME fiber. The performance of the developed g-CN fiber was compared to two commercial fibers, namely, 100 μm PDMS and 85 μm Car/PDMS, for determination of deltamethrin, nerolidol, amphetamine, dodecane, ametryn, and acrylamide in potato chips.[65] EFs for all studied analytes were higher for the developed g-CN fiber than those obtained via commercial fibers, with a particularly high EF values observed for acrylamide. The method provided low detection limits, wide linearity, and good recoveries for the developed SPME-GC-ECD method. Following, Wu et al.[64] fabricated a g-CN and graphene composite fiber on a stainless-steel fiber via sol−gel for the extraction of PAHs in DI mode from cosmetic samples before GC-MS analysis. For this fiber, a single layer of g-CN was hydrothermally grown over graphene, which suppressed the restacking of graphene sheets and increased the extraction efficiency of the developed coatings. The extraction performance of the g-C_3N_4@G fiber (100 μm) for the six PAHs under study was compared with those of the 3D-G fiber (100 μm), the g-C_3N_4 fiber (100 μm), and the commercial PDMS fiber (100 μm). The developed fibers provided better EF values than 3D-G and g-C_3N_4 fibers and a much better performance than the commercial PDMS fiber. Hollow fibers coated with g-CN by physical ultrasonication were applied for the extraction of uric acid from urine and serum samples to develop a direct extraction and simultaneous derivatization and desorption method. Boron nitride nanotubes/sheets are structural analogues of CNTs /graphene, and are formed by replacing carbon atoms in graphitic carbon nitride nanotubes, with alternating B and N atoms having the same atomic spacing.[100] However, boron nitride nanotubes/sheets have different properties than CNTs owing to the presence of partial ionic bonds. In addition, BN structures are

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

reported to have better thermal and chemical stability compared to their counterpart graphitic carbon nitride. These structures are characterized by a high surface area (up to 1427 m^2 g^{-1}) and mass uptake (3300%) due to the combined effect generated by their super hydrophobicity, porous structure, and swelling ability.[101] These properties make such materials a good adsorbent for various chemicals and gases. BN materials have been used in applications involving gas separation, organic pollutant removal, drug delivery, gas storage, etc. In SPME, sol−gel coated boron nitride nanotubes on a stainless steel fiber were used for extraction of PAHs from water samples coupled with GC-MS/MS.[66] The resulting fibers had greater thermal and chemical stability than CNTs and yielded very low limits of detection with a wide range of linearity. The superior extraction of analytes obtained by this coating was ascribed to the hydrophobic effect and strong $\pi-\pi$ stacking interactions between the aromatic rings of PAHs and boron nitride nanotubes.

Metal Organic Frameworks (MOFs). MOFs are porous polymeric materials consisting of metal ions as a center and an organic ligand as a repeating, or more precisely, bridging unit. These materials have topologically diverse and pleasing structures which can be naturally attributed to the chemical properties of its central metal atom and the attachment of ligands. They are crystalline and possess a high surface area, tunable pore size, and adjustable internal surface properties. Owing to these properties, these materials have been used in a wide variety of applications, including in the adsorption of gases, detection of toxic chemicals, catalysis, gas storage, sensing, and as potential drug carriers, among others. MOFs extract analytes from varied interactions. Ligands in the framework provide hydrophobic interactions, $\pi-\pi$ stacking between analytes, and aromatic rings present in the backbone. Functional ligands increase extraction efficiency by providing sites for hydrogen bonding, ionic interactions, and dipole−dipole interactions. Metal sites which have uncoordinated sites offer Lewis acid−base interactions. Depending upon the ligand and metal's coordination number, the size of pores formed in the framework also determines the extraction affinity of the material. Most applications to date utilizing MOFs have focused on fiber format, with MOFs-coated fibers having been highly explored in SPME. From the literature, it is evident that stainless steel fibers were the most common choice as a substrate for the manufacture of MOFs-coated fibers, followed by fused silica, quartz, and nichrome as alternative substrates. The prevalence of stainless steel (SS) over others can be attributed to the properties afforded by this substrate, such as easy modification and superior thermal and physical stability. SS fibers are etched by dipping them in acid or base, by ultrasonication in a solvent, or by functionalization with silane groups. Etching or modification of the fiber surface will render the fiber surface coarse or increase its functional groups. This provides nucleation sites for MOFs when they are directly grown over fibers and eases mobilization of the extraction phase onto the fibers. General methods used for assembling MOFs onto the fiber surface can be classified as physical, chemical, sol−gel, electrodeposition, gluing, and *in situ* hydrothermal deposition. Since their first application in SPME by Cui et al., MOFs have been used for extraction of a wide variety of compounds from environmental and biological samples. The most commonly used metal ions for making MOFs are transition metal ions. The most commonly used MOFs in SPME have, as metal backbones, elements such as Zn, Cu, Cr, Al, Yb, Co, Ni, Ti, Fe, Cd, Ga, In, and Zr, whereas terephthalic acid and 1,3,5-tricarboxylic acid are most commonly employed by researchers as ligands in the synthesis of MOFs.

MIL-101 was used in HS mode for determination of BTEX, substituted benzene, and PAHs from river, tap, and lake water.[102,103] Fibers were made via layer-by-layer and sol−gel. The developed fibers were demonstrated to yield better recoveries for the studied analytes than PDMS and PA fibers and could be reused for up to 150 cycles, even at 300 °C. Metal organic aerogel (MOA)/MIL-53(Fe) was fabricated by gluing them on a nichrome wire using silicone glue.[74] MOA was prepared by removing solvents present in the gel through supercritical drying. The resulting MOF was aptly termed an aerogel. These fibers had high surface area (1400 m^2 g^{-1}) and were stable through 50 cycles. They had higher thermal stability, high porosity, and good extraction efficiency, in addition to having a coating of only 10 μm thickness. Indeed, the MOA/MIL-53(Fe) coating had superior EFs for chlorobenzenes when compared with PDMS (30 μm) and metal organic gel (MOG) fibers. MIL-53(Fe) was also immobilized on polydopamine functionalized stainless steel fibers for extraction of polychlorinated biphenyls (PCBs) from soil samples in HS mode.[104] The fibers were stable up to a temperature of 300 °C and had reusability even after 50 extractions/desorption cycles. In a comparison with DVB/Car/PDMS fibers, the MIL-53 coated fiber was shown to exhibit superior extraction capacity for PCBs. MOF coatings were also prepared by using 2-aminoterephthalic acid and Al salts and termed MIL-53 (Al). These MOFs were employed for extraction of organochlorine pesticides, synthetic musks,[105] and PAHs.[106] For determination of PAHs, the formed MOFs were first carbonized and then used for the enrichment of said analytes. In a comparison between the developed fibers and PDMS, PA, PDMS/DVB, and graphene, MOF-199/GO, and C18 composite fibers, the developed fiber was shown to yield better recoveries for PAHs. In a unique approach, a trimetal center MOF with Al, Ga, and In as metal centers and 4,4-(hexafluoroisopropylidene)-bis(benzoic acid) as ligand was synthesized.[75] The developed MOF was then exploited for extraction of four different types of pollutants, namely, BTEX, PAHs, *n*-alkanes, and anilines. Fibers made from the MOFs of individual metals, the developed trimetal MOF, and PDMS were then compared. The tested single-metal MOFs and PDMS fibers were shown to yield lesser recoveries for these analytes in relation to those obtained via the trimetal center MOF. A Yb-MOF[107] coating was also developed by using two different ligands at a time. This MOF had unusual thermostability, sustaining temperatures up to 343 °C. The developed fiber was tested for extraction of PAHs, then compared with 30 μm PDMS, 65 μm PDMS/DVB, 50/30 μm DVB/CAR/PDMS, and bare-etched stainless steel. Yb-MOF had higher EFs, stability, lower LODs, and sustained no losses in EFs for 100 cycles. Zn metal-containing MOFs with various ligands were immobilized on stainless steel fibers and needles for extraction of VOCs, phenols, polychlorinated compounds from food, wastewater, and river water samples. Aiming to increase the stability and extraction of the developed fibers, MOFs were combined with different organic or inorganic materials. MOF-5@SBA-15[108] was synthesized to utilize the high surface area and mesoporous properties of SBA-15. MOF-5 was also grown over a graphene oxide sheet and then covalently immobilized over an aminopropyltriethoxysilane (APTES)-modified fiber.[109] An MOF/GO composite was attached through a reaction of −COOH groups present on GO sheets and the $-NH_2$ groups of APTES. The resulting fiber was then successfully applied for

DOI: 10.1021/acs.analchem.7b04502
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the extraction of triazole fungicides from food samples in DI SPME. The obtained extracts were shown to yield higher peak areas for triazole fungicides in comparison to 100 μm PDMS and 65 μm PDMS/DVB fibers. In another application, three types of MOFs with Zn and Cd as metal centers were synthesized with 4,4-biphenyldicarboxylate, terephthalic acid and 2,6-naphthalene dicarboxylate (Cd) as ligands.[73] The resulting coatings were dispersed in a PANI solution and electrodeposited on a stainless-steel needle. Among them, the MOF with Cd as a metal center yielded the best recoveries for extraction of chlorobenzenes from water samples in HS mode. The utilization of the MOF-177 coating with 30 μm thickness on a stainless steel fiber provided better recoveries for PAHs[110] and phenols[111] in HS analysis from water samples of different origins. Huo et al. reported a dual ligand MOF known as Bio-MOF-1 for enrichment of PAHs from water.[72] The MOF had 4,4′-biphenyl dicarboxylic acid as a bidentate ligand and adenine as a biocompatible ligand. Fibers were prepared by *in situ* hydrothermal synthesis of Bio-MOF-1. A fluorous MOF@PI coating yielded good extraction of benzene, other benzene homologues, hydrocarbons, and phenols from water samples.[112] The fibers were fabricated by hydrothermal growth of FMOF over PI coated stainless steel. The developed fiber provided higher enrichment factors for benzene; 38, 66, and 127 times larger than figures obtained for PDMS, CW/PEG, and PA fibers, respectively. Lan et al.[113] prepared MOF by *in situ* cathodic electrodeposition, with triethylamine and benzene dicarboxylic acid connecting Zn metal ions. The resulting fibers were employed for extraction of ethinylestradiol, bisphenol A, diethylstilbestrol, and hexestrol from milk samples. Fibers were thermally and chemically stable for up to 120 extractions and desorption cycles. UiO-66,[114] UiO-67,[115] and PCN-222[76] MOFs were prepared for extraction of PAHs, substituted nitrobenzenes, and nitrated PAHs from water and soil samples, respectively. The fibers UiO-66, UiO-67, and PCN-222 were prepared via *in situ* solvothermal, sol−gel, and hydrothermal growth, respectively, on silica and stainless steel wires. Carbonized MIL-125 yielded higher recoveries for phthalate esters from tea samples in DI SPME than the noncarbonized coatings.[116] The enrichment capacities of these fibers were unchanged for up to 160 extraction and desorption cycles. While a cursory comparison of the above-discussed MOFs would certainly indicate that such fibers are capable of better recoveries for organic pollutants and toxic compounds in DI and HS SPME as compared to commercially available fibers, it should be kept in mind that every MOF has a different surface area, porosity, and pore size, all which affect the extraction capabilities of the developed fibers. As such, the abovementioned parameters should be taken into account prior to selection of an MOF-coated fiber for a given application. Other factors, such as coating thickness, thermal stability, and compatibility with the matrix under study, should also be taken into account during the selection process.

Zeolitic Imidazole Frameworks. Zeolitic imidazole frameworks (ZIFs) are a special class of metal organic frameworks comprised of imidazolate linkers and metal ions, with structures similar to conventional aluminosilicate zeolites.[117,118] In ZIFs, the Zn or Co atom takes the place of Si, while imidazole anions replace oxygen in a zeolite structure. ZIFs have inherent porous physiognomies, diverse functionalities, and the extreme thermal and chemical stability inherent of both MOFs and zeolites. In addition, ZIFs generally display properties that combine the advantages of both zeolites and MOFs, such as ultrahigh surface areas, unimodal micropores, and high crystallinities; as such, ZIFs make suitable candidates for SPME coatings. In this regard, ZIF-90 was used for extraction of polar endocrine disruptors in HS mode from water and soil samples.[68] The coatings were covalently bonded over silica fibers via the solvothermal reaction of Zn(II) and imidazolate-2-carboxylate. The free aldehyde in the imidazolate-2-carboxyaldehyde was utilized for immobilization on the fiber through the imine condensation reaction between the NH_2-groups of APTES. The fibers had high endurance and reusability, maintaining their original capabilities up until 170 cycles of extraction. Under the same conditions, the ZIF-90 bonded fiber (20 μm) was demonstrated to yield better performance when compared to those of the commercial PA (85 μm) and PDMS/DVB (65 μm) fibers for SPME of polar phenolic endocrine disruptors. The higher EFs values of the ZIF-90 bonded SPME fiber for phenolic endocrine disruptors were attributed to the combined effects of the large surface area and unique porous structure of the ZIF-90, hydrophobic effect, hydrogen bonding interactions between aldehyde and the −OH group of phenolic groups, and $\pi-\pi$ stacking interactions between the studied analytes and the framework imidazolate-2-carboxyaldehyde molecules. Zhang et al. fabricated a ZIF-90 nanoporous carbon (ZIF-90-NPC) coated SPME fiber via a physical adhesion approach for SPME of selected pyrethroids from different fruit and vegetable samples. ZIF-90 and furfuryl alcohol were used as precursors to make nanoporous carbon.[119] The ZIF-90-NPC coating showed high adsorption affinity, satisfactory recoveries, and reusability up to 100 cycles. Aiming to simplify the linkage of ZIFs on the surface of substrates, researchers used polydopamine as a coating on the inner surface of PEEK tubing.[120] Employment of polydopamine eliminated the need of additional linkers to immobilize the coating on the substrate. This ZIF-8 modified PEEK tubing was employed toward the extraction of PAHs via online in-tube SPME. Lan et al. coated ZIF-8 on SPME arrows by physical adhesion, using PVC as adhesive.[121] ZIF-8 SPME arrows were exposed to HCl in HS to modify pore size and applied for adsorption of volatile, low molecular weight alkylamines from salmon, mushroom, and wastewater samples. ZIF-8/PVC arrows demonstrated comparable results and lower limits of detection in comparison with commercial PDMS/Carboxen 1000 based arrows. Recently, ZIF-8 coated SPME fibers loaded with the derivatization agent isobutylchloroformate were employed in DI mode for determination of nonvolatile aliphatic amines from fish samples.[119] The loading of the derivatization agent on the prepared fibers prohibited their hydrolysis, and facilitated simultaneous derivatization and extraction. In comparison with commercial PDMS fibers, the ZIF-8 fibers yielded better performance, good stability, and adequate sensitivity.

Covalent Organic Frameworks. Covalent organic frameworks (COFs) are analogues of metal organic frameworks that lack metal in their structure. They are made up of light elements, which are part of repeating organic molecules held covalently to give two- or three-dimensional amorphous or crystalline materials. COFs have a highly porous tailorable architecture with periodic voids, high surface areas (2500−4000 m^2g^{-1}), low density (0.17 g cm^{-3}), and high thermal (up to 300 °C) and physical stability.[122] Unlike their counterpart MOFs, COFs are stable in aqueous media, under extreme pH conditions, and in redox environmental conditions. Owing to these advantageous properties, COFs have been used in the areas of catalysis, energy storage, membrane production, light conversion, and

DOI: 10.1021/acs.analchem.7b04502
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separation.[123] The organic frameworks present in these materials enable the employment of functional group modifications before and after their synthesis. The presence of an organic backbone and various functional groups in the final structure provides multiple interactions for the adsorption or absorption of analytes. Use of COFs in SPME was first reported by Pan et al. In this work, microporous COF SNW-1 was synthesized with the use of melamine and terphthalaldehyde, then coated on a glycidyl propyl trimethoxysilane functionalized silica fiber. The fiber was applied for the extraction of volatile fatty acids from tea leaves and tobacco samples in HS mode. They were reported to be stable under harsh pH, solvent use, temperature, and ionic conditions. The performance of the developed fibers (14 μm) was compared with those of commercially available PDMS (100 μm), PDMS/DVB (65 μm), Car/PDMS (85 μm), and PA (85 μm) fibers and found to yield superior performance for the selected analytes. Limits of detection were obtained in the range of 0.014−0.026 μg L^{-1} on GC-MS. The superior enrichment performance was attributed to the $\pi-\pi$ affinity and acid−base interactions provided by the planar hydrophobic aromatic rings and the nitrogen- and oxygen-containing functional groups, respectively.[124] The same COFs coating was used for extraction of phenols from honey samples, except that in this case, the support used was a stainless steel fiber. In this application, limits of detection in the range of 0.06−0.2 ng g^{-1} were achieved on GC-MS.[82]

A hydrazine-based COF prepared by reaction of 1,3,5-benzenetricarboxaldehyde and terephthalic dihydrazide and immobilized on a polydopamine functionalized stainless-steel fiber was applied in HS mode for the analysis of pyrethroids in vegetables and fruits. The functionalized stainless-steel fibers were made in three steps. Polydopamine was first coated on an etched fiber by physical deposition for 24 h. Next, the fiber was further functionalized with APTES to act as a linker. This linker was then reacted with the previously mentioned reagents to grow 15 μm hydrazone COF membranes on the surface of SSF. Using this fiber, the developed method yielded an enrichment factor in the range of 307−2327 for the selected analytes. The performance of the developed fiber was compared with those of the commercially available PDMS (100 μm), Car/PDMS (85 μm), PA (85 μm) fibers, as well as with those reported in the literature for MWCNT/polypyyrole and ionic liquid coated fibers.[81] Its superior performance was attributed to its unique configuration; as the hydrazone COF possesses abundant phenyl rings and −C═N groups, they provide strong $\pi-\pi$ stacking interactions with pyrethroids, which are endowed with a $\pi-\pi$ conjugated structure due to the presence of phenyl rings and −C=C− formations.[81] In another application reported by the same group, cross-linked hydrazone COFs were prepared via the thiol-ene "click" reaction and applied for the extraction of pesticide residues with GC-electron capture detection (ECD). The obtained enrichment factor was in the range of 2190−10 998, with limits of detections in the range of 0.0003−0.0023 ng kg^{-1}. The extraction efficiency of the cross-linked hydrazone COF was shown to be superior to those of single COFs, PDMS (7, 85, 100 μm), Car/PDMS (85 μm), and PA (25 μm) fibers.[125] Zhang et al. reported the use of amide-functionalized microporous organic polymers, known as COF-SCU-1, for the extraction of volatile benzene homologues from indoor air samples. The fibers were made via physical adhesion. SCU-1 COF was synthesized by reaction of trimosyl chloride with *p*-phenylenediamine, then adhered on a stainless-steel fiber by epoxy glue. Extractions were performed in the HS at 40 °C for 20 min. Fibers were stable up to 300 °C and gave higher enrichment factors when compared with the commercial PDMS and PDMS/DVB fibers for extraction of benzene homologues. An extraction mechanism study elucidated that compounds capable of facilitating $\pi-\pi$ stacking are extracted in larger quantities by SCU-1 COFs than other hydrophobic compounds due to the π-conjugated aromatic groups available in the coating.

To increase the extraction efficiency of COFs, fibers were made by combining gel[78] and ionic liquids[79] with COFs. These materials, termed porous aromatic frameworks (PAFs), are made up of highly conjugated repeating aromatic monomers. Compared to other COFs, they are comprised of strong enrichment abilities for benzene homologues due to a $\pi-\pi$ affinity between the sorbents and the target molecules. The combination of PAFs, ionic liquids, and gel format capitalizes on the individual properties of these materials to enhance extraction and facilitate mobilization of PAFs on the supporting fiber. In other work, PAF/IL coated fibers were employed for determination of organochlorine pesticides on GC-ECD from juice and milk samples. The PAF/IL coating was prepared in three steps. First, PAFs were synthesized from 2,2′-bipyridyl, bis(1,5-cyclooctadiene)nickel(0) ($[Ni(cod)_2]$). Next, the produced material was functionalized with NH_2 groups and then finally reacted with ILs. The PAF/IL composite was then coated onto a quartz fiber by gluing. The produced fibers were stable up to a temperature of 250 °C and afforded reusability up to 100 extractions. In an extraction efficiency comparison of PAF and PAF/IL coated fibers, while both fibers were revealed to extract analytes by hydrophobic interactions and $\pi-\pi$ interactions, IL-containing fibers were shown to also extract analytes via electrostatic interactions between PAF/IL and organochlorine pesticides.[79] Similarly, PAF-48/gel coated fibers were fabricated on a silica fiber via sol−gel. PAF-48 was synthesized by reacting $AlCl_3$ with 1,3,5-triphenylbenzene. The resulting fibers were then compared with commercial Car/PDMS 75 μM, PDMS/DVB 65 μm, and 100 μm PDMS fibers for extraction of styrene and volatile aromatic compounds from materials used in food packaging. The prepared fibers were shown to afford higher selectivity efficiency over alcohols, phenols, aromatic amines, and alkanes from aromatic hydrocarbons. In another approach, Huang et al. studied the extraction phenomena associated with COFs by synthesizing three different COFs, all with a mesoporous structure, but consisted of different pore volumes.[126] The synthesized coatings were then applied toward extraction of BTEX and PAHs in HS mode. Through this study, pore volume was shown to be a significant factor influencing the extraction efficiency of these fibers. Succinctly, the obtained findings showed that porous organic polymers with a high surface area and small pore volume afforded less extraction efficiency than those consisting of a higher pore volumes and smaller surface areas, with the material consisting of the smallest pore volume and surface area yielding the worse performance among the prepared materials. These findings were attributed to fact that molecules of a smaller size than the pore size can be more efficiently adsorbed into said pores due to their larger volume. In summary, the different adsorption abilities of the prepared materials associated with analyte uptake were shown to be more dependent on the volume of the pore rather than its size or the surface area of the material.[126]

Aptamers. Most coatings developed in SPME are targeted for extraction of nonpolar and semi polar compounds, with some of the developed coatings exhibiting certain selectivity

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

and binding affinity toward moderately polar analytes. However, most SPME coatings lack the ability to extract highly polar compounds. To overcome this limitation, aptamer-mediated extraction was developed.[127] Aptamers, a new class of single stranded DNA/RNA molecules, possess advantages such as high specificity and binding affinity, good stability, low cost, nontoxicity, ease of synthesis, and easy, controllable modification abilities. These properties make such molecules promising and dynamic in environmental and biological applications. To that end, aptamer-functionalized SPME fibers were applied for extraction of adenosine from human plasma.[127] These fibers exhibited 20 times higher enrichment efficiency than commercial coatings and were shown to extract the target analytes selectively and specifically. In another application, an aptamer with adenosine triphosphate as a ligand was immobilized on the surface of a polymer coated fiber to extract adenosine triphosphates from human serum samples.[128] The prepared device exhibited a selectivity coefficient of 22.1 compared to the scrambled oligonucleotide functionalized fiber, and selectivity factors over other analogues ranging between 6.1 and 77.5. Such findings indicate that the devised Apt-PP-fibers could be used for highly efficient separation and enrichment of trace ATP, ADP, and AMP in human serum sample. Du et al.[83] covalently immobilized an aptamer ligand on electrospun microfibers made with the hydrophilic polymer poly(acrylonitrile-*co*-maleic acid) (PANCMA) on stainless steel rods for extraction of α-thrombin from human plasma. The developed probe exhibited highly selective capture, good binding capacity, high stability, and good repeatability for extraction of thrombin from 20-fold diluted human plasma samples. The devised fibers were also applied for the analysis of clinical human plasma samples, with the attained results indicating that the developed method can be applied for selective enrichment of a given targeted protein from complex samples *ex vivo*, even though the extraction efficiency of the method was reduced in undiluted human plasma as compared to that attained in the previously diluted standard solution. In a recent paper, a novel three-dimensional (3D) M × N type aptamer-functionalized SPME fiber array (M represents the number of targets; N represents the number of samples) was developed for selective enrichment of multiplex antibiotic residues from milk samples, using three chloramphenicols (CAPs) as models.[84] A thiol-functional aptamer was also immobilized in this study via a covalent bond between Au-S on gold nanoparticles over gold wire. The extraction efficiencies of three different fibers, all which contained aptamers, were then compared. The 3D aptamer functionalized fiber yielded a 500-fold enrichment factor, which was 3.1 times higher than that of the 2DApt@AuNPs−ITO fiber and 6.6-fold higher than that of the 1D-Apt@Au wire−ITO fiber. The developed SPME fiber assay coupled with HPLC detection afforded advantages such as high-throughput, selectivity, and adsorption capacity in one run. In the same study, a type of M × N fiber extract array was also prepared for the simultaneous extraction of multiple amide alcohol antibiotics from 12 samples in one run.

Molecularly Imprinted Polymers. Although SPME has been employed for the extraction of a range of organic pollutants or analytes from environmental and biological samples, most available coatings used for such applications have been designed either for general use (wide coverage) or toward extraction of a specific class of compounds; in other words, such coatings are not selective for particular analytes. Aiming to address the lack of selectivity of SPME coatings, in 2001, Koster et al.[129] began exploiting the capabilities of molecular imprinted polymers (MIPs) toward the development of compound-specific coatings. They functionalized a silica fiber via a silane group and coated a layer of methacrylate polymer with MI sites for the extraction of clenbuterol from human urine samples. The MIPs were successfully synthesized by using brombuterol as a dummy template to avoid the leaching of residual analytes in the synthesized MIPs. In this proof-of-concept study, the developed MIP fiber was demonstrated to provide an LOD of 10 ng mL^{-1} for clenbuterol. Since then, a plethora of papers focused on MIP fibers have been published in the literature. The main drawback of early MIP SPME fibers was that the silica-based fibers were very fragile; however, such limitations were overcome through the manufacture of MIP-SPME devices on metal supports. To this extent, researchers have used aluminum and stainless steel as a support for the manufacture of MIP-coated SPME fibers. However, in recent years, much research focus has been shifted toward MIP monoliths and plane surfaces coated with MIP in place of MIP-coated fibers for extraction of targeted analytes. This section focuses on the scientific progress made over the last 2 years in terms of MIP coated materials and their application in SPME. Stainless steel fibers coated with molecular imprinted polymers were applied in various works for extraction of abacavir,[130] ciprofloxacin,[131] and luteolin and its metabolites.[132] In these works, stainless steel fibers were modified before polymerization was initiated on their surface. Modification was generally carried out by etching the fibers in oxidizing agents or by coating them with chemicals with functional groups capable of providing anchorage to immobilize MIP groups. In the case of abacavir and ciprofloxacin imprinted fibers, MAA was used as a functional monomer and EGDMA as the cross-linker. For luteolin imprinted fibers, acrylamide was used as functional monomer and EGDMA was used as a cross-linker. Luteolin imprinted SPME fibers were employed for *in vivo* analysis of metabolites of luetolin from rat liver. The developed method extracted three analytes, namely, apigenin, chrysoeriol, and diosmetin. This *in vivo* study marked the first instance where apigenin was detected via MIP-SPME, as previous *in vitro* analyses failed to detect this compound. Next, the developed MIP-SPME fiber was compared with the PDMS fiber. The PDMS fiber could only extract luetolin, while the other metabolites were not extracted. In other work, a monolithic SPME fiber based on molecular imprinted polymer was fabricated for extraction of sarcosine, a marker of tumors, from urine samples.[77] Monolithic fibers were prepared by heating a glass capillary filled with a prepolymerization mixture at 60 °C for 12 h. The selectivity of the prepared fibers was investigated by extracting sarcosine in the presence of other amino acids such as glycine, alanine, valine, lysine, and histidine with both MIP and NIP fibers. The recoveries for sarcosine were found to be higher than those of other amino acids on MIP. In a comparison of extraction efficiency between NIP monolithic and PDMS fibers, MIP monolithic fibers were shown to afford superior recoveries. In a recent paper, a dummy molecular imprinted monolith was prepared via sol−gel in a tip of a micropipet for extraction of vanillin and methyl vanillin from milk powder.[133] The monolith was prepared by polymerizing a prepolymerization mixture in the sealed tip after degassing with nitrogen at 60 °C for 24 h. The molecular imprinted monolith provided better recoveries of vanillin and methyl vanillin when compared to nonimprinted monolith. Moghaddam et al.[134] used pyrrole as a template to manufacture a MIP-monolith fiber for the extraction of furan

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

from water samples in HS mode. Here, furan was not used as a template due to its low boiling point, which limits the template monomer stability when the polymerization reaction is carried out at high temperatures. The extraction capability of the developed monolithic fiber for furan was compared with that of the Car/PDMS fiber, yielding recoveries of 94% and 85%, respectively. The MIP materials reported for extraction of sarcosine, vanillin, methyl vanillin, and furan were manufactured with the use of methacrylic acid and ethylene glycol dimethacryalte as a functional monomer and cross-linker, respectively. Molecular imprinted polymer synthesis generally involves a template, a functional monomer, solvent, initiator, cross-linker, and porogen. In a novel approach, a single cross-linking monomer was used with only a template, solvent, and initiator to form a polymer. This eliminated a number of processes, such as the selection of a monomer and cross-linker as well as the optimization of the monomer cross-linker ratio. A similar approach was used by Alvarez et al.[135] to fabricate paraben-imprinted monolithic fibers. *N*,*O*-Bismethacryloyl ethnolamine was used as monomer and cross-linker, benzyl paraben as template, AIBN as initiator, and acetonitrile as porogen. Free radical polymerization was induced by UV irradiation at 15 °C for 60 min. The resulting fibers were compared with fibers made using a conventional approach using methacrylic acid and ethylene glycol dimethacrylate as functional monomer and cross-linker, respectively. The one monomer cross-linker approach provided better selectivity for the parabens from soil and sediment samples than the traditional approach of manufacturing these fibers. Moein et al.[136] prepared acesulfame imprinted polymers on stainless steel bars by the electro-spinning method for extraction of sweeteners[137] from beverage samples. In this method, 3-(triethoxysilyl)-propylamine was used as a functional monomer to imprint the analyte by hydrogen bonding, Vander Waals, and dipole−dipole interactions, while nylon-6 was used asa backbone and support of the precursor in MIP sol−gel synthesis by electro-spinning. The developed devices were reusable for up to 50 cycles and achieved limits of detection as low as 0.23 ng mL^{-1} for the targeted analytes. While the MIP-fibers afforded stability in most of the solvents used for sample preparation, they were susceptible to formic acid and *N*,*N*-dimethyl formamide, as these solvents can easily dissolve Nylon-6. In another application, and MIP-based, water compatible SPME fiber was developed on silica fiber via sol−gel using calixarene as a functional monomer for extraction of organophosphorous pesticides from apple and pineapple samples.[138] Three different fibers, MIP, NIP, and blank, were synthesized. Parathion-methyl was used as template and calixarene as functional monomer, whereas the blank fiber was made by using other components of the prepolymerization mixture without the template and functional monomer so as to investigate the effect of said mixture on extraction. MIP and NIP fibers yielded better recoveries when compared to the blank, PA, PDMS, DVB/PDMS, and Car/DVB/PDMS fibers. However, MIP provided slightly higher recoveries than NIP at an analyte concentration of 2000 $\mu g\ L^{-1}$. A diclofenac imprinted hollow fiber was developed for HF-SPME extraction by Pebdani et al.[139] Here, molecular imprinted polymers were formed on the surface of MWCNTs, then reinforced into the polypropylene hollow fiber to form an *in situ* gel network, with methacrylic acid and vinyl triethoxysilane used as functional monomer and cross-linker, respectively. The selectivity of the developed fibers toward diclofenac was tested by extracting mefenamic acid and carbamazepine, compounds with similar molecular structure, demonstrating that the developed fibers extracted other drugs by less than 10% as compared to their extraction of diclofenac. The targeted drug was also extracted from tap water, well water, mineral water, plasma, and urine samples, providing recoveries in the range of 95.1−104.2% and LODs in the range of 0.48−0.7 $\mu g\ L^{-1}$. Nickel foam supported MIPs were developed for the extraction of floxacin[140] and ofloxacin[141] from environmental and biological samples. Nickel foams were modified with polysulfone and dopamine /3-Methacryloxypropyltrimethoxysilane to adhere floxacin MIPs on the support surface. A thin layer of MIPs was synthesized on the surface of the nickel foam by optimizing the needed amount of polymerization solvent and the reaction time. The developed methods yielded limits of detection for floxacin and ofloxacin in the range of 0.9−1.9 $\mu g\ L^{-1}$ and 4.2−6.0 ng mL^{-1}. While MIP is able to impart selectivity to SPME fibers for extraction of analytes of interest from various matrixes, the use of these materials also suffers from limitations. MIP-coated fibers are known to suffer from template bleeding, nonspecific bindings, and thermal instability. Of these drawbacks, template bleeding is of significant concern in trace analysis applications. Even after submitting the prepared materials to exhaustive washing with solvents, template molecules from MIP may remain in the fiber coating, causing them to bleed during the extraction process and thus yield false recoveries. Such a limitation has been addressed through employment of analogues of template molecules, although this method yields lesser molecular recognition in comparison to MIP coatings prepared with the targeted template. On the other hand, nonspecific binding sites present on the surface of MIP and NIP provide interactions for interfering components present in matrixes, thus decreasing the selectivity of the method. This can be attributed to the large number of functional groups present in the coating that result from the use of higher concentrations of functional monomers during synthesis. This drawback can be eliminated or minimized with the use of lesser amounts of functional monomer; by introducing washing step(s) to the workflow, which should include careful optimization of an appropriate washing solvent, or by synthesizing MIPs via the covalent or semicovalent approaches.[142]

Ionic Liquids. Ionic liquids (ILs) are organic salts present in their liquid phase at room temperature or below 100 °C due to the presence of poorly coordinated ions. They are composed of a cationic organic part and organic/inorganic anions, which can be tuned according to the intended application. They possess high thermal stability, good conductivity, variable miscibility, and viscosity in diverse solvents, tunable analyte selectivity, and low volatility. Their unique ionic structure as well as the presence of organic moieties in their structure provides ion dipole, ion pairing, $\pi-\pi$ interactions, hydrogen bonding, and hydrophobic interactions for the extraction of analytes. These inimitable properties have led to their widespread use as novel coating materials in SPME applications. Detailed information regarding employment of ILs in SPME can be found in recently published reviews.[143,144] In recent years, efforts have been made toward the synthesis and use of polymeric ionic liquids (PILs) as extraction phases for SPME instead of ILs. PILs are polyelectrolytes consisted of repeating units of monomers of ionic liquids, which maintain all the properties of ILs, while affording additional intrinsic features of polymers. Such materials are soluble in polar organic solvents but not in water, making them more suitable for various applications in SPME. Insolubility in water can be attributed to reduced columbic interactions and

DOI: 10.1021/acs.analchem.7b04502
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the hydrophobic character of counterions present in PILs. Recently, porous ILs fibers were used for extraction of organic acids from food samples. The coating material was prepared by polymerization (1-vinyl-3-(4-vinyl-benzyl)imidazolium chloride) in the presence of azobisisobutyronitrile (AIBN) then coated on a microwave-induced plasma etched stainless steel wire with the use of PAN glue.[145] Microwave induced etching provided better wettability and adhesion for coatings. The resulting fibers had very a long lifetime and good durability. PILs coated fibers were applied in vacuum-assisted HS-SPME for determination of organic phenols and fatty acids.[146] Two different coatings were prepared; the first was fabricated by using 1-hexadecyl-3-vinylimidazolium bis[(trifluoromethyl)-sulfonyl)]imide (C_{16}Vim-NTf_2) as IL monomer and dicationic,1,12-di(3-vinylimidazolium)dodecane bis[(trifluoromethyl) sulfonyl)]imide ($(ViIm)_2C_{12}$-$2NTf_2$) as cross-linker, while the second coating was fashioned with the use of 1-hexadecyl-3-vinylbenzylimidazolium bis[(trifluoromethyl)sulfonyl)] imide (C_{16}VBim-NTf_2) as monomer and the dicationic IL cross-linker 1,12-di(3-vinylbenzylimidazolium)dodecane bis[(trifluoromethyl)sulfonyl)] imide ($(ViBIm)_2C_{12}$-$2NTf_2$). The cross-linked IL materials were immobilized on nickel-titanium wires using the spin coating method. However, when compared to Car/PDMS, DVB/Car/PDMS, PDMS, and PA fibers, the Car/PDMS fibers were shown to provide better results for the selected analytes in vac-HSSPME.

Cross-linked PILs, poly(1-trimethyl-(4-vinylbenzyl) aminium chloride-*co*-divinylbenzene/ ethylenedimethacrylate), were used in a multiple monolithic fibers (MMF) configuration of SPME for extraction of endocrine-disrupting chemicals from water and urine samples.[85] These MMF-SPME fibers provided better recoveries than other fibers due to the presence of ionic, hydrophobic, and hydrophilic functional groups present in the structure of the coating. Chen et al.[147] prepared an MIP-based MMF with a poly(ionic liquid) as a functional monomer. These fibers were used to determine phenolic acids from beer and fruit samples. The developed method had a recognition coefficient of 11.6 for 3,4-dihydroxybenzenepropanoic acid in DI SPME. In other work, matrix-compatible PILs were prepared by Cagliero et al.[148] for extraction of acrylamide from coffee powder and brewed coffee. The extraction capabilities and sensitivity of PIL fibers toward acrylamide were attributed to the presence of hydroxyl groups in the cationic structure of the coating. Sun et al.[149] prepared a PIL-doped graphene oxide (GO) monolith to enhance the extraction capacity of phenols in aqueous solution. Its superior performance was attributed to functional groups present on GO, the formation of hydrogen bonding or electrostatic interactions by PIL, and the $\pi-\pi$ interactions of the phenyl groups with the delocalized π-electron system of graphene oxide. This method provided LODs in the range of 0.2−0.5 $\mu g\ L^{-1}$.

ILs have been generally employed for SPME extraction of small molecules. Recently, Nacham et al. developed an SPME method using PILs for purification of mRNA from complex biological samples and quantified it using a real time reverse transcription quantitative polymerase chain reaction assay.[87] Here, a PA coating was first modified with an amine functional group. The amine-modified PA was then functionalized with oligo dT20 (20 deoxythymidylic acid residues), which increased the mRNA extraction performance of the coating. The developed method provided better extraction performance at lower concentrations of mRNA from whole RNA in short analysis times when compared to phenol/chloroform LLE. The manufactured PIL SPME coatings provided a cheap and reusable alternative to commercially available yet expensive, single-use silica kits.

Biocompatible SPME Coatings. In the context of SPME, the biocompatibility of a given coating can be considered in several ways, including whether the material is nontoxic and noninjurious for a living system, a crucial requirement for *in vivo* studies, and whether it provides inertness to matrix components that may cause biofouling, which would have an adverse effect on the performance of the extraction phase as well as diminish its reusability. The first generation of biocompatible SPME coatings, developed for analysis of biofluids, were constituted by PAN as binder for sorptive particles.[150] Lately, several biocompatible SPME products have been introduced to the market, such as SPME LC tips made of C18 functionalized silica particles and polystyrene(PS)-DVB polymeric particles immobilized in a biocompatible binder (PA), and coated onto biocompatible nitinol microwire. The negatively charged polyacrylonitrile minimizes the binding of macromolecules (i.e., proteins) and allows for selective permeation of small molecules to the extraction phase. These fibers can be mounted in disposable micropipet tips and placed in a 96-pipet holder, a functionality that makes them compatible with commercial multichannel pipettors and automated liquid handling systems; as such, these devices are mainly designed for laboratory use. In this line of developments, an LC fiber probe was recently introduced as a biocompatible sampling device suitable for *in vivo* sampling. This fiber is essentially made of the same material as described above for the LC tips, except that in this case, the fiber is not attached to a micropipet tip but is instead assembled in a needle. In this design, the needle assembly not only protects the extraction phase from any kind of damage and contamination, it is also used to puncture the tissue and guide the fiber into position prior to its exposure to the sample. Indeed, owing to their convenient design, various bioanalytical applications have to date reported the use of these fibers.[151−153] While both the abovementioned fiber probes and LC tips are designed as single-use devices, owing to their designated use in clinical applications, where employment of single-use devices is mandatory; historically, SPME fibers have been developed on the premise of their reusability. In fact, reusable devices are still in high demand. In this context, the reusability of a given device is strictly dependent on the capability of the coating to minimize the accumulation of matrix constituents on the coating surface after each extraction cycle, which can affect both the coating chemistry and its morphology. In this regard, in addition to selecting materials with good antifouling properties, it is important that a smooth coating surface is attained during the coating preparation process. Considering these factors, a PDMS-based coating was developed for DI SPME analysis of complex food matrixes. The SPME fiber, namely, PDMS/DVB/PDMS, consists of a DVB/PDMS fiber overcoated with a thin and smooth layer of pure PDMS (10−30 μm) that gives adequate matrix compatibility without jeopardizing the uptake kinetic of the analytes into the extraction phase. Several studies were carried out in order to optimize the overcoating procedure[51] and to understand the fundamentals behind the mass transfer process of analytes with different polarities and molecular weights from the matrix into the coating.[154] Indeed, owing to its superior performance, various applications using the PDMS/DVB/PDMS coating have since been developed, demonstrating the advantages associated with the use of this coating for DI-SPME in a variety of complex matrixes (e.g., fruits, vegetables, and juices). More recently, coatings based on hydrophilic

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

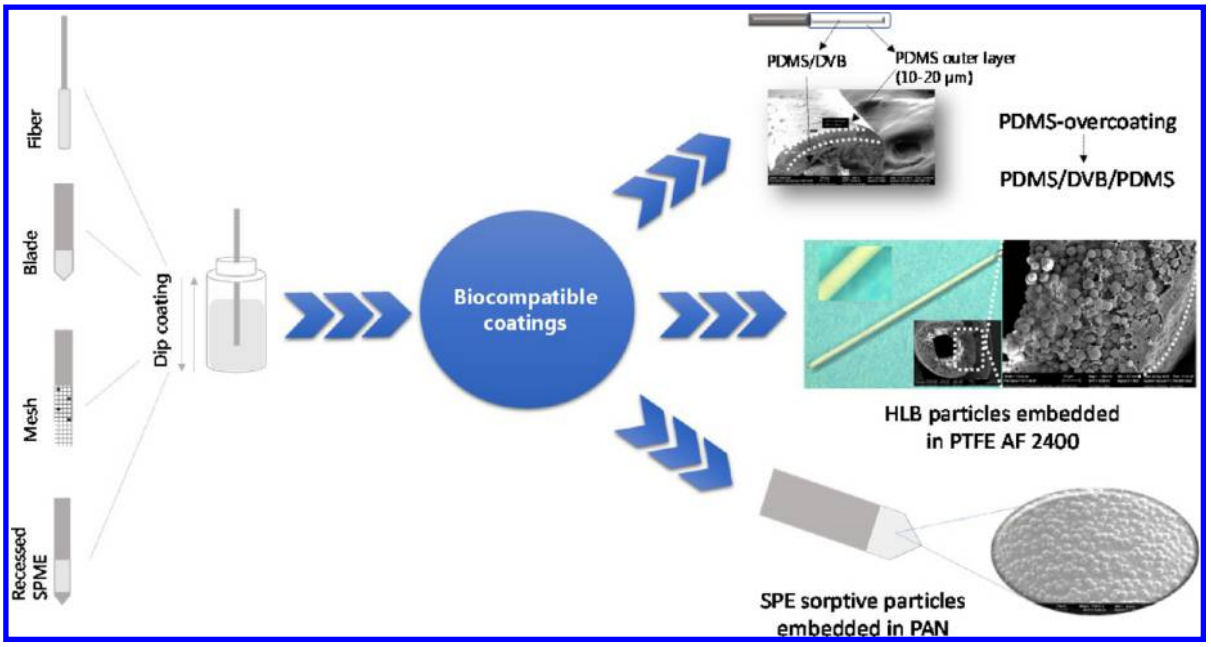

Figure 3. Biocompatible coatings based on PDMS, PAN, and PTFE AF 2400 for different geometries of SPME devices.

lipophilic balanced polymeric particles (HLB) incorporated in a biocompatible fluoroplastic (PTFE AF 2400) were introduced as a new generation of SPME devices suitable for both solvent and thermal desorption.[53] The PTFE AF 2400 polymer presents several advantages over other binders, such as sufficient thermal stability for thermal desorption in gas chromatography (GC), inertness against conventional solvents for liquid chromatography (LC), good biocompatibility, and comparable kinetic uptake compared to other polymers, namely, PAN and PDMS, which are conventionally used for production of SPME coatings. The new PTFE AF-HLB SPME fiber was successfully evaluated in terms of extraction coverage, robustness, compatibility, and efficiency toward both GC and LC analysis, and biocompatibility.[53] It is worth emphasizing that the above-mentioned coating materials are suitable to be used in any of the different SPME configurations available (Figure 3).

SHAPES OF SUPPORT

SPME technology has emerged in a variety of geometries and configurations, such as fiber, thin film, in-tube, dispersed particles, among others. Regardless of the configuration employed, the basic principles of extraction remain the same for all of the conceived forms, while the flexibility in configuration provides case-specific solutions where other sample preparation approaches fail. Among the various SPME geometries available to date, the fiber and thin film geometries have been predominantly advancing in a variety and design in order to address very specific needs of many research fields. Herein, recent progress made in the fiber, thin film, dispersed magnetic nanoparticles based SPME (d-SPME), and stir bar sorptive extraction (SBSE) formats is summarized. More comprehensive information regarding SPME associated geometries can be found in a recent review published by Piri-Moghadam et al.[15]

SPME Fiber: New Developments. Although the first developed format of SPME was the fiber geometry, its technological development is still under evolution. The advancements made in this field explicitly incline in parallel to the progress in material science, clinical and pharmaceutical insights, and in relation to the increasing demand of numerous industries, where, owing to its suppleness in design, SPME technology can offer specific solutions to a variety of applications. One of the main advancements made in recent years is associated with improvements in its physical stability for persistent reusability. To this end, Supelco has been working on product development that presents better stability. In this context, GC-amenable Stableflex SPME fibers were introduced as an improvement to fiber endurance by coating a flexible fused silica core with the same extraction phases used in traditional fused silica core fibers. In addition to the flexibility offered by the core material, the extraction phase is also partially bonded to the core, resulting in additional coating and fiber endurance. More recently, Supelco has launched SPME fibers based on different metal alloys that bring the stability of SPME fibers to a superior level. These metal alloy based fibers are constructed with a flexible material that imparts better inertness than stainless steel and can be used in the needle, plunger, and fiber core of the SPME assembly. The thinner metal alloy employed in the needle provides extra flexibility, while the thicker alloy used in the plunger reinforces the needle. Moreover, to assist with the septa piercing of this new thin and flexible needle, the tip is beveled. As can be expected, in this design, more frequent septa coring may occur as a result of the beveled tip and the thin needle wall; therefore, the use of septumless sealing systems is suggested in such cases. Since their debut, the developed fibers have been adopted in a variety of published applications, presenting rewarding results.[155−160] However, development in this field is continuously ongoing. For instance, CTC Analytics has launched the SPME arrow, where a thicker extraction phase is coated on a relatively wider stainless steel rod, while the tip of the fiber is equipped with an arrow tip to easily pierce a standard GC septum. The primary aim of this modification is to increase the volume of the extraction phase, similar to the mechanism utilized by the Stir Bar Sorptive Extraction format reviewed below, for enhanced sensitivity, and to provide extra stability to SPME fibers.[161,162] Helin et al. has reported the use of SPME arrows for determination of volatile amines in wastewater and air samples.[162] This study revealed that the SPME arrow, with its larger

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

extraction phase, can successfully enable the determination of volatile amines present at trace levels without additional, tedious derivatization steps added to the workflow. However, slower desorption was observed compared to regular format SPME as larger GC liners need to be employed to accommodate the SPME arrow resulting in lower linear flow of the carrier gas. Recently, a recessed SPME device was introduced by Poole et al., where a thin layer of sorbent is deposited in a recession in the fiber support with the use of the biocompatible binder PAN.[163] The main benefits of this fiber include its thin extraction phase, which enables fast equilibrium times, as well as the added protection offered by the recession, which protects the extraction phase from possible damage as it penetrates through outer protective tissues (e.g., fish scale) of sample. In addition to protecting the extraction phase during hard-tissue sampling, the developed design also provides a simple approach to sampling of living systems (e.g., fish). This adaptation can be accomplished by integrating the SPME fiber to a custom-made projectile, enabling the shooting of the sampling devices from an air-soft gun at freely moving targets. In addition, as the fiber is retracted within the needle during the penetration of the needle in target tissue, the recession serves to protect the extraction phase from smearing the surrounding tissue during penetration. This is especially critical when a spatial resolution type of analysis is desired.[163] Further developments in fiber SPME technology include ongoing efforts in the miniaturization of SPME fiber devices, aimed at applications involving diminutive samples. Areas of interest for such technology include the development of technology for single cell analysis, where the miniaturized SPME fiber can be used to directly prick the cell wall and monitor elusive chemical information not otherwise easily obtained. To this end, a surface-functionalized miniature SPME fiber was developed with a conical, tip shaped titanium wire consisted of a tip diameter of 2 μm, enabling precise positioning of the fiber in very small objects (e.g., *Daphnia magna* and its egg cells).[164] However, this method requires tedious surface modifications steps and suffers from a burdensome coating thickness tuning process. Recently, polypyrrole (PPy) coated miniaturized fibers were introduced; the developed device is consisted of a fiber tip as small as 5 μm with a coating thickness of 5 μm and is prepared through a coating process based on controlled electrochemical-deposition polymerization of pyrrole to polypyrrole on the fiber support.[29] In this approach toward SPME fiber preparation, the coating thickness can be tuned simply by controlling the time span of the electrochemical-deposition process. This miniaturized device not only enables single cell determinations by SPME; it also facilitates fast extractions owing to the radial diffusion principles governing the mass transfer process when using SPME devices of small dimensions (as discussed in the Fundamentals section). However, it should be kept in mind that this type of coating preparation is limited to electropolymerizable extraction phases, thus excluding the use of well-known polymeric particles with good extraction capabilities. Alternatively, extraction particles of several micrometers to submicrometer in size can be introduced on the fiber tip via the dip coating approach. This method was successfully applied for preparation of miniaturized SPME fibers of 5−7 μm coating thickness and 2 mm coating length. This was achieved by deposition of a single layer of 5 μm HLB particles dispersed in a PAN biocompatible binder on a nitinol fiber support (200 μm in diameter). The applicability of the miniaturized SPME fibers to high throughput, nondepletive *in vitro* investigations, with sample volumes as small as 100 μL, was demonstrated in work carried out by Boyaci et al. (unpublished work). Such miniaturizations of sampling devices allow for time course investigations of the same sample without causing disturbances to the equilibrium of said system; determinations of free and total concentrations of analytes and reliable protein−drug binding determinations as well as attainment of relevant information related to pharmacokinetic and pharmacodynamic investigations. Moreover, as growing scientific and ethical concerns related to the use of animals as surrogates for toxicity tests of drugs and other chemicals have spurred the search for alternative approaches to such investigations, the development of *in vitro* cytotoxicity assays is on the rise. Given that such investigations require the use of small sample volumes due to their limited availability, the employment of miniaturized SPME devices in such investigations can facilitate the time course investigations of metabolomic changes following stimuli, provide pharmacokinetic clearance data regarding a given stimulant, and finally complement other cytotoxicity data. As such, the continued growing adaptation of ultrathin miniaturized SPME devices for a wide variety of applications in the pharmaceutical and cosmetic industries is highly anticipated. While numerous SPME extraction phases are introduced yearly, aspiring to provide solutions for specific problems, at the global level, one of the biggest challenges to the adaptation of SPME methodology can be attributed to a lack of fibers that are fully compatible with both GC and LC platforms. For instance, most GC-amenable coatings exhibit swelling when exposed to common desorption solvents compatible with LC, while most coatings developed for LC-based applications to date are not thermally stable enough for GC applications. Considering the recent emerging developments in metabolomic studies and the potential of adapting SPME toward such investigations, SPME fibers that are compatible both with solvent and thermal desorption are highly desirable. Opportunely, a new SPME fiber that enables both thermal and solvent desorption from the same coating, thus integrating the GC and LC platforms, has been recently introduced.[53] This new fiber is based on a primary extraction phase (HLB) incorporated in a polyfluorinated biocompatible polymer (PTFE AF 2400), which serves as a binder. The polyfluorinated polymer has several unique advantages over other binders; for instance, it possesses sufficient thermal stability for thermal desorption in GC, shows inertness against all known LC solvents, and provides good biocompatibility, making it an excellent binder for SPME. Similarly, the selected extraction material has numerous merits. Commercially available HLB polymeric particles have gained wide popularity in SPE applications as a result of their good coverage of polar and nonpolar compounds, although this material was first introduced as a stationary phase for GC columns. Lately, these particles have been increasingly utilized and recognized as an emerging extraction phase in TF-SPME applications, given their compatibility for both thermal and solvent desorption, as well as their balanced coverage of polar and nonpolar compounds. Another critical element of this coating is its biocompatibility. In contrast to other biocompatibility approaches reported in the literature, where it is necessary that the extraction phase be particularly modified/coated with additional layers of biocompatible polymeric layers such as polyaniline[165] and polynorepinephrine,[166] PTFE AF/HLB fibers present biocompatibility without the requirement of additional preparation steps. Further details are provided in the section corresponding to Coatings.

DOI: 10.1021/acs.analchem.7b04502
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Thin Film SPME (TFME). The thin film geometry of SPME (TFME) was introduced with the primary objective of improving the sensitivity of SPME. This is accomplished by spreading a larger volume of extraction phase in a thin film with a thickness similar to that found on traditional fibers; consequently, the effective surface area of the extraction phase that interacts with the sample is enlarged. In this way, TFME not only provides better analytical sensitivity but also ensures fast extraction kinetics. While the extraction phase of traditional SPME fibers is essentially a thin film deposited on a fiber, in this case, TFME refers only to extraction phases developed on relatively larger surface areas, with larger volumes of extraction phase as compared to that afforded by traditional fiber geometry. In terms of instrumental compatibility, TFME development can be divided in two main categories, namely, thermally- and solvent-stable TFME.

Thermally stable, GC-amenable, thin films are called TFME membranes and are among the first developed thin film devices.[27,167] The preparation of TFME membranes involves polymeric materials similar to extraction phases used in SPME fibers, such as PDMS or DVB particles embedded in PDMS, where in the case of DVB, the primary function of PDMS is gluing and providing support for DVB particles. Preparation of TFME membranes requires employment of extraction phases, binders, and supports that are thermally stable under typical GC injection temperatures. Earlier membrane preparation was carried out by mixing a PDMS base and curing reagent in a 10 to 1 ratio, then spreading the resultant slurry on a smooth surface. Subsequently, the film was thermally cured so as to obtain a rubbery extractive material. Extractive particle-loaded membranes can be prepared with the use of a similar strategy that entails the mixing of extractive particles in the same slurry.[27,168] The polymerization/cross-linking reaction in this method is realized with the Pt catalyst present in the curing reagent. One of the limitations of such membranes, however, entails the sizable bleeding of oligomers from PDMS during the thermal desorption process carried out in the GC injection port. The bleeding is even more pronounced in the case of particle-loaded membranes, due to disruption of the cross-linking on PDMS by embedded particles. On the other hand, these membranes impart several advantages, including, for instance, their physical flexibility, which allows for their easy manipulation during manual extractions, in addition to enabling good contact with sampling surfaces which are not flat or smooth. For instance, the use of DVB-PDMS membranes was successfully demonstrated for sampling of skin volatiles of dietary biomarkers of garlic and spirit intakes.[168] In the same study, PDMS membranes were used for a comparison of direct contact sampling versus HS sampling from skin. HS skin sampling was undertaken by placing membranes on a stainless steel mesh to avoid direct contact with the skin surface. Interestingly, while the attained results revealed no significant differences between the two approaches for extraction of volatile compounds from the skin, semivolatile compounds showed lower intensity in HS sampling, while some heavy compounds were only detected in direct contact sampling. However, a high background signal in direct contact mode was also reported, owing to contamination of the membrane from lipids excreted on the skin surface. The second benefit of these membranes is their versatility in design, as such materials can be easily cut to fit different geometries and size requirements. Small sizes may benefit studies where a small region of sample is targeted (e.g., skin lesion), while larger membranes (e.g., on-site sampling) can be used in studies that require high sensitivity, such as cases where ultratrace levels of analytes are targeted. However, in cases where on-site sampling is to be carried out with large membranes, particularly in environments exposed to high convection conditions, the inherent physical flexibility of these membranes may actually be disadvantageous due to their low rigidity, which might induce high variations in experimental findings. For such applications, membranes with the polymeric compositions described above can be developed on sufficiently stiff supports. An example of such study has been conducted by Kermani et al., where two types of extraction phases, namely, DVB-PDMS and Car-PDMS, were deposited on a glass wool fabric. In the same study, membranes were also cut in a house-like, triangular shape with dimensions of 2 cm × 2 cm as a base and sides of 1 cm in height and successfully applied for determination of nitrosamines in water samples.[169] A comparison of the same-sized PDMS membranes to the substrate-supported membranes demonstrated the necessity of a substrate to keep the flat shape of the extraction phase for sampling under convection conditions.

As previously mentioned, bleeding still remains a significant drawback of such membranes. To this end, efforts have been ongoing to improve the abovementioned bleeding, as well as resistivity under elevated convection conditions. In recent times, carbon mesh supported DVB-PDMS membranes were developed as a "state of art" to address all of the above-mentioned limitations of earlier TFME membranes.[170] In this approach, a high viscosity PDMS (PLOT) was used instead of the PDMS base to immobilize DVB particles. In addition, the Pt-based catalyst was replaced with a peroxide-based catalyst in the cross-linking of the polymer. Membranes fashioned via this approach have been demonstrated to incur lower bleeding, while the thermally stable supporting carbon mesh has been shown to contribute to the extraction of analytes. The main limitation of the new membranes lies in their restricted flexibility, owing to the higher cross-linking in PDMS as compared to earlier membranes. Since the newly developed membranes cannot be folded, the operative size is limited to the diameter of liner of the thermal desorption unit (TDU) of the MPS autosampler (GERSTEL GmbH, & Co., Germany). Following, the carbon mesh supported DVB-PDMS membranes were evaluated in an interlaboratory study for performance versus LLE, an official U.S. EPA method, toward the determination of 23 pesticides selected from different families encompassing a broad range of physicochemical properties.[171] The results obtained for surface water samples revealed similar precision for both methods, although TFME provided better sensitivity and detection limits, down to low ppt levels, thus showcasing the superior capabilities of this technology.

Similar to thermally stable membranes, the rationale for solvent stable TFME (so-called TFME blades) is to improve the sensitivity of SPME for LC-based applications. In its most known format, TFME blades consisted of a stainless steel support coated with an extraction phase.[172] In its pedestal, the stainless steel support is shaped in a comb-like geometry consisted of 12 blades. Eight of theses combs, separated by plastic separators, are joined together to build a brush that contains 96 blades (8 combs with 12 blades in each), in dimensions suitable to fit commercial 96-well plates,[173] a deliberate design choice that aids in its commercialization. Initially, TFME blades were prepared via spray coating, as this method was found to provide the most stable coatings among the various methods tested, a critical parameter for reusability of TFME blades.[173] Using the

DOI: 10.1021/acs.analchem.7b04502
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spray-coating process, these TFME blades are coated with a relatively thick layer of extraction phase (200 μm−1 mm coating thickness), often resulting in exhaustive recoveries when used to extract from the small sample volumes employed in the 96-well format; therefore, such membranes act as an open bed SPME device. In this context, these membranes are unsuitable for applications that require nondepletive extraction, such as protein binding evaluations and free concentration determinations. Moreover, the thickness of their coating also limits their application in workflows that require quick equilibrium times or fast desorption from the blade surface (i.e., direct coupling to mass spectrometry). In order to address these limitations, the dip coating strategy was employed in the development of new ultra thin coated TFME blades, which afford coating thicknesses between 50 and 5 μm. This method is based on dipping the blades in a slurry where small diameter particles (less than or equal to 5 μm) are suspended in PAN glue.[174] This approach not only enables fine-tuning of the coating thickness, it also affords homogeneous surface coating, yielding a stable and reproducible extraction phase. In general, TFME blades are made from a stainless steel support, which endows the blades with higher reusability. Indeed, reusability evaluations have demonstrated good performances even in complex matrixes; however, such devices do not meet the needs of particular studies, such as in clinical and doping analyses, where, aiming at good turnover analysis times and elimination of cross-contamination risks, laboratory regulations have set the use of disposable materials as mandatory. Aiming to address the requirements for single use disposable devices, Reyes-Garcés et al. introduced TFME devices that utilize HLB particles coated on rods and blades made of polybutyleneterephthalate substrate, a thermally stable plastic material, thus providing a low cost product that can be utilized for such purposes.[175] The new blades were used for analysis of selected doping compounds in urine, plasma, and whole blood, with experimental findings demonstrating good performance for the new devices as well as reusability, thus affording the flexibility of using the devised blades either as single use or as reusable devices. TFME has also emerged in thin film coated mesh format, a new configuration that uses the same basis for extraction as any other SPME technology. Essentially, the thin-film coated mesh is introduced as a sampling and sample preparation device, allowing for the coupling of transmission mode direct analysis in real time (DART) and mass spectrometry. In earlier versions, the mesh was prepared via brush painting, which resulted in the uneven distribution of the extractive phase on the surface and random blocking of the holes, which prevented users from taking full advantage of the system.[176] Owing to recent modifications to the mesh coating procedure, later designs have shown the outstanding advantage of this technique,[177,178] for which further details are provided in the section corresponding to Perspective on Future Directions.

As mentioned earlier, TFME blades in the 96 blade format were designed particularly for automation, thus enabling high-throughput analysis. The automation of the workflow is accomplished with the use of the Concept 96 (available from PAS Technology), an autosampler originated explicitly for automation of all sample preparation steps associated with SPME.[172] In accordance with its purpose, the Concept 96 is equipped with four stations to perform the in-line conditioning, extraction, rinsing, and desorption steps. Most importantly, the second and the fourth stations are equipped with heaters, which serve to implement additional steps as required. For instance, the heating option in the second station can be used for sample hydrolysis in cases where the deconjugation of metabolites is required or used to perform extractions under controlled temperatures. Similarly, the fourth station of the autosampler, dedicated to the desorption step, can be heated for solvent evaporation or used to perform derivatization reactions. Such additional steps can be adapted to the sample preparation workflow of the autosampler without any difficulty. As can be predicted, there are many advantages associated with the automation of TFME. First, it decreases the number of experiments during the optimization stage. For example, it allows for the evaluation of different extraction phases and various solvent combinations in a single experiment. Therefore, its automation reduces the decision time for selection of optimum experimental conditions. Second, the automation of the entire sample preparation workflow, particularly for extractions under pre-equilibrium conditions, reduces experimental variations. Finally, taking into account that extraction times associated with SPME can be relatively long when the highest possible sensitivity is required (e.g., doping studies), performing 96 extractions sequentially significantly reduces turnaround times of analyses. Consequently, high-throughput TFME has been utilized in various research areas, such as doping analysis[175,179] and clinical analyses, for instance, where fast turnaround times are particularly desired as well as in environmental,[44,180−183] food,[54] and metabolomic investigations,[55,184] with continued proliferation in many emerging fields where high-throughput, sensitive, and robust sample preparation methods are in high demand. Further examples and details related to applications carried out using the already discussed SPME geometries and configurations will be given in the following sections.

Dispersed Magnetic Nanoparticles as an Emerging Geometry of SPME (d-SPME). As expressed in the section corresponding to Fundamentals, device geometry can play a critical role in the mass transfer kinetics of extraction. In brief, decreases in the size of the extractant device have been shown to result in faster equilibrium times. Bearing in mind that fast turnaround times are essential for numerous types of applications, the achievement of rapid extractions at the sample preparation stage plays a large role in the total turnaround time of a given approach. In the context of SPME, the most practical way to achieve rapid extraction times is to employ the smallest possible spherical extractive particles toward extraction. To this end, the use of nanoparticles in a dispersed mode of extraction is presented as a promising approach. However, this approach is limited by the cumbersome collection of nanoparticles after extraction, a method that often requires the employment of additional steps such as centrifugation and filtration, making such an approach both labor intensive and low throughput. As such, the use of nanoparticles that can be easily and reproducibly separated from the sample is highly appreciated in applications seeking fast quantitative results. In this regard, magnetic particles/nanoparticles (MNPs) have been considered for their potential use in dispersed mode solid phase extraction (d-SPE) applications since the early 1970s and, nowadays, are counted among one of the emerging geometries of SPME and SPE. In this method, extraction of an analyte is achieved by adding a certain amount of extractive magnetic particles to the sample; following extraction, said nanoparticles are then collected via an external magnet. In the next step, extracted analytes are desorbed in a suitable solvent and then quantified with the use of an appropriate analytical instrument. The synthesis and functionalization of MNPs are well studied,

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

as such materials have been extensively used in sample preparation (i.e., SPE and SPME) as well as in biomedical applications such as drug delivery and *in vivo* imaging (e.g., fluorescent and MRI).[185,186] Magnetic nanoparticles are often prepared by coprecipitation, microemulsion, thermal decomposition, and solvothermal methods, among others.[187] Generally, MNPs are made of ferrite oxides such as maghemite (γ Fe_2O_3) and magnetite (Fe_3O_4), and less frequently, from other magnetic metals (e.g., nickel and cobalt), with the predominant use of the ferrites mainly owed to their high magnetic moments, ease of preparation, biocompatibility for *in vivo* studies, and their stability.[185] Predominantly, however, such particles are chosen on the basis of their unique properties; Fe_2O_3 and Fe_3O_4 particles with diameters smaller than 100 nm are superparamagnetic, an imperative feature for homogeneous dispersion of the extractive particles in the absence of an external magnetic field and instantaneous magnetization by application of an external magnet. As such, the use of this approach enables the shortest equilibration time possible by taking full advantage of the available surface area of these particles. Owing to the abovementioned merits, a myriad number of studies have been published to date reporting the preparation and functionalization of MNPs suitable for specific needs. In general, extractive magnetic particles can be prepared and functionalized through the use of one of four main approaches: (a) as pure magnetic nanoparticles, (b) composites of magnetic and other metallic particles, (c) a magnetic core, which later is encapsulated in a shell with selective extraction properties, and (d) magnetic particles synthesized on another core of supporting nanoparticles (e.g., on silicate nanoparticles). Figure 4 illustrates common structures and functionalization of magnetic nanoparticles reported in different studies.

Figure 4. Most frequently used magnetic nanoparticles and their functionalization (MOFs, metal organic frameworks; MIPs, molecularly imprinted polymers; CNTs, carbon nanotubes).

Indeed, numerous extractive magnetic nanoparticles have been developed for different applications, with their application toward d-SPME on the incline. This subsection presents some of the most recent applications of this technology for SPME. For instance, Ghorbani and co-workers reported the synthesis of a magnetic ethylenediamine-functionalized graphene oxide nanocomposite as d-SPME for extraction of naproxen and ibuprofen from cow milk, human urine, river, and well water samples. Extraction was assisted by ultrasound, and extraction parameters were optimized by experimental design. The attained results disclosed an extraction time of 30 s as optimum, showcasing the clear advantage of using dispersed nanoparticles together with ultrasound assistance for extraction.[188] Moreover, differently from most classical SPME extraction phases, MNPs enables extraction of metal ions.[189−191] To this extent, a magnetic MoS_2-Fe_3O_4 nanocomposite was reported in d-SPME, with enrichment of Pb(II) and Cu (II) ions from water, poppy seeds, and chamomile prior to determination via flame atomic absorption spectrophotometry (FAAS).[190] Kazemi et al. reported the preparation and use of magnetic graphene oxide as a sorbent for separation and preconcentration of ultratrace amounts of gold ions in the d-SPME format, with a preconcentration factor of 500, and using FAAS for detection.[191] Once more, the attained results highlighted the fast extraction (less than 5 min) and enhanced sensitivity (LOD of 4 ng L^{-1}) capabilities of the method. In an interesting approach, a chip-based magnetic SPME coupled online with micro high-performance liquid chromatography connected to inductively coupled plasma mass spectrometry (HPLC−ICPMS) was reported in the literature. In this system, magnetic nanoparticles with sulfhydryl moiety were synthesized and self-assembled in microfluidic channels using an external magnetic field. The chip-based system was used for speciation of mercury in HepG2 cells in order to better elucidate the cytotoxicity effect of the mercury species as well as the corresponding protection mechanism of the cells.[192] For this study, an enrichment factor of 10 and close to exhaustive recoveries were reported. As evidenced by this example, in many cases, the use of MNPs may result in exhaustive or close to exhaustive recoveries as well as high enrichment factors of analytes from samples, thus enabling enhanced sensitivity, as well as fast turnaround times that are facilitated by rapid extraction. Undoubtedly, such advantages place this approach as one of the emerging technologies in the field of sample preparation.

Stir Bar Sorptive Extraction (SBSE). Stir Bar Sorptive Extraction (SBSE) is another format of SPME that, similarly to TFME, uses a larger volume of extraction phase to enhance the sensitivity of the extraction. However, conversely from TFME, where a simultaneous improvement in sensitivity and kinetics is expected, SBSE primarily focuses on increasing the sensitivity of extraction by use of a thicker extraction phase; therefore, its equilibration takes longer than a typical TFME.[193] As its name implies, SBSE consists of a magnetic stir bar or stainless steel wire placed in the core of a glass jacket (usually 10−20 mm in length) and an outer layer of extractive phase covering the glass jacket. This configuration allows self-stirring of the sample by the extractive bar in cases where extraction from a given collected sample takes place on a stirring plate. However, the stirring process has been shown to often be abrasive to the extractive phase due to the resulting inevitable friction. As this drawback limits the lifetime of thin coated bars, commercial extraction phases are primarily made with coating thicknesses of 0.5−1.0 mm. As explained above, one of the disadvantages of using such thick extraction phases is the long equilibration times required for equilibrium-based studies or in cases where the best efficiency from a given application is required; accordingly, long extraction times, up to 24 h, have been reported.[194] On the other hand, as shown by eq 3 for percent recoveries of SBSE ($(R(\%))$, where φ is the extractant to sample volume ratio, and K_{es} is the distribution constant of analyte between the extractive phase and the sample, the use of large extraction phases in certain cases may result in exhaustive recoveries, which allows for a simple quantitation approach and facilitates superb sensitivity.[195] Commercially, SBSE has been prepared with the same/similar extractive materials that are available and amenable for thermal desorption as those used for SPME fibers (i.e., PDMS, PA, and EG-silicone). The preparation of extraction phases for SBSE has progressed alongside with advances in material science, allowing for extensions of this methodology in the sample preparation field for a variety of applications. The directions taken toward coating development aim at preparing thin and mechanically stable extractive phases, while

DOI: 10.1021/acs.analchem.7b04502
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other coating developments have focused on improving coating selectivity toward a specific group of analytes. Recent publications specifically focused on extractive phases for SBSE[196,197] and recent applications of SBSE are summarized in several reviews.[198−200] As a commercial product, SBSE is available under the brand name Twister from Gerstel. Twister can be coupled with the large volume thermal desorption unit provided by the same company that further enhances its sensitivity due to the quantitative introduction of all extracted analytes to the gas chromatograph. In this regard, the SPME arrow, denoted earlier in this section, where a thicker extraction phase is coated on a relatively wider stainless steel rod with aims of increasing the volume of the extraction phase for enhanced sensitivity as well as provide extra stability to SPME fibers, can be said to essentially be the fully automated version of thick film approaches. Although the Twister SBSE is not fully automated, one of the main advantages of this approach lies in the fact that the stir bar configuration provides an opportunity for more than one Twister to be exposed to the same sample at a time. In this sense, one of the Twisters can be placed in the HS of the sample to extract volatile analytes, while the second stir bar is directly immersed in the sample, facilitating the agitation of the sample for fast mass transfer kinetics from the sample to the HS, while extracting nonvolatiles and semivolatiles from the sample via DI. Alternatively, two stir bars with two different chemistries can be placed in the same sample, where one of them is used in agitation mode, while the second one is suspended in the sample by aid of a magnetic clip embracing the sample vial from the outside. Both of these strategies aim to cover a wide range of analytes in a given sample, while enhancing the lifetime of the less robust EG-Silicone Twister by keeping it suspended in the sample rather than stirring at the bottom of the vial.[201] Such approaches are very useful in multiresidue and untargeted metabolomics studies as well as in flavor, fragrance, and odor analyses. For instance, this approach, through the employment of multi stir bars, was successfully demonstrated for determination of free acids and phenols. In this study, four sample preparation approaches using Twisters were tested: (A) one PDMS SBSE was placed in a 20 mL vial containing 10 mL of sample and then stirred for 2 h at a rate of 900 rpm; (B) one PDMS SBSE was placed in the sample, while one PDMS SBSE was placed in the HS of the sample, with the same experimental conditions described in part A; (C) sequential extractions were performed, first by placing one PDMS SBSE for 1 h, followed by salt addition (20%) to the sample, then another PDMS SBSE was introduced for 1 h; and (D) one PDMS SBSE was introduced to the sample and one EG-Silicon SBSE was submerged in the sample. The results of this comparative study revealed that employment of the two Twisters, PDMS and EG-Silicone, significantly improved the sensitivity of analysis for polar compounds in comparison with the other approaches. Such findings substantiate the multi SBSE method as a valuable strategy for the determination of a difficult-to-detect class of compounds. Another interesting approach for SBSE includes its adoption in a direct analysis approach. Birdoux et al. reported the use of PDMS Twister for extraction of phosphoric acid alkyl esters from water samples.[202] After extraction, the SBSE was inserted in an open-ended glass tube, which was then placed between a direct analysis in real time (DART) source and an Orbitrap mass spectrometer. Good linearly for the method, in a range of 0.1−750 ng mL^{-1} in water samples using deuterated internal standards for correction, were reported. The method demonstrates the possible application of the SBSE for on-site applications, where only the extractive tool is transferred to the laboratory, thus avoiding the transfer of large volumes of sample. Another critical development area of SBSE technology is to improve the kinetics of extraction. As previously mentioned, the employment of thick coatings for extraction results in long extraction times, which are not desired in many cases. On the other hand, the use of thin coatings under the conditions applied in SBSE may result in damage to said coatings. Therefore, significant effort has been devoted to improving extraction phase stability on the stirring bar. For instance, Zhang et al. proposed a jacket-free configuration of SBSE, where a thin extraction phase is deposited directly on a stainless steel wire. The main challenge faced by researchers in this endeavor revolved around the difficulties related to chemical immobilization of the extractive phase on the relatively inert stainless steel surface.[203] To prepare a stable coating, the researchers first modified the wire surface with a stable layer of polydopamine via an *in situ* polymerization reaction. Then, a highly stable surface cross-linked layer of poly(EGDMA-AA) was synthesized on the bar, with a coating thickness of 4 μm. Good stability for the coating was reported toward mechanical (i.e., stirring, ultrasonication) and chemical conditions (i.e., organic solvents, strong acids, and bases), with 50 cycles of reusability. In addition to the added stability of the SBSE device, low detection limits (0.06−0.15 ng mL^{-1}) were reported in quantitative analysis of protoberberines in herb and plasma samples. Another interesting approach, developed to overcome the long extraction times associated with SBSE methods, is the use of magnetic nanoparticles (MNPs) with stir bar, without their permanent immobilization to its surface.[204] The MNPs consisted of oleic acid-coated cobalt ferrite ($CoFe_2O_4$@oleic acid) and used for extraction of UV filters in seawater samples prior to their HPLC-UV determination. In the absence of stirring, the MNPs were attracted on the surface of the magnetic bar, while under slow agitation conditions, since the rotational forces were not stronger than the magnetic forces, the MNPs remained on the surface of the stirring bar, enabling the SBSE mode for extraction. However, once agitation conditions were elevated, the MNPs overcame the magnetic forces and extraction followed d-SPE mode. Undeniably, this approach enabled the use of significantly shorter extraction times, with no statistically significant differences observed between extracted amounts at 5, 10, and 20 min, while at the same time providing good figures of merits, such as detection limits in the low ppb levels and high enrichment factors (11−148), thus demonstrating the advantage of using d-MNP. Another approach for improving the long extraction times associated with SBSE involves the use of monolithic extraction phase coated stir bars. Monoliths provide high permeability and large surface area, as well as allow fine-tuning of the extraction phase chemistry based on the analytes of interest. Therefore, it offers high extraction efficiency and relatively shorter extraction times compared to the commercial SBSE. For instance, Gilart et al. reported a new polar monolith of poly(poly(ethylene glycol) methacrylate-*co*-pentaerythritol triacrylate) (poly(PEGMA-co-PETRA)) as SBSE material for extraction of pharmaceuticals and personal care products in water samples prior to LC-MS/MS[205] The monolith was prepared by directly immersing a wire in the center of a prepolymerization solution. The resulting monolith was 1 mm in thickness and cut to 12 mm of length, with each monolithic SBSE phase reported to be useable for at least 20 extraction cycles. Certainly, in comparison to the reusability of the commercial SBSE phases, which enable 200

DOI: 10.1021/acs.analchem.7b04502
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Table 2. Representative Applications of SPME in Different Fields of Study and Their Diverse Experimental Configurations

area of study	application	SPME mode and coating	extraction and desorption conditions	instrumentation	year and reference
food analysis	characterization of human breast milk lipidome	DI, C18/PAN fibers	5 min extraction, 5 min desorption in 2-propanol	LC-MS	2017[211]
	screening of apples (Malus × domestica Borkh.) metabolome changes due to fruit maturity	DI, DVB/Car/PDMS and PDMS overcoated-DVB/Car/PDMS fibers	60 min extraction, 25 min desorption at 270 °C	GC × GC-MS	2016[156]
	characterization of edible oils components	DI, PDMS/DVB	45 min extraction, 5 min desorption	GC-MS	2017[212]
	determination of the volatile metabolites of saprotroph fungi	HS, DVB/Car/PDMS	35 min extraction	GC × GC-MS	2015[213]
	multiresidue pesticides analysis in grapes	DI, PDMS/DVB/PDMS	30 min extraction, 10 min desorption at 260 °C	GC-MS	2015[214]
	development of an extraction method for analysis of avocado samples	DI, PDMS/DVB/PDMS	40 min, 5 min desorption at 270 °C	GC-MS	2017[215]
	determination of cannabinoids in human breast milk	HS, PDMS 100 μm	40 min extraction	GC-MS	2017[216]
	determination of ochratoxin A in wine	DI, C18 packed in tube SPME	loading 6 min at 0.2 mL min^{-1}; desorption in water/ACN/acetic acid (45.5:45.5:1, v/v/v)	LC-MS/MS	2017[217]
	SPME interlaboratory validation of pesticides from surface waters, versus LLE	DI, DVB/PDMS SPME fibers	30 min extractions at 30 °C from 15.5 mL of sample agitated at 500 rpm, pH of 3.0, 4 g NaCl added, desorption at 270 °C for 10 min	GC-MS	2016[218]
	TF-SPME interlaboratory validation of pesticides from surface waters, versus LLE	DI, DVB/PDMS TF-SPME membranes	30 min extractions at 30 °C from 30 mL of sample agitated at 900 rpm, pH of 2.5, 10% NaCl. TDU desorption at 250 °C for 5 min using 60 mL min $^{-1}$ He with cryofocusing at −80 °C	TDU/GC-MS	2017[171]
environmental analysis	on-site extraction of benzene and naphthalene from city air	spot air sampling averaged to TWA using DVB/PDMS TF-SPME membranes	1 h equilibrium extractions at measured ambient temperatures with air flow of 3.6 m s^{-1} desorption at 250 °C for 5 min using 60 mL min $^{-1}$ He with cryofocusing at −120 °C	TDU/GC-MS	2014[219]
	on-site derivatization and determination of free vs aerosol bound formaldehyde from car exhaust	in situ DVB/PDMS SPME fiber and in situ Tenax/Car 1000/Car 1001 NTD	In-excess preloading of PFPH DA, both cold (16.3 °C) and hot (45.7 °C) exhaust measured in situ for 60 and 30 s by SPME respectively and 10 mL extraction by NTD. Desorptions at 280 °C for 1 min	portable GC-MS	2016[220]
	extraction of PAHs from certified soil samples	pressure-balanced HS, PDMS CF-SPME	7 mL of air removed from 10 mL vial containing 1 g sand to balance pressure at 200 °C extraction, Fiber cooled to 30 °C for 30 min extraction. Desorption at 250 °C	GC-FID, GC/MS	2016[221]
	TWA determination of biocides and UV-blocking agents from river water	TWA DI, spot sampling DI. C18/PAN and HLB/PAN TFME blades	TWA extractions performed for 90 days in copper retracted devices. Desorption in 1.8 mL of MeOH/ACN/IPA 50/25/25, v/v/v for 30 min using 1500 rpm vortex agitation.	LC-MS/MS	2017[44]
	rapid screening of select pharmaceuticals from treated wastewater samples	DI, HLB/PAN blade spray device	DI extraction performed for 10 min from 9 mL of sample at 1200 rpm orbital agitation. Quick rinse in DI water. Desorption in 15 μL 5:95 H_2O/MeOH with 12 mMol AA + 0.1% FA. Sprayed at +4 kV	direct-to-MS/MS	2017[222]
	on-site identification of unknown contaminants from a construction-impacted lake	DI, DVB/PDMS TF-SPME membranes	10 min on-site extractions at 16.5 °C (ambient) using 350 rpm drill agitation. TFME HVD-to-NTD desorption at 250 °C for 5 min using 30 mL min $^{-1}$ He, NTD desorption at 280 °C for 1 min	portable HVD-NTD/GC-MS	2016[170]
bioanalysis (biological fluids, animal tissue and cell studies)	analysis of several doping compounds in urine, plasma, and whole blood	DI, HLB-PAN TFME (on plastic support)	90 min extraction and 20 min desorption in 4:1 methanol/acetonitrile	LC-MS/MS	2015[175]
	analysis of VOCs in urine samples as a means to monitor levels of exposure in children living at different environmental conditions	HS, Car/PDMS	15 min extraction (at 30 °C) and 0.2 min desorption at 240 °C (additional 5 min of desorption to avoid carryover)	GC-MS	2016[223]
	analysis of repaglinide and two of its main metabolites in human liver microsome media	DI, C18-PAN TFME	60 min extraction and 90 min desorption in 1:1 acetonitrile/water	LC-MS/MS	2015[224]

DOI: 10.1021/acs.analchem.7b04502
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Table 2. continued

area of study	application	SPME mode and coating	extraction and desorption conditions	instrumentation	year and reference
	profiling of *E. coli* metabolome in response to natural antibacterial agents (cynnamaldehyde, eugenol, and clove oil)	HS, DVB/Car/PDMS fibers and DI, HLB/PS-DVB-PAN TFME	HS: 30 min extraction (at 37 °C) and desorption at 270 °C DI: 120 min extraction and desorption in 1:1 acetonitrile/water	LC-MS/MS and GC × GC-MS	2016[55,225]
	analysis of the volatilome in breast cancer cell lines and normal human mammary epithelial cells (cells and culture media)	HS, DVB/Car/PDMS fibers	45 min extraction (at 37 °C) and desorption at 250 °C	GC-MS	2017[226]
	analysis of the volatilome of urine samples collected from patients with mesangial proliferative glomerulonephritis, IgA nephropathy and normal controls	HS, Car/PDMS fibers	20 min (at 40 °C) and desorption at 200 °C	GC-MS	2015[227]
	analysis of the cellular lipidome in human hepatocellular carcinoma cell lines (comparison of SPME and Bligh & Dyer method)	DI, C18-PAN TFME	90 min extraction and 60 min desorption in 1:1 methanol/isopropyl alcohol	LC-MS	2017[228]
	profiling of *cis*-diol containing nucleosides and ribosylated metabolites in urine samples collected from cancer and healthy controls	in-tube SPME using boronate-affinity organic-silica hybrid capillary monolithic column	loading flow rate, 5 μL/min; washing volume, 35 μL; desorption volume, 25 μL	LC-MS/MS	2015[229]

extractions, the prepared device has significantly small reusability. On the other hand, such a fine-tuned coating provided better balanced coverage for both polar and nonpolar analytes as compared to the commercial SBSE. With aims of enhancing the lifetime of SBSE, Mao et al. suggested protecting the SBSE device within a membrane. For this purpose, coated C18 particles were first coated on a bare bar by the aid of PDMS glue. Following, the prepared C18 functionalized bar was protected in a PTFE membrane saturated with methanol.[206] The prepared membrane was shown to impart several benefits. First, it decreases friction on the extractive phase, thus facilitating its mechanical stability. Second, it provides a protective layer toward matrix components (i.e., macromolecules) in complex samples. Finally, the mass transfer of analytes is improved as the pores of the membrane are impregnated with methanol, facilitating the fast transfer of analytes from the sample to the coating on the stir bar. Indeed, the researchers reported improved reusability for the membrane-protected SBSE (50 times) as compared to the corresponding unprotected SBSE (20 times) for extraction of ketoprofen and naproxen, nonsteroidal anti-inflammatory drugs, in wastewater samples, showing an alternative and easy way to enhance the lifetime of homemade SBSE devices.

APPLICATIONS

The use of SPME as sample preparation tool for a broad range of studies has been vastly documented in recent years. A summary of the most significant developments and relevant workflows involving the use of SPME for food, environmental, and bioanalytical studies is presented in this section. Table 2 summarizes representative applications of multiple SPME formats and configurations in the aforementioned fields of study.

Food Analysis. Food analysis covers a broad range of purposes that involve both targeted and untargeted screening of endogenous and/or exogenous compounds. Because of the complexity and diversity of food matrixes, the development of sample preparation methods intended for food samples must consider their heterogeneous nature (e.g., vegetable and fruit commodities, oils, spices, etc.) and the individual challenges associated with a particular matrix of interest. SPME has been used for food applications ever since the very beginning of its introduction in 1989, and each year, the number of published research articles on the topic shows an increasing trend. SPME is frequently used in the field of food analysis for a variety of purposes, including aroma profiling, food safety assessments (determination of contaminants), chemical fingerprinting, metabolomics investigations, and determination of nutraceutical values, among various other applications.[5,11,207,208] In addition, many studies have been carried out by SPME on materials intended for food packaging. Given the complexity and diversity of matrixes in the area of food commodities,[209] the versatility afforded by SPME in terms of geometries, extraction phases, and automation make the technique amenable to the various challenges related to the efficient isolation of target analytes and their sequential introduction to a given analytical instrument. Historically, SPME use in food-related investigations has been confined to HS approaches due to the scarcity of robust extraction phases compatible with complex food matrixes.[11,210] HS-SPME can provide optimized and fully quantitative methods for analysis of various food matrixes that involve greener and faster protocols with minimized use of organic solvents. The use of HS-SPME approaches is suitable for analysis of volatile species and helps to preserve SPME coating integrity when very complex matrixes are analyzed as well as avoid the occurrence of artifacts associated with the attachment of macromolecules to the coating surface, which can cause coating deterioration and instrumental contamination.[11] However, this sampling mode presents significant limitations for targeted analytes with medium to low vapor pressure values, particularly in terms of achievable limits of quantitation (LOQ), due to their scarce partition into the HS of the sample. Moreover, in cases where

DOI: 10.1021/acs.analchem.7b04502
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untargeted analysis is desired, the HS sampling mode is not able to guarantee balanced coverage of analytes, as analytes with poor solubility in the matrix and good volatility readily enrich the HS of the sample, whereas compounds with good solubility and poor volatility will offer high resistance toward partitioning into the HS.[158,230] Therefore, especially under pre-equilibrium conditions, the HS extraction of complex matrixes is not always representative of the whole chemical composition of the system. In such cases, more comprehensive analyte coverage can be attained by DI mode, since the diffusion coefficients of the analytes in a certain matrix, which define the mass transfer properties of the extraction mode, are similar for all small molecules present in the system. In addition, selection of methodology should take into consideration that the fiber coating is more prone to saturation in HS mode, with consequent competitive adsorption, than when employed in DI mode, especially when complex systems are analyzed by SPME devices with solid porous coatings.[230] In fact, various reports have documented the occurrence of competitive adsorption for HS *ex vivo* analysis of different food matrixes,[158,231,232] although the competitive adsorption phenomenon can be generally avoided by properly selecting extraction mode, extraction time, extraction phase, and other sample treatment parameters.[158,230] The advantages of DI-SPME extractions, especially for complex matrixes, catalyzed the research on new SPME coatings with antifouling properties, which are able to overcome the limitations imposed by conventional SPME coatings in terms of robustness and coating deterioration due to exposure to complex media.

Analysis of Fruits, Vegetables, Juices, and Beverages. The food commodities included in this section are certainly the most analyzed by SPME for food safety assessment. Among the various types of contaminants often determined in food commodities, agrochemicals represent one of the top-priority classes to be monitored due to their extensive use in agricultural practices and the acute and chronic human health effects related to their toxicity. Classically, HS-SPME approaches have been used for both screening and quantitation of various classes of agrochemicals, such as organochlorine pesticides (OCP), organophosphorous pesticides (OPP), carbamate pesticides (CP), phenyl urea pesticides (PUP), and pyrethroid pesticides (PP) from fruit and vegetables through the use of both commercially available and lab-manufactured SPME coatings.[208] Usually, HS-SPME methods involve extra sample pretreatment steps that improve the partition of the targeted analytes into the sample HS. As an example, Abdulra'uf et al. ultrasonicated samples of apple, tomato, cucumber, and cabbage for 5 min prior to HS-SPME extraction of 14 pesticides,[233] while Sang et al. prepared turnip, green cabbage, french beans, eggplant, apple, nectarine, and grapes samples for HS-SPME extraction of 11 OPPs by addition of 100 μL of methanol/acetone (1:1 v/v) as a matrix modifier and 10% (w/v) aqueous NaCl solution to make up a total sample weight of 5.0 g, followed by agitation of each sample for 1 min prior to incubation and extraction.[234] In cases where DI-SPME was used with coatings not compatible with complex food matrixes, additional sample pretreatment steps such as centrifugation and supernatant collection, dilution, or filtration were also necessary in order to obtain clean extracts and preserve coating integrity.[235−239] Among the commercial SPME coatings classically used for DI-SPME in complex matrixes, the most used and suitable to withstand direct exposure in complex food media are PDMS coatings.[5] Several studies have shown that PDMS SPME coatings, in comparison to other commercially available coatings, are more inert toward irreversible fouling caused by food matrix components due to their nonporous, smooth surface, which helps avoid irreversible attachment of nonvolatile macromolecules.[160,240−243] On the other hand, other commercially available coatings were shown to suffer precocious deterioration after direct exposure to such matrixes due to the rough and porous surface imposed by sorptive particles. However, such particles provide substantially higher extraction capacities than pure PDMS.[51,215,243−245] Aiming to merge the antifouling properties of PDMS with the higher extraction efficiency of sorptive particles often used for SPME, e.g., DVB, a new matrix compatible coating, PDMS/DVB/PDMS, was developed as described in the section corresponding to Biocompatible SPME Coatings. This new coating, introduced in 2012,[243] was shown to demonstrate similar extraction performances for the extraction of triazole pesticides from water as compared to that of the conventional PDMS/DVB fiber. However, the main innovation related to its use was its ability to endure 130 extraction/desorption cycles while sampling whole untreated grape pulp before a 20% deviation in the extracted amount of triazole pesticides could be observed. Under the same extraction conditions, the PDMS/DVB coating lost up to 89% of its extraction capability after a mere 20 consecutive DI-SPME extractions in grape pulp.[243] With the robustness of new coating assessed, a quantitative method for the determination of triazole pesticides in grape and strawberry pulp was developed.[246] The performance of the method was compared to a modified version of a QuEChERS AOAC method, where the cleanup step was performed using PSA (primary-secondary amine) in view of the low lipid content of the targeted fruits. The DI-SPME method not only achieved LOQ values at least 1 order of magnitude lower than the QuEChERS method, it also reduced interferences, translating into relatively cleaner chromatograms with fewer extraneous peaks.[246] Moreover, the authors implemented a quick predesorption rinsing step and a postdesorption washing step in deionized water for each extraction cycle. This additional step was performed in order to provide further cleaning of the coating surface and to enhance its lifetime.[246] Subsequently, a method for the determination of 40 pesticides, belonging to 21 different classes, was optimized for extractions from grape pulp by means of Experimental Design (DoE), using the matrix compatible PDMS/DVB/PDMS coating.[214] Considering the large amount of targeted analytes and their diverse chemical moieties, the predesorption rinsing conditions were reassessed to avoid losses of analytes in the rinsing solution. To this extent, addition of a 10 s rinsing step in deionized water was shown to not incur any statistically significant losses of analytes as compared to procedures where rinsing was not included in the SPME routine.[214] Further developments regarding the PDMS/DVB/PDMS coating involved selection of the most suitable PDMS polymer for overcoating purposes, with the optimized devices tested in grape juice for extraction of a selection of 11 contaminates with wide range of polarities and diverse chemical moieties.[51] In the case of the grape juice matrix, the washing step was modified to guarantee optimum coating cleaning, with a mixture consisted of 1:1 (v/v) water/methanol used to wash the coating for 5 min after desorption.[51] The same group of 11 contaminates was also used to evaluate the performance of PDMS/DVB/PDMS coatings in blended raw vegetables (tomatoes, spinach, carrots) using the rinsing/washing approach developed for grape juice.[247] The use of PDMS/DVB/PDMS also enabled the quantitative extraction of pesticides from pureed prune baby food, while providing a

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

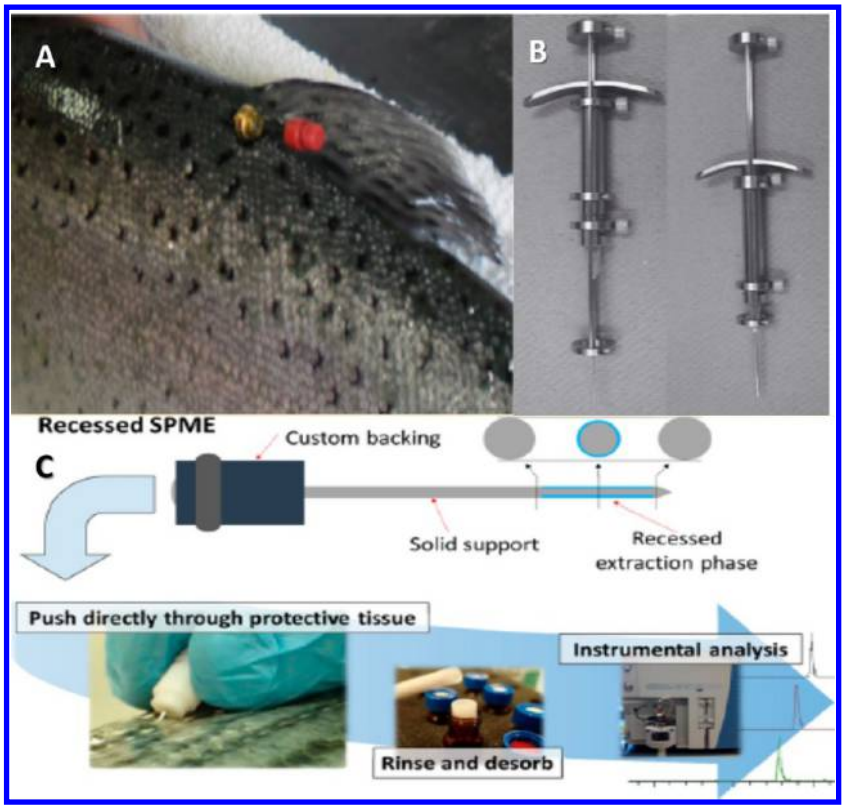

Figure 5. (A) *In vivo* sampling performed in rainbow trout,[160] [Reproduced from Bai, Z.; Pilote, A.; Sarker, P. K.; Vandenberg, G.; Pawliszyn, J. *Anal. Chem.* **2013**, *85* (4), 2328−2332 (ref 160). Copyright (2013) American Chemical Society]. (B) *In vivo* SPME sampler,[267] [Reproduced from Development and evaluation of a new in vivo solid phase microextraction sampler, Togunde, O. P.; Lord, H.; Oakes, K. D.; Servos, M. R.; Pawliszyn, J. *J. Sep. Sci.* **2013**, *36* (1), 219−223 (ref 267). Copyright (2012) Wiley]. (C) Recessed SPME device,[163] [Reproduced from Poole, J. J.; Grandy, J. J.; Yu, M.; Boyaci, E.; Gómez-Ríos, G. A.; Reyes-Garcés, N.; Bojko, B.; Heide, H. V.; Pawliszyn, J. *Anal. Chem.* **2017**, *89* (15), 8021−8026 (ref 163). Copyright (2017) American Chemical Society].

lower chromatographic background as compared to that of the PDMS/DVB coating.[248] Owing to its superior demonstrated performance, the PDMS/DVB/PDMS coating was adopted in the development of a DI-SPME method for quantitative determination of pesticide residues from spaghetti sauce.[245] The SPME method was validated and its performance compared to that of the AOAC Official Method 2007.01 based on QuEChERS. In this comparative study, the DI-SPME method was shown to yield better sensitivity and accuracy, circumvent the use of organic solvents, and provide lower chromatographic background due to the improved selectivity enabled by the antifouling properties of the SPME coating.[245]

Other sources of food contamination can derive from toxic or undesirable compounds formed during various food processing steps, such as during heating, baking, roasting, grilling, canning, hydrolysis, or fermentation. In this regard, SPME was also successfully applied toward the identification and quantification of various food processing contaminants from various matrixes. Cagliero et al. employed matrix-compatible polymeric ionic liquid (PIL)-based SPME coatings for trace-level extractions of acrylamide in brewed coffee and coffee powder by DI-SPME-GC-MS.[86,148] Various PIL-based coatings, designed and screened for extraction of acrylamide, exhibited higher sensitivity toward the targeted analytes compared to the commercially available SPME sorbent coatings. Furthermore, the hydroxyl moiety appended to the IL cation was observed to significantly increase the sensitivity of the PIL coating toward acrylamide. The quantitation of acrylamide in brewed coffee and coffee powder was performed with good analytical precision, linearity, and interfiber reproducibility.[86,148] Furan was also determined by HS-SPME-GC-MS with the use of a 75 μm Car/PDMS fiber in 76 commercial baby food samples of different composition, including fruit and vegetable purees, for estimation of daily intake and risk assessment.[249] Moreover, following the recommendation of the European Food Safety Authority (EFSA), variations in furan content were evaluated after home preparation of foods, particularly targeting heating and handling practices by consumers.[249] Several cases of "salicylate sensitivity", stemming from the intake of food rich in salicylate derivatives, have promoted the development of methods for assessment of these compounds in food. To that end, Aresta et al. developed an SPME-LC-UV/DAD method for the simultaneous determination of salicylic, 3-methyl salicylic, 4-methyl salicylic, acetylsalicylic, and benzoic acids in fruit and vegetables, including kiwi, beans, blueberries, tangerine, lemons, oranges, and derived beverages.[238] While the coating chosen was a PDMS/DVB 65 μm, which is typically used for gas-chromatographic applications, in this work, the authors desorbed analytes from the SPME device by soaking the fiber into the mobile phase (acetonitrile/phosphate buffer (pH 2.8;2 mM) mixture (70:30, v/v)) for 5 min in a special fiber desorption chamber (total volume, 60 μL) installed in place of the sample loop.[238] However, in view of the poor matrix compatibility of the PDMS/DVB coating, the method adopted several sample pretreatment steps, which were carried out before DI-SPME.[238]

Toxins represent a distinguished class of toxic chemicals, whose production exclusively derives from plants, animals, and microorganisms. As toxins are another source of food

DOI: 10.1021/acs.analchem.7b04502
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contamination, it is important to develop selective methods for their determinations for screening purposes. As an example, a method for the determination of Ochratoxin A (OTA) in wine was developed by use of packed in-tube SPME followed by HPLC-MS/MS. The in-tube SPME device consisted of a PEEK tube packed with C18 particles (10 μm, pore size 100 Å), and red and white wine samples were filtered in a cellulose ester membrane filter (porosity 0.22 μm) prior to analysis. The analysis workflow included various sequential steps: cleaning, conditioning, and extraction/separation. The desorption process was carried out by passing the mobile phase through the in-tube SPME device, then transferring the solution to the analytical column where separation took place, followed by MS/MS detection. Matrix-matched calibration was used, and good linearity was obtained, with limits of detection (LOD) and quantification (LOQ) of 0.02 μg L^{-1} and 0.05 μg L^{-1}, respectively.[217]

Analysis of Fatty Food Matrixes. The threshold for differentiation between "fatty" and "non-fatty" food matrices is set at ~5% fat content. High fat content foods are among the most complex and challenging matrixes to handle as the extraction of contaminants is susceptible to lipid coextractives, which are often hard to avoid and may constitute a serious source of contamination for separation and detection systems.[250] In this regard, SPME was applied in several recent investigations involving edible oils and their consumption effects. HS-SPME-GC-MS and ^{1}H NMR were used for a simultaneous and global investigation of a broad variety of oxidative markers during *in vitro* digestion of edible oils rich in omega-3 and omega-6 lipids, using flax seed[251] and sunflower oil, respectively, as model matrixes.[252] Utilizing a DVB/Car/PDMS fiber, HS-SPME sampling was carried out from nonoxidized and slightly oxidized oil samples, their corresponding digests, and the juices submitted to digestion conditions in the absence of food as well as from mixtures made of starting oil samples and juices submitted to digestion conditions, mixed in the same proportions as in the digests. Through this work, the authors were able to confirm the occurrence of an epoxidation reaction in flax seed oil[251] and lipid oxidation in sunflower oil.[252] In a similar approach, the degradation of omega-3 and omega-6 lipids and, for the first time, of vitamin A, was studied in cod liver oil during *in vitro* gastrointestinal digestion, with the antioxidant effect of a synthetic antioxidant, 2,6-ditert-butyl-hydroxytoluene, also evaluated. The attained findings suggest that intake of antioxidants with cod liver oil should be considered in order to increase polyunsaturated lipid and vitamin A bioaccessibility and to avoid the formation of toxic oxidation compounds such as oxygenated α,β-unsaturated aldehydes.[253] As it pertains to the extraction of contaminants from fatty matrixes, few SPME approaches are present in the literature due to the intrinsic challenges related to SPME extraction from such matrixes. To enable the extraction of PAHs from olive oil, Purcaro et al. developed a strategy involving an initial liquid−liquid extraction from olive oil with acetonitrile, where the supernatant was collected and then re-extracted with hexane.[254] A Carbopack Z/PDMS 15 μm fiber was then directly immersed in the hexane extract for 30 min to allow for extraction. Prior to injection into a GC-MS system, the coating was further rinsed for 1 min in hexane. The developed method enabled the attainment of LOQ values below the performance criteria required for PAHs under the European Regulation 836/2011. Although PDMS-based coatings are generally known to exhibit swelling as a result to exposure to hexane, in this work, the authors were able to use a single Carbopack Z/PDMS fiber for more than 500 extractions.[254]

Another recent application of SPME to fatty matrixes involved the development of a strategy that enabled the direct immersion of a matrix-compatible PDMS/DVB/PDMS coating into avocado puree for extraction of contaminants belonging to different chemical classes.[215] The avocado puree was diluted to 1:1 (w:w) with water so as to reduce sample viscosity, thus allowing application of DI-SPME under agitation conditions without incurring fiber core breakage. Predesorption rinsing and postdesorption washing solutions previously applied to other vegetable matrixes with low lipid content[51,246] did not provide sufficient cleaning, resulting in poor reproducibility and instrumental contamination. In response, these parameters were further optimized for solvent type, rinsing/washing time, and degree of agitation employed. Optimum performances were obtained by rinsing the coating after extraction for 5 s in acetone/water (9:1, v/v) at 425 rpm. Desorption took place in the GC injection port for 5 min at 270 °C in splitless mode, followed by 30 s of postdesorption washing in acetone at 425 rpm. Through the use of this approach, the matrix compatible coating showed good performance for more than 100 consecutive extraction cycles.[215]

Analysis of Products of Animal Origin. Most of the research carried out by SPME on products of animal origin for human consumption regards the monitoring of VOC composition and its perturbation due to various factors, such as origin, type, storage, cooking, and/or processing practices. As discussed in the following sections, various studies have also been performed for detection and quantitation of contaminants, such as veterinary drugs (especially in meats products and derivatives), contaminants from food packaging, food processing contaminants, and pesticides in products of animal origin (e.g., honey).

Meat Analysis. In regards to meat, the determination of meat spoilage markers plays a vital role in industry and food safety applications, as such markers offer a quality control tool for the monitoring of products on the market and can provide vital information regarding the efficiency of different storage strategies.[220,255,256] In this context, Argyri et al. explored the use of HS-SPME as a tool for rapid assessment of minced beef spoilage under different packaging and storage conditions.[255] In this work, a DVB/Car/PDMS 50/30 μm SPME fiber was used to capture dynamic biochemical changes occurring during various meat storage conditions, providing information on the microbiological quality of the assessed meat in relatively shorter times than that needed for typical microbiological analysis applications.[255] In some cases, analysis of meat spoilage biomarkers requires derivatization procedures prior to injection into the analytical system. Poole at al. proposed a convenient and green approach using a PFPH (pentafluorophenyl hydrazine)-generating vial for fast and efficient on-fiber derivatization of short chain aldehydes, as markers for meat spoilage, using PDMS/DVB 65 μm and PDMS 100 μm fibers.[220] In relation to contamination assessments, an HS-SPME-GC-MS method was proposed for analysis of clenbuterol in meat samples. The authors optimized an HS-SPME on-fiber derivatization strategy using bis(trimethylsilyl)trifluoroacetamide (BSTFA) as derivatization reagents loaded on a PA SPME fiber.[257] More recently, Ye at al. developed a rapid DI-SPME protocol for extraction of clenbuterol from pork by employing a low-cost, homemade PDMS SPME fiber, followed by derivatization with hexamethyldisilazane. The procedure was performed by suspending the fiber in the HS of a vial saturated with the derivatization reagent.[240] As previously mentioned, the contamination of meat samples can also derive

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

from food packaging materials. In this regard, a multiple HS SPME approach was adapted in a migration study to quantitatively assess contaminants from self-stick labels in fresh sausage samples.[258] In similar work, cold fiber (CF)-SPME was used to assess the presence of phthalates in roasted meat stored in plastic bags.[259]

In view of the increased release of pharmaceutical and contaminants in municipal wastewater effluents, which affects fish via the bioconcentration and biomagnification of these chemicals in fish flesh and consistent market demand for high-quality products of suitable taste, the analysis of fish has gained substantial, increased attention in regards to quality evaluations over recent years, particularly pertaining to the determinations of off-flavours and contamination monitoring. Owing to its miniaturized format, as well as the variety of calibration techniques suitable for *in vivo* sampling, SPME has been positioned as a convenient and viable strategy for analysis of fish, with the aforementioned increased demand spurring the development of various applications in recent years. Bai et al. developed an *in vivo* SPME method for determination of geosmin and 2-methylisoborneol (2-MIB) produced by cyanobacteria and actinomycetes, which are major sources for the "earthy" and "muddy" flavors in fish.[160] The authors were able to quantitatively asses the amount of geosmin and 2-MIB in live fish using a PDMS 100 μm fiber. Moreover, two kinetic calibration approaches, namely, on-fiber standardization and measurement using a predetermined sampling rate, were both validated by traditional methods.[160] Togunde et al. proposed a nonlethal approach for the determination of pharmaceuticals in Rainbow trout (*Oncorhynchus mykiss*) and Fathead minnow (*Pimephales promelas*) following short-term wastewater exposure.[260] C18/PAN fibers and thin films were used for sampling, followed by desorption in methanol/water (3:2) for 90 min; liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) was then employed to determine pharmaceutical bioconcentrations.[260] *In vivo* and *ex vivo* SPME methods were also developed for determination of anesthetics,[261] tetrodotoxin,[262] histamine, and tyramine,[263] trihalomethanes,[264] personal care products,[265] and biogenic and aliphatic amines[119,121,266] in fish. In view of the relevance of fish tissue analysis by SPME, and aiming to provide efficient, selective, and noninvasive sampling technologies, many efforts have been made toward the development of convenient sampling devices[163,267] as well as SPME extraction phases designated for such purposes.[119,242,268] A novel SPME sampler designed for *in vivo* sampling of fish tissue was proposed by Togunde et al.[267] The new device (Figure 5B), comprised of a matrix compatible PDMS probe (165um thickness), enables a simplified one-step, *in vivo* sampling procedure that circumvents fish anaesthetization, a necessary practice for insertion of conventional SPME assemblies into fish tissue[160] (Figure 5A). As a proof-of-concept, the new sampler was utilized for investigations of the uptake and bioconcentration potential of waterborne contaminants, such as pharmaceutical residues, in fish muscle.[267] More recently, Poole et al. proposed an innovative sampler which incorporates an extraction phase recessed into the body of a solid needle (Figure 5C).[163] The design of the device enabled the puncturing of fish scales without the need for employment of a sheathing needle or additional support during the process of puncturing through protective tissue. The robust geometry of this device, where the SPME coating is protected via recession into the needle, not only circumvents the use of additional sheathing needles, it also overcomes the need for prepuncturing of fish tissue prior to the introduction of the extraction device. This device was successfully used in *ex vivo* determination of PUFA from salmon and on-site/*in vivo* sampling of wild Muskellunge for the untargeted screening of anthropogenic compounds related to bioaccumulation and bioconcentration.[163] Moreover, the SPME technique has been successfully used to investigate results of exposure of fish to water contaminants.[269,270]

Other Food Commodities of Animal Origin. In addition to being the primary source of nutrition for all infant mammals, milk, as an agricultural product extracted from nonhuman mammals, is widely consumed by humans worldwide and used as a basic ingredient for both dairy products as well as in a wide range of processed foods. In recent work, the monitoring of fluoroquinolones in milk was carried out by DI-SPME-LC-MS/MS, using multiple monolithic fiber solid-phase microextraction (MMF-SPME) based on a poly (apronal-*co*-divinylbenzene/ethylenedimethacrylate) monolith (APDE).[271] To enable application of DI-SPME without the incurrence of coating damage, milk samples were treated with trifluoroacetic acid prior to SPME analysis so as to allow for the precipitation of proteins and removal of milk fat. Following, the supernatant obtained was transferred and diluted to 20 mL with ultrapure water. The developed method showed improved performance compared to other approaches.[271] OCP residues were also monitored in bovine milk samples by an HS-SPME-GC-ECD method optimized by Doehlert design.[272] Despite the complexity of milk as a matrix and the lipophilicity of organochlorine pesticides, good limits of detection and quantitation were obtained for the 5 studied pesticides according to their currently defined maximum residue levels (MRLs).[272] More recently, D9-tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN) were quantified in human breast milk via a fully validated HS-SPME-GC-MS method with the aims to provide a forensic toxicology analytical tool for assessment of intoxication in infants during the breastfeeding period.[273] Moreover, rapid characterization of the human breast milk lipidome was assessed via SPME-LC-MS with the use of C18/PAN fibers.[211] The developed method was able to detect 25 classes of lipids from 6 lipid categories without addition of sample pretreatment steps such as protein precipitation or the use of organic solvents for extraction.[211] Milk is generally considered to be a complex matrix due to its composition, which consists of water and other nutrition components such as lactose, fat, proteins, and minerals. In a study by Lin et al., the effect of matrix composition on analyte uptake during SPME was investigated.[274] A comparison of the sampling kinetic parameters (e.g., desorption time constants) in milk samples at different dilution factors indicated that the presence of certain matrix components can actually enable faster uptake kinetics, further corroborating the aforementioned hypothesis regarding the role of binding proteins in the mass transfer of analytes.[275] Moreover, a calibration method that considered the effects of complex matrixes was proposed for pre-equilibrium SPME when applied to milk sampling of PAHs. The method was validated, providing LODs and LOQs for six PAHs ranging from 0.1 to 0.8 ng g^{-1} and 1.4 to 4.7 ng g^{-1}, respectively.[274] An alternative modus operandi of HS-SPME consists of applying low-pressure conditions into the sampling vial.[276] This approach, termed vacuum(Vac)-HS-SPME, has been shown to enhance extraction kinetics, thus improving the efficiency of pre-equilibrium SPME sampling.[277] Using this strategy, free fatty acids and phenols were successfully determined in milk samples, using shorter extraction

DOI: 10.1021/acs.analchem.7b04502
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times and lower sampling temperatures than regular HS-SPME. Such factors play a large role in the sampling of complex food samples, as excessive heating of samples as well as extended sampling times may both facilitate alterations in matrix composition.[146]

Eggs are another class of complex food matrixes that are widely used for cookery and store significant amounts of proteins and choline. While eggs have high nutritional value, potential health issues may arise from insufficient egg quality, improper storage, individual allergies, and contamination from pharmaceuticals administered to fowl. In this regard, HS-SPME was used to detect and quantify thymol from egg yolk for the purpose of evaluating the transference and bioavailability of thymol after domestic chickens were supplemented with thyme essential oil, aiming to elucidate the dose−response relationship of this compound.[278] Li et al. developed an HS-SPME-GC-MS method using a PDMS/DVB 65 μm fiber for the extraction of volatiles from egg white antioxidant proteins (EWAPs). By monitoring the changes in aroma under different storage conditions, the authors were able to identify 3-ethyl-2,5-dimethylpyrazine and benzothiazole as key volatiles responsible for aroma changes. The obtained results can be used in the development of strategies to prevent or retard the deterioration of eggs, and are also expected to contribute to further research on the stabilization and production of EWAPs as a nutritional and functional food.[279] Fluoroquinolones are antibiotics used for the treatment of veterinary diseases in food-producing animals. Thus, their administration to fowl can result in the contamination of eggs. Naddaf et al. synthesized silica-coated magnetite nanoparticles modified with anionic surfactant aggregates that were used for magnetic SPME of the enrofloxacin antibiotic from egg samples. Extraction was carried out by formation of ion-pair complexes with surfactants. Optimization of various parameters such as sample pH and ionic strength, amount of surfactant, sorbent, donor phase volume, extraction time, and desorption conditions was carried out for the development of a robust method that not only showed comparable performance to other approaches previously reported in the literature but also involved a simpler and greener analytical routine.[280]

As a food matrix of animal origin, while honey does not have significant nutritional value, it is nonetheless a valuable food commodity often used as a sweetener, with its distinctive flavor making it a worldwide, highly commercialized product for human consumption. As honey is produced by bees from the sugary secretions of plants, it can possess characteristic aroma bouquets related to the region and plants of production but also concentrate various contaminants present in the secretions of said plants. In view of the demand for quality assessments of marketed honey, Wang et al. developed a convenient derivatization/SPME approach for determination of sucrose in honey, which is an indicator of possible adulteration of the product.[281] A PA 85 μm fiber was used to extract the acetylated derivative of sucrose after a derivatization reaction was carried out with 100 μL of *N*-methylimidazole and 800 μL of acetic anhydride in a 100 mL aqueous sample. The method was validated and successfully used to detect adulteration of honey by sucrose addition.[281] A multiresidue method was developed by Al-Alam et al. for determination of 90 pesticides, 16 PAHs, and 22 PCBs from honey via a QuEChERS-SPME method.[282] The honey samples were first extracted following typical steps of the QuEChERS approach (extraction with acetonitrile, addition of citrate buffered extraction salts, transfer of the supernatant in PSA primary-secondary ammine-PSA tube, shaking and centrifugation, and evaporation of the obtained extract, and reconstitution with acetonitrile). Next, the attained extracts were divided into two aliquots; one was directly analyzed by LC-MS/MS for determination of 30 LC-amenable pesticides, while the other was diluted to 20 mL with water containing 1.5% of NaCl, then submitted to DI-SPME for extraction of the remaining targeted analytes prior analysis by GC-MS/MS. Two SPME coatings were used in this study, including PDMS 100 μm for analysis of OCPs, PAHs, and PCBs, while PA 85 μm was adopted for extraction of the remaining GC-amenable pesticides.[282] The method, which included the use of a matrix-matched calibration approach, was fully validated, providing LODs in the low ng g^{-1} level.[282]

SPME in Food Metabolomics. In food analysis, metabolomics investigations, intended as the comprehensive analysis of small molecules characterizing a certain system, have been carried out in various studies of quality characterization, traceability, authentication, and nutraceutical value assessment, among others. In 2009, Cifuentes introduced the term foodomics as "a discipline that studies the Food and Nutrition domains through the application and integration of advanced -omics technologies".[283] Among the -omics technologies, metabolomics has shown marked growth in potential due to recent strides in analytical technology, increasingly attracting the interest of the scientific community in view of the amount of information it is able to provide regarding a given system. Metabolomic approaches can be generally grouped as either "profiling (targeted)" or "fingerprinting (untargeted)" strategies. Metabolomics profiling approaches consist of the analysis of a given set of known metabolites that provide direct functional information and thus are targeted for identification and possible quantification.[284] On the other hand, metabolomics fingerprinting consists of the untargeted determination of as many metabolites possible, with aims of creating a "pattern" that can be used to classify samples based on type, quality, authenticity, origin, and maturity (in case of fruits); as such, it does not necessarily involve specific metabolite characterization.[284] However, beside this general classification, other terms such as "metabolite untargeted analysis" can be differentiated from fingerprinting analysis, since the former aims at the identification of metabolites extracted via a nontargeted approach, and represents the first step prior to more focused approaches such as profiling analysis. A metabolomics study is generally comprised of sampling, sample preparation, chemical analysis, and data analysis steps, with each of these steps needing careful optimization and control so as to minimize biased determinations and thus achieve a representative snapshot of the system being investigated as well as reduce the introduction of errors in the analytical routine. Generally, when metabolomics is carried out in a targeted fashion, method optimization is focused toward the achievement of the best extraction/separation/detection conditions for the targeted metabolite(s), whereas in untargeted analysis applications, the employed method should be tuned toward the extraction of the highest amount of compounds from the system with a minimum degree of discrimination among various metabolites classes. SPME can provide a convenient tool for food metabolomic investigations since it simplifies the sampling procedures and sample preparation steps of the metabolomic workflow, even merging these two stages when *in vivo*/on-site sampling is carried out, while its customizable and miniaturized geometry enables minimum invasiveness and negligible plant

DOI: 10.1021/acs.analchem.7b04502
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tissue disruption.[7,11] By taking advantage of its tuning capabilities, SPME can be employed to provide negligible depletion of analytes, thus circumventing disruptions to the binding equilibria that govern the free/bound concentration of analytes present in a given system, while the selection of appropriate SPME extraction phases toward a given application can enable the balanced coverage of analytes.[7,11]

Indeed, the various abovementioned advantages provided by SPME have enabled the use of the technique for *in vivo* applications. In this respect, the majority of metabolomic investigations of food commodities reported to date have focused on the determination of volatile organic compounds (VOCs) by HS-SPME, both by *ex vivo* and *in vivo* approaches. Particularly as it pertains to metabolomics investigations of food commodities, the implementation of SPME-GC × GC platforms has proven to be particularly effective in view of the variety and quantity of compounds that SPME is able to simultaneously extract as well as the enhanced separation power and detection that GC × GC systems are able to provide. Recent applications of untargeted metabolomics studies carried out by HS-SPME include analysis of apples (*ex vivo*),[158] saprotroph fungi (*in vivo*),[213] cocoa nibs,[285] crucian carp meat,[286] sugar cane honey,[287] edible oils,[212] and various berries,[288,289] among others. In order to obtain broader coverage of extracted analytes, most studies opted for the use of a DVB/Car/PDMS coating,[156,158,213,285,287] which has been shown to have greater potential for nonselective extraction of compounds of diverse hydrophobicities, molecular weights, and chemical functionalities as systematically compared to other commercially available SPME coatings.[158] Notwithstanding its various advantages, it should be kept in mind that employment of HS-SPME toward food metabolomics investigations is not always able to portray a realistic snapshot of the chemical composition of the system under investigation, due to the scarce HS enrichment of metabolites with poor volatility and high solubility in a given matrix. To this end, various studies have underlined the usefulness of DI-SPME as an alternative or complementary approach to HS-SPME for untargeted metabolomics investigations.[55,156,158,290] In an analysis of the apple metabolome, the effect of extraction mode on metabolite coverage was evaluated by comparing apex plots obtained by GC × GC-TOF/MS analysis after DI-SPME and HS-SPME, using a DVB/Car/PDMS fiber as extraction phase in both HS and DI modes. The attained findings revealed the detection of 906 and 555 features for DI and HS modes, respectively, with broader extraction coverage obtained by DI-SPME.[158] Moreover, changes in metabolic fingerprints in response to apple fruit maturation were assessed by *in vivo* DI-SPME, demonstrating the potential of this approach in quantitative plant metabolomics. The developed *in vivo* sampling approach was shown to yield good intra and inter fruit repeatability, and among the metabolites extracted, esters were found to be upregulated in response to fruit maturity level.[156] In DI mode, obtained GC × GC chromatograms were populated by broad peaks corresponding to products of Maillard reactions, which occur at high temperatures (e.g., SPME desorption conditions) between the free amino group of amino acids and the carbonyl group of reducing sugars. The occurrence of these artifact-producing reactions was hypothesized to be related to the attachment of nonvolatile matrix constituents on the coating surface due to its scarce matrix-compatibility. In light of this, PDMS-overcoated DVB/Car/PDMS coatings were tested for the same type of sampling, with results revealing that the occurrence of Maillard reactions was minimized due to the more effective cleanup afforded by the outer PDMS coating layer.[156] Exploiting the capability of PDMS-overcoated DVB/Car/PDMS coatings for unselective extraction and matrix-compatibility, Fontanive et al. developed a method for metabolomic profiling of Brazilian Cachaça by DI-SPME-GC × GC-TOF/MS. The extraction coverage capabilities of HS-SPME and DI-SPME were also compared in this study, demonstrating the capability of DI-SPME to yield a more comprehensive coverage of extractable metabolites.[290]

Environmental Analysis. Among the different steps involved in the analytical process, the sample collection and preparation steps can certainly be said to be the most critical to the attainment of reliable results for environmental applications.[170] Such a consideration stems from the relatively high likelihood that errors performed during said samplings can easily go unnoticed due to the highly variable nature of real world environments as well as the comparatively low levels of replication and quality control measures that can be reasonably employed in comparison to those found in a traditional laboratory setting.[220,291,292] Furthermore, as sampling precedes all other steps of the analytical process, any error made during this step will be propagated throughout the rest of the analysis, potentially resulting in false or weakened conclusions.[293] As such, it is imperative that samplers designed for environmental applications remain sensitive enough to extract given compounds of interest while still being robust and easy enough to handle such that they are approachable by those working in the industry.

Since the initial introduction of the SPME approach in 1989,[294] SPME techniques have been very well explored within the environmental analytical chemistry field, with a query of the Web of Sciences database yielding over 1000 related publications since 1992 (as of September 2017). In fact, as an environmentally friendly sampling technology, it is unsurprising that much of the initial SPME research targeted environmental applications. In the first publications of SPME bare or PDMS-coated silica fibers were employed for the extraction and thermal desorption of chlorinated organic contaminants from water. These contaminants, consisting of various PCBs, chlorinated aliphatic hydrocarbons, and a BTEX mixture, represented the first compounds to ever be extracted by use of SPME as a sampling methodology in publication.[294,295] These early GC-SPME fibers, although not as repeatable or sensitive as their contemporary counterparts, posed an inherent advantage over traditional solvent-based sample preparation methods, as they vastly increased analytical throughput while avoiding the use of the very same organic solvents they were intended to measure.

More contemporary works have continued to explore these advantages, as exemplified by an interlaboratory study conducted by Rodriguez-Lafuente et al.[218] This study involved the direct comparison of analytical figures of merit obtained via SPME-GC in lieu of liquid−liquid extraction (LLE) (US-EPA 8270) for the determination of 25 different pesticides from surface water and groundwater samples.[218] The findings of this study revealed that in addition to providing a much faster, fully automated analytical throughput, the DVB/PDMS SPME-GC methodology also provided noticeably lower limits of detection, allowing for the positive detection of 342 of the 350 compounds tested versus the 287 detections attained via LLE. This sensitivity difference was most pronounced at the 0.8 ug L^{-1} spike point, which is below that of the reporting detection limit

DOI: 10.1021/acs.analchem.7b04502
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of the LLE method performed by the partnered accredited laboratory. Furthermore, only one SPME-GC run, using 15.5 mL of sample, was required to determine all 25 pesticides from a given sample, while the US-EPA 8270 method required 3 runs per sample (encompassing acidic, neutral, and basic conditions) consuming a total of 800 mL of sample and 150 mL of dichloromethane. Unsurprisingly, the SPME method was considered far more environmentally friendly, with an Eco-scale greenness factor of 82 (out of 100) versus a value of 51 for LLE.[296] The two techniques were verified to have a comparable level of accuracy, with 65% of the SPME results and 71% of the LLE results (n = 280) falling within the 70−130% range of the true concentrations of compounds when double-blind split analyses were performed.

SPME Samplers for Varying Environmental Matrixes. Beyond the standard fiber morphology, SPME technologies have continued to develop and change to address specific challenges imposed by the varying samples and locations targeted in the environment. When one considers environmental pollution and their related sampling matrixes, the vastness of potential applications can initially appear daunting. Coming from all three of the earthly phases of matter, most pollution studies can be categorized as either air, water, or soil based, with further subcategorizations possible beyond that initial classification. Although by no means the panacea of sample prep, various SPME-based solutions to address each of these categories have been explored in recent years. Technologies such as needle trap devices (NTDs) for air sampling, CF SPME for determination of soil contaminants, and the previously described (Shapes of Support section) GC-TFME for the ultratrace detection of pollutants in surface waters[171] and metropolitan air[219] are just a select few of such specialized morphologies.[3,27,297] Like any technique, however, these samplers still require routine quality control and an initial validation. As such, the repeatable delivery of standards tailored for SPME-based extractions that can be performed on-site is also necessary.

Standard Gas Generating Vessels. In-vial standard gas generation has been recently emerging as a means to further ensure the quality control of both in-lab and on-site SPME based extractions.[292,298] These standard analyte generators act as a high capacity, self-replenishing reservoir for analytes of interest, essentially allowing them to serve as a quasi-infinite volume system to sample from when using SPME. These analyte generators use polymeric sorbents such as PDMS or PS-co-DVB to sorb small organic molecules, which are then allowed to come to equilibrium with a sampling matrix in an enclosable vessel.[292,299] The most common embodiment of this device would be the standard HS generating vial configuration, where a standard HS is generated by placing the analyte-laden sorbent in a common HS vial with a septa cap.[300] As the sorbent has a much higher affinity for the analyte at equilibrium, the air contained in the vial remains at a relatively low concentration, and only a miniscule fraction of this standard is made available for extraction. As a result, these standard gas generating vessels may be used hundreds of times.

Such repeatability was first demonstrated by Gomez Rios et al. with a standard McReynolds compounds HS generating vial, which was prepared using PS-co-DVB particles and a hydrocarbon oil composite sorptive matrix.[298] The intravial % RSDs for all of the McReynolds probes tested were found to be under 4%, even after 160 consecutive extractions were performed for 1 min at 35 °C, using a 50/30 μm DVB/Car/PDMS SPME fiber for HS-SPME extractions. This design was then further improved in 2015 when Grandy et al. utilized a silicon oil/PS-co-DVB composite matrix in lieu of the former hydrocarbon oil based sorbent.[292] The newer silicon oil based design was shown to exhibit retention capabilities 2−4 times greater than that of the hydrocarbon oil/PS-co-DVB. This improvement allowed for intravial % RSDs of <2.5% after 208 consecutive extractions under the same conditions. Furthermore, the depletion of analytes was plotted and determined to be less than 3.3% for all McReynolds probes. The attained results of this investigation also revealed that depletion could be confidently predicted theoretically by means of a mass balance expression, as shown in eq 27, where X_{adj} is the predicted extraction amount for the nth + 1 extraction, X_n is the actual amount extracted at the nth extraction, is the average amount extracted over n runs, n is the number of extractions from the vial, and M_0 is the initial amount of standard present in the vial.[292] Such corrections, however, would be unnecessary for most practical applications, as depletion would only became significant after multiple-hundreds of extractions had been performed. Moreover, one could simply use another vial, as vials from different batches were shown to be statistically identical at a 95% level of confidence.

$$X_{adj} = X_n + \left((\bar{x} \times n)\left(\frac{\bar{x}}{M_0}\right)\right) \tag{27}$$

In-line with environmental applications, following these initial developments, a variety of standard gas generating vessels prepared with varying standards have since been used for many studies. For instance, a C_7−C_{20} n-alkanes generating vial was prepared for the on-site generation of a linear retention index plot as a means to identify unknown contaminants from an industrial impacted lake via TFME and portable GC-MS instrumentation.[170] In other work, a vial containing pentfluorphenyl hydrazine (PFPH) was applied for the on-site derivatization of formaldehyde from car exhaust.[220] Similarly, a vial based on a crushed PDMS sorbent with a 13 component mixture was used for the specific application of mass spectral tuning of field portable GC-MS instrumentation.[299] Likewise, a pentafluorobenzaldehyde (PFBAY) generating vial was used to facilitate the on-fiber derivatization of short-chain aliphatic amines from surface water samples.[301] In addition to the abovementioned specific applications, these standard generators are most commonly used as a simple quality control device to ensure stable response, as they can be easily placed in a heated block on a GC autosampler or transported on-site in a battery-operated block heater to perform quality control injections on portable GC-MS instrumentation before and after samplings.[170]

SPME and NTD for Air Analysis. Gaseous air samples lend themselves well to being sampled directly with standard SPME fibers, as the diffusion coefficients of most volatile organic compounds (VOCs) are high enough to allow for appreciable levels of extraction within short periods of time.[293,302,303] However, issues can arise once the analyst wishes to target organic compounds that are only semi volatile (SVOC) in nature, as SVOCs have a tendency to bind to airborne particulate matter or aerosol-type particles, making them unavailable to SPME fibers which, as previously described, are only sensitive to the free analyte fraction.[293,297,304] Furthermore, the characterization of the environmental fate of a given compound, i.e., the percentage of a given compound that is particulate-bound, can yield additional information regarding the system under study.[305,306] With this application in mind, further developments in needle

DOI: 10.1021/acs.analchem.7b04502
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trap devices, which conversely to SPME are able to capture both the free-form and bound fractions of small organic molecules, have been an ongoing endeavor to further assist in the characterization of environmental air.

Needle trap devices have already been the subject of recent literature reviews, first in 2010,[304] then in 2012,[307] and then again in 2017.[308] These articles have already extensively discussed NTD design, fundamentals of operation,[304] early environmental applications,[307] and available NTD sorbents.[308] Hence, only novel environmental applications will be further explored in the current section. One of the primary advantages of these sorbent packed needles lies in their ability to act as a filter, trapping both the free form and particulate bound fraction of small organic molecules in a given gaseous sample, thus allowing for the determination of total analyte concentrations. Hence, when combined with conventional open bed SPME devices, which are themselves only sensitive to the free analyte fraction, application of NTD devices enable determinations of the particulate bound fraction of a given analyte, which can be accomplished by subtracting the free concentration determined by an SPME fiber from the total concentration determined via NTD. In an interesting exploration of this principle, Cheng et al. combined the use of 100 μm PDMS SPME fibers with a DVB packed NTD to determine the effectiveness of repellents emitted via mosquito coils,[305] and in following work, from electronic vaporization mosquito mats.[306] Particularly in the mosquito mat study, a clear trend could be seen, with the 100−120 mesh DVB NTD extracting a much greater amount of the semi volatile repellants than that extracted by the PDMS SPME design.[306] However, despite this novel advancement, this aforementioned study failed to fully explore the advantages of the approach by calibrating and comparing the free and particulate bound concentrations of the extracted analytes under study. Conversely, Reyes-Garces et al. better explored this advantage by comparing the free vs total levels of alpha-pinene emissions from a pine branch on-site, which were found to be 3.3 and 7.8 ng mL $^{-1}$, respectively, using an SPME and NTD-enabled portable GC-IMS instrument.[309] This vast concentration difference is to be expected, as the midvolatility alpha-pinene, with a boiling point of 155 °C, would much prefer to remain in the particulate-bound fraction at 23 °C.

In a similar but much more recent study, Poole et al. were able to generate some surprising results regarding the environmental fate of formaldehyde as emitted from car exhaust, using a combined SPME and NTD portable GC-MS method.[220] In this study, samplers were first preloaded with PFPH with the use of the aforementioned HS generating vial. Following this preloading, both SPME and NTD extractions were performed and analyzed on-site from cold (16.3 °C) and hot (45.7 °C) car exhaust. The bound fraction of this compound in cold car exhaust extracts was found to be approximately 0.19 ng mL^{-1}, accounting for approximately 51% of the total concentration of formaldehyde, despite formaldehyde being a very volatile organic compound (VVOC). Although initially surprising, it was later realized that as car exhaust represents a saturated humidity environment, formaldehyde was likely dissolving into the aqueous phase of small aerosol particles, again highlighting how the full characterization of a system under study may allow for a better understanding of the environmental fate of a given organic contaminate.

In addition to these novel free versus total studies, NTD technologies have also been used on their own for the simple quantification of total pollutants in environmental air. In terms of more recent examples, NTDs employing a novel silica aerogel have also been used for the quantification of formaldehyde from indoor and outdoor air[310] and chlorobenzenes from a standard air sample.[311] A bondesil C18 packed NTD was applied to develop a quantitative and fully automated HS method for the determination of nine multiresidue musks from real wastewater treatment facility samples.[312] A high-resolution qualitative comparison of different marine diesel fuel emissions was accomplished by use of a tribed PDMS, Carbopack B, and Carboxen 1000 NTD, introduced into a unique GC/REMPI/SPI-TOFMS, which is a form of NTD-GC enabled photoionization time-of-flight mass spectrometry.[313] A Silica composite carbon nanotube sorbent was applied to both SPME fibers and NTDs and compared in terms of MLODs vs DVB/PDMS analogues for the in-laboratory determination of perchloroethylene in air.[314] Finally, an entirely new approach to use smaller NTDs to preconcentrate large volume air samples, such as those from 3.5 in. sorbent tubes, was validated while incorporating the use of a hand-portable thermal desorption module.[315] This module essentially transfers analytes from 3.5 in. sorbent tubes onto an 18-gauge NTD, which can then be directly introduced to a standard GC injector. This methodology may have great implications in terms of future on-site analytical approaches; to date, it has already been coupled to portable GC-MS instrumentation and to the much more sensitive GC-TFME samplers. Hence, its possible applications will be further discussed as a future direction.[170]

Cold Fiber SPME (CF SPME) for Soil Analysis. The sampling of soil may prove to be the most complex in terms of ensuring representative and reliable results. Contemporary techniques such as Soxhlet and accelerated solvent extraction (ASE) have been generally well accepted in terms of analytical results but require copious amounts of solvent and can be difficult to fully automate to analytical instrumentation.[3] Standard SPME techniques, on the other hand, have an advantage in their solvent-free and automatable nature but can be inadequate in terms of reliability. This limitation stems from matrix effects associated with the multiphase nature of a soil particles, which requires large amounts of energy, in terms of heat (or solvent interaction), to fully liberate the analyte from the soil matrix.[3,293] This high level of heat has the undesired consequence of lowering the affinity of the analyte toward the SPME fiber, effectively decreasing the partitioning coefficient, K_{es}. To overcome this limitation, researchers have explored multiple solvent-based avenues such as an HS SPME above an organic, solvent-modified aqueous slurry[316,317] or an initial extraction by organic solvent techniques with subsequent evaporation and reconstitution in water, followed by SPME sampling.[318] Although these techniques were found to be relatively reliable by their respective authors, they still necessitated the use of organic solvents to facilitate extraction. To that end, CF SPME was developed to take advantage of the high temperature release of analytes from the soil matrix, while using an internally cooled SPME fiber to maintain a high K_{es} and analyte affinity.[3,319]

CF devices have quite recently been the subject of two separate review articles focusing on the determination of soil contaminants.[3,319] In terms of new applications, a recent study successfully demonstrated a simple methodology to use liquid nitrogen delivered from a Dewer flask toward a copper coil, which can be wrapped around any commercial SPME needle.[320,321] This newer development employed the use of an internally cold commercial particle-loaded DVB/PDMS SPME fiber to extract

DOI: 10.1021/acs.analchem.7b04502
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acrolein (2-propenal) from an in-lab HS analogue and real human breath.[321] The main advantage to this technique is that it can be adopted at relatively low cost for manual CF implementation; however, it does lack the automation seen by other CF methodologies.[3] Another study involved the preparation of a new graphene oxide CF SPME device, which was prepared for the extraction of alkyl-benzenes from a more complex wastewater sample.[322] Although not as difficult of a matrix as soil, the methodology was able to show the effectiveness of a thermoelectrically cooled SPME device to reliably quantitate VOCs from a complex matrix. Despite these advancements, neither of these apparatus explore an automatable approach for soil sampling. Initial publication on automated CF-SPME approaches involved the use of a CO_2 cooled PDMS SPME fiber with an internal thermocouple for temperature control on a customized CTC autosampler mounted on a GC instrument.[3,319]

Automated or not, in order to liberate small organic molecules from the soil lattice in CF-SPME techniques, it is not uncommon to use temperatures approaching 200 °C. Such high temperatures can have the negative side effect of increasing the pressure within the sealed HS vial. Unfortunately, on top of forcing high pressure force analytes back into the solid matrix, losses can occur when the large 18 gauge CF-SPME needle pierces the septum of the pressurized vessel, resulting in unacceptable % RSDs.[221] To improve upon this constraint, Xu et al. recently proposed the methodology of pressure-balanced CF SPME as a way to further improve the performance of CF-SPME soil samplings.[221] This methodology employs the concept of vacuum assisted HS-SPME, originally proposed by Psillakis et al., which involves the application of vacuum conditions to the headspace of a sample prior to HS-SPME extractions.[276] However, as opposed to sampling at vacuum conditions, the goal of pressure balancing is to remove just enough air from the HS vial such that the pressure is near ambient at the sampling temperature.[221] This balance ensures no movement of air occurs when the large CF-SPME device pierces the septum, thus preventing analyte loss or dilution, and improving repeatability. In fact, when compared to a standard CF-SPME approach for the determination of PAHs from certified reference soil standards, % RSDs were shown to decrease by at least a factor of 2. Furthermore, this approach was determined to accurately quantitate the certified PAH soil concentration at a 95% level of confidence using a standard *Z*-test.

Use of High Surface Area TFME Devices for the Passive Extraction of Water Samples. SAs previously described in the section corresponding to the Shapes of Support, the use of high volume, high surface area TF-SPME samplers has been shown to drastically decrease the limits of quantitation approachable for environmental applications.[170,171] In addition to allowing for the determination of contaminants such as pesticides from surface water samples with LOQs several orders of magnitude lower than that of accredited liquid−liquid extraction methodologies,[171] such membranes have also been successfully used for the time-weighted average sampling of VOCs associated with vehicle exhaust in busy city streets.[219] Although most environmental works incorporating the use of TFME devices utilize GC-based separation and detection systems,[27] many pollutants of interest are more detectable via HPLC-based approaches, with appropriate membrane techniques having been developed for such determinations.[27]

Of these approaches, quite recent works by Ahmadi et al. present a novel and environmentally friendly means to simultaneously measure and calibrate various hydrophilic and hydrophobic biocides and UV-blocking agents from aqueous environments by means of a TFME-HPLC-MS/MS method and an in-lab standard river system.[44] A retracted thin film blade device was developed to incorporate HLB-PAN and C18-PAN devices for TWA based sampling. This development was accomplished by constructing a thin film blade within a PTFE holder, which was then placed in a biofouling copper holder with a PTFE spacer to set the diffusion path length, *Z*, as described in eq 22. Uptake of the targeted analytes was then validated to remain linear for up to 70 days in-lab with the use of the novel standard river system, which is able to deliver a constant aqueous concentration of hydrophobic compounds for extended time periods. The retracted device was then successfully deployed on-site for 90-day time periods in wastewater-affected portions of the Grand River, Ontario. Open bed grab samples were also performed to cross validate the results, with good agreement obtained between the methodologies.

Coupling SPME to Portable GC-MS Instrumentation. As eluded to in previous sections, SPME-based techniques ultimately lend themselves well to the performance of entirely on-site environmental analyses. However, in order to accomplish such a feat, appropriate field portable instrumentation must also be available as well as be as hand-portable as SPME samplers. For adequate performance during in situ analysis, a field instrument must be compact and lightweight, with low power consumption so as to allow for battery operation.[323−325] The instrument and accompanying SPME device should also be durable enough to withstand both transportation and the operating environment.[324] An additional caveat is that many on-site end-users are likely to be nontechnical in nature; hence, the entirety of the analytical process should be easy to perform. Such simplicity is essential in security applications, where the user is unlikely to have any formal training in analytical chemistry.[323,325]

Early portable instruments such as the vehicle portable, SRI developed GC-FID and GC-PID instruments have been in use for over 15 years.[302] Although older compared to more recently developed portable GC-MS instruments, these SRI systems highlight some of the earliest developments toward completely on-site SPME approaches and were able to achieve detection limits for BTEX in air ranging from 1 to 3 ppb with % RSDs below 5%, using standard 65 μm DVB/PDMS coatings.[302] Despite a high degree of quantitative reliability, the SRI GC instruments are not without limitations. Without a mass spectrometer, it can be difficult to confidently determine the identity of unknown compounds from a given sample by use of GC retention indices (RTI) alone. Besides, the SRI GCs are also quite large, susceptible to moisture, and can only be considered portable if on a hand cart or when operated out of the back of a vehicle.[302]

However, recent technological advancements have allowed for the development of low power, miniaturized mass analysers, which have been successfully coupled with high speed, low thermal mass gas chromatography (GC) systems.[323−326] By miniaturizing the mass analyzer, the size and power consumption of the MS vacuum system can also be minimized. Maintaining an acceptable degree of quantitative ability, these systems are now capable of separating and identifying a large degree of unknown chemical compounds while operating solely on battery power.[327] When ruggedized and combined with field portable SPME devices, such portable gas chromatography-mass spectrometry (GC-MS) systems are able to meet all of the aforementioned qualifications, enabling their suitability for true in situ chemical analysis.

DOI: 10.1021/acs.analchem.7b04502
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A fairly comprehensive review entailing various current miniature mass analyzers, covering a broad range of sample introduction interfaces, was just recently published in 2016.[328] However, on-site instrumentation is a continuingly advancing field, especially in terms of recent environmental approaches. In terms of solid sample analysis, one such application utilized a 100 μm PDMS fiber for the on-site determination of PCBs from soil.[329] However, as previously discussed, without cold-fiber techniques, an inorganic modifier consisting of $KMnO_4$ and H_2SO_4 needed to be added to release analytes from the soil matrix. Furthermore, in order to facilitate quantitative results, Zhang et al. utilized EPA method 8082, which compares the mass spectral peak areas of the unknown PCBs found in soil to that of certified Arochlor standards. Although the portable SPME-GC-MS methodology was found to not impart the same repeatability as that achieved by comparable benchtop methodology, it still served as a good semiquantitative means to quickly identify PCB-contaminated soil.[329] In line with the forensic capabilities that many portable GC-MS instruments were initially designed for, Visotin et al. were able to employ such instrumentation with a 65 μm DVB/PDMS SPME fiber to accurately identify 38 of the 49 ignitable liquid residues in simulated arson samples in firefighting studies.[330] Although only qualitative in nature, such studies represent how approachable such methods may be to nontechnical end-users.

In terms of future analytical approaches, however, one major limitation imposed by miniaturized MS instrumentation remains as the inherent loss in sensitivity that accompanies lowering the power requirements and size of the mass analyzer. In the interest of improving such shortcomings, Grandy et al. have shown that better sample preparation approaches can allow for these portable instruments to exhibit limits of quantitation similar to that of their benchtop counterparts.[170] To accomplish this goal, TFME devices where coupled to a portable GC-MS instrument by placing them in empty 3.5 in. sorbent tubes. Using the aforementioned high-volume desorption module, analytes could be transferred from a DVB/PDMS TFME membrane onto an NTD for injection on the portable GC-MS instrument.[170,315] This transfer was validated to be quantitative in nature, ensuring there was no detectable breakthrough of analytes on the NTD or carry-over from the TFME device. These TFME devices were then shown to extract approximately 24 times more of a given analyte in the pre-equilibrium regime than a comparable 65 μm DVB/PDMS SPME fiber, allowing for the sub ppb detection and quantification of multiresidue pesticides from spiked water samples in as little as 15 min. Finally, to conclude this study, a fully on-site and untargeted TFME-GC-MS determination of industrial contaminants from surface water was performed while using a BTEX generating vial to ensure stable response of the portable GC-MS. This on-site TFME-GC-MS setup is described and shown in Figure 6A,B. Interesting enough, this untargeted screening approach was able to identify 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TXIB), a plasticizer, and tris(1-chloro-2-propyl)phosphate (TMCP), a polyurethane flame retardant, which is very likely related to the concurrent pouring of a polymer reinforced concrete bridge and application of polyurethane spray in foam into the void between the drainage culverts and the bridge. Although a proof of concept in nature, this application demonstrates how, when combined, all of the tools discussed herein may guide the future of environmental analytical approaches. In the future, this combined approach could be even further improved upon by including new generations of environmental SPME-HPLC samplers, like those shown in Figure 6C, as to characterize the chemical profile of a given environmental system more completely. In fact, Figure 6D shows just how both GC and HPLC based SPME samplers can be combined in hopes to fully characterize complex environmental systems in the future.

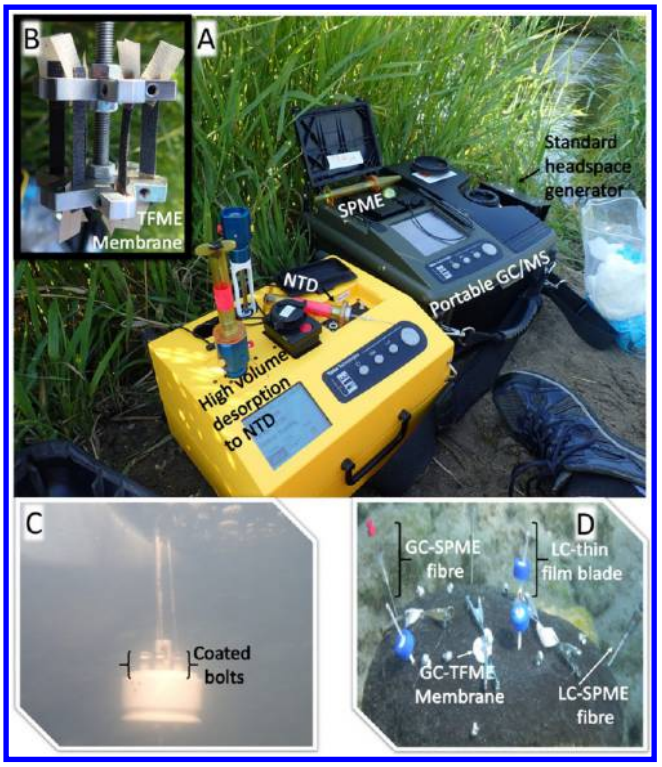

Figure 6. On-site investigation of aquatic environments with select SPME devices, including (A) complete GC-MS portable setup deployed on-site using a combination of SPME, NTD, TFME, and HS standard vials for on-site screening of river contaminats, (B) TFME membrane holder used to perform six replicate extractions from river water at 2000 rpm, (C) self-sealing, coated bolt SPME device deployed via kayak at outflow of wastewater treatment facility, (D) combination of standard SPME fibers for direct sponge tissue sampling, TFME membranes for ambient water surrounding sponge, and thin film blades placed within sponge vents, all applied for an investigation of the biodegradation capabilities of sponges.

Bioanalysis and Cell Studies. SPME has been demonstrated as a suitable tool for the analysis of complex samples of bioanalytical and clinical interest. Multiple SPME formats and coatings have been successfully used for the determination of a diverse range of analytes in various biological matrixes, including several biofluids and tissue types as well as matrixes such as breath, sweat, and feces.[8,12,331−333] Generally, such studies can be classified into two main groups: one involving the analysis of volatile or semivolatile analytes via thermal desorption and GC and a second group, targeting the determination of nonvolatile compounds via solvent desorption and LC, where in the majority of cases, both GC and LC instruments are coupled to MS analyzers. As it pertains to the analysis of volatile compounds in biological matrixes, given its convenience in minimizing the coextraction of matrix interferences and extending the lifetime of employed coatings, HS-SPME likely stands as the most traditionally adopted approach for such applications. Recent studies reporting the application of HS-SPME for the analysis of various biological samples have employed commercially available coatings such as Car/PDMS and PDMS/DVB for the extraction and further analysis of different VOC pollutants

DOI: 10.1021/acs.analchem.7b04502
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and metabolites, via either GC-MS or GC × GC-MS.[334−338] For instance, aiming to provide a tool for determination of human levels of exposure to VOCs, Antonucci et al. recently reported the application of HS-SPME, using Car/PDMS fibers and GC-MS for the sensitive determination of 10 common outdoor and indoor VOC contaminants in urine samples.[223] The proposed methodology proved to be cost-effective and simple and was successfully applied to quantify the selected analytes in urine samples from 40 children living under different environmental conditions. Similarly, Meyer-Monath et al. were able to quantify various VOCs, including chlorinated solvents, in meconium samples.[339] LOQ values within the low ppb range demonstrated the feasibility of using such methodology for assessment of fetal exposure to various VOCs. In the same line of research, Rahman et al. and Sommer et al. used HS-SPME together with GC-ICPMS for the measurement of mercury species in whole blood.[340,341] In spite of adapting intensive multistep sample preparation procedures, involving the addition of several matrix modifiers, the proposed workflows enabled the determination of inorganic-, methyl-, and ethylmercury species with rewarding limits of quantitation. Undoubtedly, such applications confirm the appropriateness of HS-SPME as a sample preparation approach for the convenient determination of multiple target VOC pollutants in complex biological samples. Other relevant studies involving HS-SPME for analysis of volatile analytes in matrixes of biological interest include metabolite profiling studies and untargeted investigations. In both human and animal studies, HS-SPME has been effectively implemented for the identification of volatile metabolites capable of discriminating samples such as breath, sweat, serum, blood, saliva, and urine collected from subjects belonging to different studies or clinical groups.[331,332,342−346] For instance, multiple reports have shown the use of HS-SPME to characterize the urine volatilome in studies involving smokers, autistic children, gender biomarkers, cancer, and various renal diseases.[346−350] As a matter of fact, in a recent work by Monteiro et al., an HS-SPME/GC-MS workflow was adapted for an investigation of volatile metabolite differences between urine samples of renal cell carcinoma patients and healthy controls.[346] Although burdened by several limitations stemming from sources of unwanted variation among the studied individuals, the results of the work were nonetheless encouraging, as two specific VOCs were shown to yield consistent statistical differences between the compared groups. Positive results have also been achieved in the profiling of fecal volatile metabolites via HS-SPME.[333,351,352] A comparative work carried out by sampling from fecal samples obtained from patients presenting diarrhea-predominant irritable bowel syndrome, active Crohn's disease, ulcerative colitis, as well as from healthy controls showed that HS-SPME GC-MS offers a promising strategy for the diagnosis of gastrointestinal disorders.[333] In this study, the authors were able to identify 240 volatile metabolites; among them, short chain fatty acids, cyclohexanecarboxylic acid, as well as its ester derivatives were correlated with diarrhea-predominant irritable bowel syndrome ($p < 0.05$), while aldehydes showed higher intensities in cases of inflammatory bowel disease ($p < 0.05$). Matrixes such as brain and liver have also been analyzed via HS-SPME in studies aiming to find significant markers of disease or contamination exposure in the tissue volatilome.[353,354] On the basis of the abovementioned reports, it is clear that the suitability of HS-SPME to easily and selectively extract a broad range of compounds based on their volatility (Henry constants) through the employment of reusable and commercially available sampling devices has played a large role in the acceptance of this microextraction tool. Alternatively, the use of DI-SPME with matrix compatible coatings has been shown to be a feasible approach for investigations that require effective and simple analysis of semivolatile or nonvolatile compounds in biological matrixes. To this end, several DI-SPME workflows have been described for different biological matrixes as well as for investigations of either GC amenable or LC amenable target analytes. For instance, for analyses of a relatively simple matrix such as urine, in the sense that said matrix does not contain proteins or other macromolecules, commercially available extraction phases can often provide acceptable performance via DI extractions prior to GC instrumental analysis. Such a strategy has been recently employed in the analysis of compounds such as biogenic amines and their metabolites (after derivatization with alkyl chloroformate) as well as contaminants such as pesticides, benzothiazoles, benzotriazoles, and benzosulfonamides in urine samples.[355−357] However, said SPME extraction phases are not well-suited for analysis of more complex matrixes via DI. For such applications, employment of alternative strategies may be required, a topic which will be discussed further in this section.

Aiming to achieve improved sensitivity and selectivity for the extraction of various target analytes, several authors have reported the application of novel GC-amenable coating materials either for HS-SPME or DI-SPME extractions in complex biological matrixes. Indeed, various carbon-based extraction phases, which have been discussed in detail under the Coatings section, have been reported to date for the abovementioned applications, including electrochemically reduced graphene oxide, graphene-based nanocomposites, and graphitic carbon nitrides immobilized in hollow fiber wall pores. Such carbon-based coatings have been used for extraction of analytes such as tricyclic antidepressants (via HS) and uric acid (via DI and after solvent desorption and derivatization) in different biofluids prior to GC analysis.[358−360] Sol−gel based extraction phases with functionalities such as β-cyclodextrin, polyethylene glycol, and methacrylic acid have also been proposed as mechanically stable coatings capable of facilitating the extraction of polar compounds from urine and serum samples.[361,362] Despite the promising results provided by such coating chemistries in selected applications, their applicability in novel SPME studies is somewhat limited by the fact that such materials are mostly made in-house, and therefore, are not easily available for evaluations in new applications. In addition to the employment of alternative coatings, alternative strategies have also been reported to date in bioanalytical applications, such as the use of an electromembrane (EM) to facilitate the analysis of complex biological matrixes via DI.[363] In this approach, an SPME device with conductive characteristics is placed in the lumen of a hollow fiber with an organic liquid membrane immobilized in its pores. By using the SPME device as an electrode, a potential between the sample matrix and the SPME device, which is surrounded by the membrane upon exposure to the sample matrix, is applied to enable the migration of ionized analytes toward the coating. Satisfactory results have been obtained via EM-SPME, employing extraction phases such as pencil lead, nanocarbonaceous sorbent, polypyrrole nanocomposites, among others, for the extraction of several drugs from urine, plasma, and blood prior to GC-FID analysis.[363−366] However, significant restrictions associated with this technique, such as its elaborate experimental setup, the limitations associated with the exclusive use of conductive coating materials to extract charged analytes,

DOI: 10.1021/acs.analchem.7b04502
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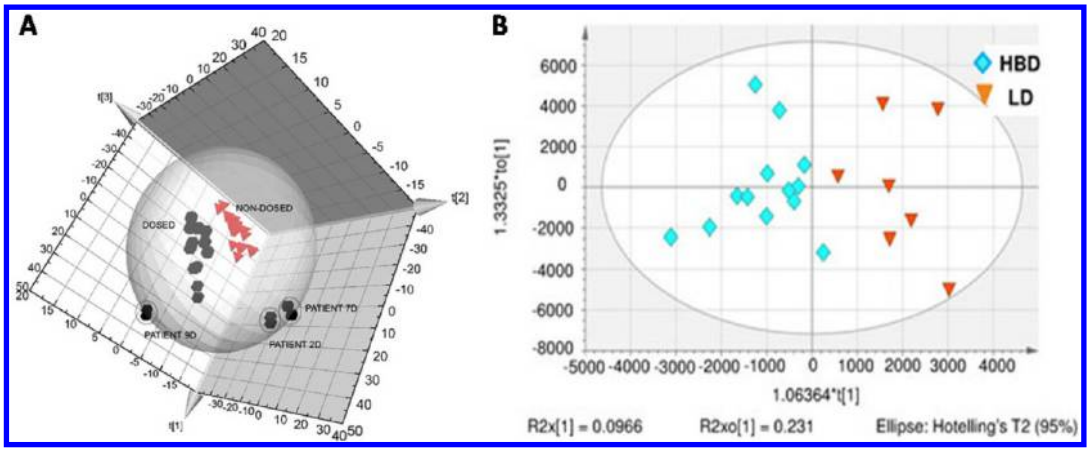

Figure 7. Applications of SPME in fiber (A) and TFME (B) configurations for plasma metabolomics studies. (A) PLS-DA score plot showing the separation of two cohorts (group of patients before (nondosed) and during surgery and drug administration (dosed)) [Reproduced from Bojko, B.; Wąsowicz, M.; Pawliszyn, J. *J. Pharm. Anal.* **2014**, *4*, 6−13 (ref 372) open access https://doi.org/10.1016/j.jpha.2013.03.00]. (B) OPLS-DA corresponding to data collected from heart beating brain dead donor samples (HBD, light blue diamonds) and living donor samples (LD, orange triangles) groups. [Reproduced from Yang, Q. J. J.; Kluger, M.; Goryński, K.; Pawliszyn, J.; Bojko, B.; Yu, A. M. M.; Noh, K.; Selzner, M.; Jerath, A.; McCluskey, S.; Pang, K. S. S.; Wąsowicz, M. *Biopharm. Drug Dispos.* **2017**, *38* (5), 326−339 (ref 389). Copyright (2017) Wiley].

and the necessity of diluting complex biofluids prior to extraction, should be considered prior to implementing EM-SPME in real applications. The introduction of matrix compatible PDMS-overcoated SPME fibers, which are currently commercially available, for DI extractions definitely presents another opportunity to be explored in the analysis of biological samples via GC. As such matrix compatible coatings have only been tested in food commodities to date, future perspectives in the analysis of GC-amenable analytes in biological matrixes should consider the evaluation of this extraction phase toward such applications.

The use of SPME as an alternative sample preparation tool for bioanalytical studies involving the extraction of nonvolatile compounds prior to LC analysis has been broadly reported in recent years.[8,367] A number of coating materials capable of displaying variable affinities for several target analytes, including PAN-based extraction phases, MIP, aptamers, monoliths, polypyrrole nanocomposites, among others, have been employed in various applications involving the analysis of biological samples.[367] In addition to diverse SPME extraction phases, device geometries including fibers, thin-film microextraction samplers, and in-tube SPME setups have been successfully used in such studies.[368] Indeed, in view of the wide array of available coatings and geometries available to date for SPME, several experimental conditions, including SPME device characteristics, must be carefully selected for any given application while bearing in mind the goal of analysis. For instance, the fiber geometry is a well-suited choice for studies concerning the determination of protein binding constants at negligible depletion conditions, analyses of matrixes such as tissue, and *in vivo* investigations, as well as for applications where sensitivity does not represent a major concern. In this regard, SPME fibers coated with PAN-based extraction phases, which hold in their structure C18 and MM functionalities, have been used in various studies conducted in biological samples and systems.[367] The general procedure for the use of such coatings typically involves preconditioning and rinsing steps to ensure the coating material is ready to interact with the sample matrix; extraction by directly immersing the coating into the complex matrix; a quick washing step to remove materials loosely attached to the coating surface; and a solvent desorption step, which should be optimized to guarantee minimum carryover and compatibility with chromatographic conditions. Among the most important advantages of PAN-based SPME extraction phases, features such as outstanding robustness in direct exposure applications to complex, untreated biological matrixes; high selectivity for small molecules; satisfactory biocompatibility; suitability for *in vivo* sampling; and manufacturing cost-effectiveness stand out to showcase the high usefulness of this coating toward bioanalytical applications. In this regard, target compounds of different physicochemical characteristics have been analyzed via DI with the use of PAN-based coated SPME fibers. Bojko et al., for instance, reported the use of 1 cm C18-PAN fibers for the extraction of tranexamic acid, a fairly polar drug with a log *P* of 0.3, from plasma samples.[369] Although the absolute recovery of tranexamic acid obtained in this study was below 1%, quantitation of such drug was possible by performing sample dilution in view of the high concentrations, typically in ppm levels, that are found in real samples. C18-PAN fibers were also employed in work by Birjandi et al., allowing for determinations of both protein affinity constants and changes in concentrations of several fatty acids, such as α-linolenic acid, arachidonic acid, and docosahexanoic acid, in plasma samples of patients undergoing cardiac surgery.[370] The results obtained from this study certainly corroborate the applicability of SPME toward the quantitative measurement of highly hydrophobic compounds that display significant affinity for plasma components. Aiming to facilitate the extraction of polar charged analytes, while concurrently ensuring satisfactory extraction of nonpolar compounds, MM-PAN fibers have been introduced as prototype devices by Millipore Sigma. This coating type, which has in its structure not only C18 (or C8) but also benzene sulfonic acid moieties, has been successfully tested in the extraction of 36 metabolites of different polarities (log *P* −7.9 to 7.4), showcasing its broad analyte coverage.[371] On the basis of these findings, and taking advantage of the applicability of SPME for the analysis of various complex matrixes, PAN-based coated SPME devices have been proposed as an alternative tool for metabolomics studies. In fact, to assess the performance of SPME versus other sample preparation techniques traditionally employed in untargeted metabolomics, a comparison of metabolite features extracted with SPME MM-PAN fibers versus

DOI: 10.1021/acs.analchem.7b04502
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those detected with ultrafiltration and protein precipitation was carried out using human plasma as a model matrix.[371] The results obtained in this study demonstrated that although SPME yielded a lower number of features (1592 in positive mode after 5 min extraction) than the other two sample preparation approaches (2686 for ultrafiltration (positive mode) and 2975 for protein precipitation (positive mode), this microextraction technique allowed for better recoveries of nonpolar metabolites in comparison with ultrafiltration and enabled a reduction in ionization effects when compared with protein precipitation. Indeed, by taking advantage of the features offered by MM-PAN fibers in terms of metabolite coverage, in a proof-of-concept study, Bojko et al. was able to observe differences in metabolites extracted from plasma samples of patients before cardiac surgery (nondosed) and during surgery, during which tranexamic acid administration was performed (Figure 7A).[372] These findings certainly provide support toward the applicability of DI-SPME in metabolomics studies, especially for *in vivo* applications, where the fiber geometry of SPME remains the device of choice. Conversely, TFME, owing to the enhanced sensitivity afforded by the larger surface area of such devices (as previously discussed under the Shapes of Support section of this review), is presented as a feasible geometry for *in vitro* studies involving either targeted or untargeted analysis of biofluids. Other polymeric materials that have shown promising performance in the analysis of complex biological matrixes via DI are the fluoropolymers. In recent work by Gionfriddo et al., a fluoropolymer was introduced as a binder to immobilize HLB particles for SPME, with extraction followed by instrumental analysis with GC and LC platforms.[53] The coatings developed in this study demonstrated satisfactory performance in evaluations involving 15 consecutive extractions from whole blood. Given their simple manufacturing process, which does not require a thermal curing step, their further implementation in a broader range of applications is anticipated. However, further evaluation of the performance of such fluoropolymer-based coatings in different biological matrixes is still needed.

One of the most attractive features of DI-SPME in its fiber configuration is its suitability for *in vivo* analysis when biocompatible materials are used as extraction phases. Indeed, several studies reported to date have demonstrated the applicability of this technology toward monitoring of concentrations of different target drugs and metabolites in several living biological systems.[12,373,374] As it pertains to the analysis of biofluids such as blood, DI-SPME has been successfully used for pharmacokinetic monitoring of benzodiazepines, carbamazepine, and carbamazepine-10,11 epoxide (carbamazepine metabolite) in animal models, including models such as beagle dogs and rats.[375,376] In such applications, the SPME coating is directly exposed to the bloodstream by using a catheter and/or custom-made sampling interfaces. The main advantage of this approach is that as no blood withdrawal step is required in this workflow, the risks of changes in sample matrix composition and in the free concentrations of nonstable analytes are minimized. Furthermore, since *in vivo* SPME allows for various samplings of the same animal at different time points, the feasibility of time course-based experiments such as drug pharmacokinetics studies is greatly improved. Indeed, minimizing the number of animals used in a given study is in line with the 3R principles (Replacement, Reduction, Refinement) that provide a basis for more humane animal research. Considering such principles, scientists conducting animal research seek for alternatives to either replace animal experiments with *in vitro* studies or decrease not only the number of individuals needed for a given experiment but also actively seek to reduce the overall stress animals feel throughout said procedures through implementation of less invasive techniques that are still able to provide maximum information regarding the system under study. While the SPME devices fashioned for the above-mentioned *in vivo* SPME studies have been shown to be suitable for sterilization, further investigations are required to assess the effect of sterilization on the extraction performance of different coating materials. A detailed protocol regarding the experimental parameters that should be used to determine intravenous concentrations of drugs and metabolites by application of SPME is available in the literature.[377] In addition to targeted studies, SPME has also been applied for *in vivo*, untargeted blood analyses. In this regard, one of the most attractive features of *in vivo* SPME as a tool in metabolomics is that it integrates sampling, extraction, and metabolism quenching in a single step, thus minimizing the likelihood of samples incurring the type of metabolome alterations associated with traditional procedures.[378,379] For instance, in a comparison between results attained via SPME *in vivo* blood sampling versus those obtained by *ex vivo* SPME, protein precipitation, and ultrafiltration, researchers found that unstable compounds such as β-nicotinamide adenine dinucleotide (β-NAD) were only present in extracts corresponding to *in vivo* SPME.[378] Although further studies are required in order to confirm the stability of different metabolite types extracted *in vivo* on SPME coatings, the results of the abovementioned study support the notion that SPME is capable of capturing an elusive portion of the metabolome via the employment of *in vivo* sampling strategies. Indeed, the extensive possibilities that are made accessible by *in vivo* SPME, such as the capture of intermediate compounds of different biochemical pathways, certainly merit significant consideration, although further studies are needed to validate the full advantages afforded by this technique. For cases where direct extraction from circulating blood is restricted due to a lack of an appropriate sampling interface or trained personnel, TFME format has also been proposed as a tool for the analysis of small sample volumes, i.e., drops of blood. In such an approach, also called extracted blood spot (EBS), a small volume of biofluid is placed on a coated surface for a given period of time to allow for analyte partitioning from the sample onto the extraction phase.[380] As a washing step is conducted after the extraction process, clean extracts are enabled for instrumental analysis. The simplicity of such methodology certainly would facilitate its potential adoption in animal research laboratories or the clinical environment, as it is based on routinely used blood withdraw procedures such as the tail vein puncture in rodents or finger or heel prick in human adults and newborns, respectively. However, the minute amounts of samples used as well the high binding of certain drugs/analytes may lead to poor LOD and LOQ levels when performing solvent desorption for further LC-MS analysis. As means to circumvent sensitivity issues, while taking advantage of the varied benefits of using such an approach, instrumental analysis without chromatographic separation has been proposed. Further discussion regarding the use of EBS together with direct MS analysis will be provided in the Direct Coupling of SPME to MS section.

With reference to tissue determinations, DI-SPME has been applied for *in vivo* targeted and untargeted analysis of several matrixes, such as fish, which was already discussed in the section corresponding to Food Analysis, as well as muscle, lung,

DOI: 10.1021/acs.analchem.7b04502
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liver, and also brain specimens.[381−383] The main advantages offered by SPME in tissue analysis include the viability of tuning the geometry of the device to target specific sampling sites, thus enabling spatial resolution; its low invasiveness in comparison to standard tissue sampling approaches that require biopsy; and the nondestructive nature of the extraction procedure. For instance, the use of 4 mm MM-PAN SPME fibers and LC-MS/MS enabled *in vivo* measurement of changes in the concentrations of selected neurotransmitters, namely, dopamine, serotonin, gamma amino-butyric acid, and glutamic acid, in rats brains after fluoxetine administration. Remarkably, the results obtained by DI-SPME in this study were comparable to those obtained via microdialysis (MD), the technique of choice for *in vivo* monitoring of neurotransmiters.[382] Among the many insights obtained through this study, its findings certainly support the applicability of SPME as a complementary tool to MD; as observed in this work, while SPME facilitates the extraction of nonpolar metabolites such as lipids, MD favors the detection of more polar metabolites. Thus, the concomitant use of these techniques enables monitoring of a wider range of compounds, allowing for a more complete snapshot of a given system under study. It is worth commenting that MD is a well-established method for *in vivo* tissue analysis and for brain studies in particular. However, operation of the MD system requires the use of pumps and connecting lines, a workflow that is unfavorable for potential on-site clinical studies. In this regard, SPME offers a much simpler solution, where the on-site step of the workflow can be limited to the use of an SPME probe for extraction, followed by fiber storage or transportation, procedures which can be performed directly by medical personnel. Other studies involving untargeted analysis via *in vivo* SPME sampling have been carried out to monitor metabolic changes in lung and liver grafts during transplantation in a pig model.[381,383] In this application, researchers were able to observe differentiation among extracts obtained from SPME fibers exposed to organ grafts at various stages of organ preservation throughout the transplantation process. One of the main advantages of this approach includes its feasibility toward the monitoring of organ quality with minimum invasiveness, thus minimizing the risk of compromising the organ through its submission to multiple biopsies at various sampling points. More in-depth studies with a larger number of biological replicates are being conducted to fully demonstrate the potential of SPME for this and other tissue studies. It is worth emphasizing that DI-SPME is currently being used for *in vivo* human trials for the first time. One application employed the use of SPME to monitor the concentration of an anticancer drug during *in vivo* lung perfusion, a novel technique for drug administration. Another ongoing study focuses on the utilization of SPME as a tool to differentiate brain tumor types and the brain cancer tissue boundary. Future human applications are anticipated considering the low invasiveness and simplicity of the procedure.

As abovementioned, TFME is undoubtedly the SPME geometry of choice for *in vitro* studies requiring maximum sensitivity. As described in the Shapes of Support section of this review, biocompatible coatings in TFME format coupled to the high-throughput and automation features offered by the Concept 96 systems have been used in various applications involving the analysis of biofluids such as urine and plasma.[384−386] For instance, TFME blades coated with C18 functionalized silica-based particles were used for extraction from urine of 110 doping compounds corresponding to nine classes of drugs banned by the World Anti-Doping Agency (WADA). Method optimization revealed that 30 min of conditioning, 75 min of extraction, and 60 min of desorption (total time of 2 h and 45 min) were necessary to meet the minimum required performance levels (MRPL) set by WADA.[384] Although the total analysis time needed to achieve MRPL values established by WADA seems considerably long, employment of the high-throughput capabilities of the Concept 96, which enables the concomitant processing of 96 samples, allows for a total analysis time of less than 2 min per sample for the majority of the compounds under study. Following a similar strategy, a workflow for the quantification of 25 doping substances in plasma samples was proposed by employing TFME devices with HLB-PAN coating as extraction devices.[385] The developed approach was shown to facilitate the multiresidue analysis of matrixes with high protein content, since the open-bed configuration of SPME is not vulnerable to clogging, while limitations related to breakthrough volumes are not a matter of concern due to the nonexhaustive extraction nature of SPME. The main drawbacks of this methodology include the relatively long analysis time, which was 2 h and 20 min in total, and the large sample volumes needed for analysis (1 mL of plasma per sample). However, the positive results obtained in terms of absolute matrix effects, with 24 out of 25 compounds having values in the range 100−120%, demonstrated the potential of this workflow toward other applications at conditions that allow for faster turnaround times. A similar approach was followed in the analysis of multiple doping substances in saliva samples via DI-TFME.[387] In this study, both LC and GC amenable TFME were used, with application of DI-TFME for *in vivo* saliva sampling proposed as a means to facilitate on-site analysis as well as the determination of more hydrophobic analytes. As discussed earlier in this review, the use of HLB-PAN coated TFME devices prepared on a new plastic support also provided satisfactory results in the quantitative analysis of 17 drugs with log *P* values ranging from 0.33 to 6.56 in urine, plasma, and whole blood samples.[175] The results of this study demonstrated the suitability of HLB-PAN TFME for efficient sample cleanup in untreated biofluids, as well as the versatility of PAN-based extraction phases toward different geometries and supports. On the basis of recent developments in GC matrix-compatible extraction phases, where an extra layer of PDMS is applied to PDMS-DVB fibers, the use of PAN overcoated SPME devices has been proposed as a strategy to improve SPME device biocompatibility for extractions from complex biofluids such as blood prior to LC analysis.[243,380] However, the much lower recoveries attained for certain compounds with the developed extraction phases have hindered their further application, requiring further optimization of the overcoating procedure. Progress on the evaluation and application of SPME thin-film format for high throughput global metabolomics has also been observed. In recent work, Mousavi et al. evaluated different coating chemistries for extraction of metabolites from *Escherichia coli* bacteria culture, including PS-DVB, hydrophilic−lipophilic balance (HLB), PBA, silica-based ionic liquid, and silica-based reversed phase in thin-film format.[388] With aims to expand metabolome coverage, mixtures of different sorbents were also investigated. Interestingly, a mixture of HLB and PS-DVB particles in a proportion 1:1 yielded the best results in terms of features detected and covered polarity range. Indeed, this approach saw extraction and determination of metabolites with log *P* values spanning from −7 to 15, including amino acids, peptides, nucleotides, carbohydrates, polycarboxylic acids, vitamins, phosphorylated compounds, and lipids. Further details

DOI: 10.1021/acs.analchem.7b04502
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regarding the various applications of this platform to metabolomics studies in bacteria and cell cultures will be provided in the following section. Other interesting applications conducted with TFME in its high-throughput format involve targeted and untargeted analyses of biofluid samples, such as plasma, collected at various time points in different patient groups. For instance, in a recent work, with the aim of evaluating liver and kidney functions of patients recently undergone liver transplantation, pharmacokinetic profiles of tranexamic acid and rocuronium bromide were constructed in plasma samples of recipients of liver transplantation surgery with heart beating or living donors with different cold ischemic times.[389] In addition to tranexamic acid and rocuronium bromide monitoring, the authors performed untargeted analysis of the same samples using HLB coated devices. Despite the small size of the cohort, clustering of samples corresponding to heart beating and living donors in relation to lipid oxidation products and bile acids were observed (Figure 7B).

In-tube SPME, the first fully automated SPME configuration for LC applications, has also been broadly reported as a sample preparation approach in recent studies involving analysis of biological matrixes.[8,18] This methodology has been successfully used for the analysis of various drugs, such as amitriptyline and doxepine, in urine and plasma; for the determination of alkaloids in rat plasma; and for the analysis of hexanal and 2-butanone in blood after *in situ* derivatization, among other interesting applications.[390−392] In addition to targeted studies, in-tube SPME has been also used for metabolic profiling applications. In recent work, Jiang et al. carried out the profiling of *cis*-diol containing nucleosides and ribosylated metabolites in urine samples with the use of a boronate-affinity organic-silica hybrid capillary monolithic column and LC-MS/MS.[229] The authors of this work were able to identify 45 different metabolites belonging to the targeted classes; among them, statistically significant differences were found for four compounds in urine collected from healthy and cancer-afflicted groups. A follow-up study carried out by the same authors demonstrated that employment of a zirconium oxide-silica composite enabled the enhanced extraction of *cis*-diol compounds, increasing the number of *cis*-diol-containing ribosylated compounds detected in urine as compared to the previously described column.[393] The main advantages of in-tube SPME lie in its easy automation as well as its relatively simple preparation and setup steps, factors that enable simple testing of new materials for novel applications. However, applications using in-tube SPME are restricted to investigation in relatively simple matrixes; as direct analysis of complex matrixes with high protein content, such as blood and plasma, are unfeasible due to capillary clogging and the poor sample cleanup afforded by the method. Further discussion regarding the advantages, disadvantages, applicable coating materials, and novel applications of in-tube SPME can be found in recent reviews.[8,18]

As evidenced in the current section, the varied SPME applications in bioanalysis developed to date corroborate the great potential of this technique for routine analysis and novel investigations in the clinical environment and translational research laboratories, thanks to features such as high throughput and low invasiveness. In this context, further exploration involving the direct coupling of this microextraction technology to MS without chromatographic separation foresees the possible development of rapid diagnosis tools for a variety of clinical applications, with such a line of inquiry standing out as a clear future direction of this technology. A variety of possible solutions based on SPME-MS approaches are discussed later in this review.

Cell Studies. SPME, as well as NTD and sorption tubes, have been applied for volatilome analysis of cells, bacteria cultures, and cell-containing samples.[226,394−400] HS-SPME features such as high reproducibility, automation, cost-affordability, and the easy introduction of extracted analytes into the GC with minimum risks of water contamination have encouraged the applicability of such methodology in the analysis of volatile metabolites in cell and bacterial cultures. HS-SPME has been demonstrated to provide sufficient sensitivity to monitor differences between various cell lines, while facilitating the detection of statistically significant compounds as potential biomarkers of disease, its stage/activity, or sensitivity/resistance to given drug. For instance, administration of cisplatin to A549 cell lines showed dose-dependent induction of apoptosis with a subsequent shift in the necrotic phase above a specific drug concentration.[400] In this pharmacometabolomic study, an HS-SPME method employing PDMS/DVS fibers enabled the analysis of three characteristic VOCs corresponding to cell death monitored by viability tests. In addition to drug activity, changes in the metabolite profile of bacterial cultures induced by cinnamaldehyde, a naturally active substance, have also been investigated.[225,396] In an initial approach, experiments were performed via HS-SPME-GC-ion trap MS,[396] while a similar study was carried out subsequently via high throughput DI-SPME and LC-MS (Figure 8A).[225] The results provided by both studies support that a combination of HS and DI SPME approaches is able to provide a comprehensive overview of biochemical pathways where compounds with different physical and chemical properties are involved. It should be noted that these studies employed different SPME fibers in HS and DI analyses, commercial PDMS, DVB/PDMS, Car/PDMS, and Car/PDMS/DVB fibers were used for HS analysis, while lab-made TFME devices (blades) coated with PS-DVB-WAX/HLB were employed in the latter. The studies not only revealed the mechanisms behind the inhibition of *E. coli* growth by cinnamaldehyde, they also showcased one of the most advantageous features of SPME in cell culture studies, the possibility of conducting time-profile analyses without sample consumption. This feature allows not only for cost savings but also reductions in possible variability associated with differences in cultivated cell numbers across various wells/flasks. Indeed, such an advantage is equivalent to that afforded by SPME in animal studies, where the number of animals employed can be significantly reduced along with interindividual variability. In addition to enabling the sampling of the same media multiple times, the high throughout and automation features offered by the Concept 96 proved to be highly convenient for bacteria or cell culture studies. To that end, the same approach used to investigate the effect of cinnamaldehyde on *E. coli* growth was also used to study the effect of clove oil on the same bacteria type.[401] In such work, DI-SPME and LC-MS were employed to monitor metabolic changes in the bacteria media, while HS-SPME-GC × GC-TOF was employed for profiling of volatile metabolites. The results of this study showed that introduction of clove oil in *E. coli* media induced lipid biodegradation, changes in the TCA cycle, as well as alterations in levels of amino acids and enzyme inhibitors. In total, 500 metabolites were identified by LC-MS while 789 components were detected by GC × GC-TOF/MS, with a total of 125 metabolites found to be dysregulated. The orthogonality of the approaches, enabling in-depth insight into the metabolic

DOI: 10.1021/acs.analchem.7b04502
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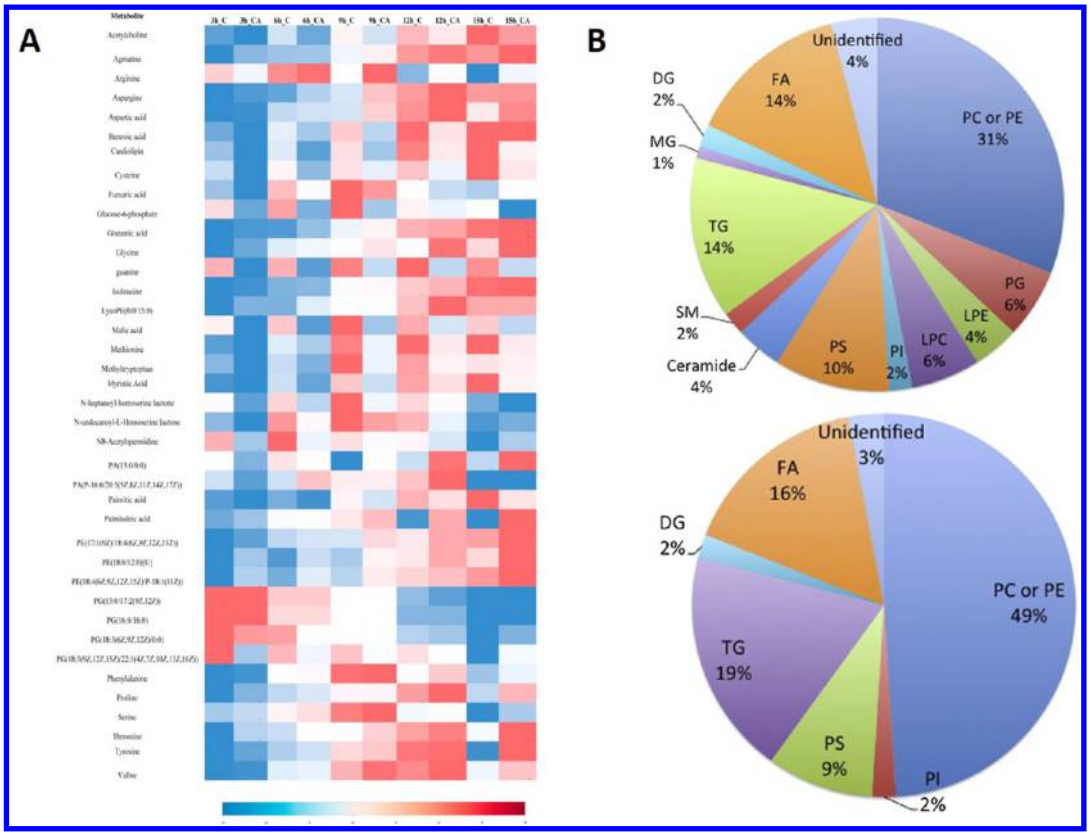

Figure 8. Representative results corresponding to the application of SPME for untargeted analysis of bacteria media (A) and hepatocellular carcinoma cell lines (B). (A) Heat map of statistically significant compounds ($p < 0.001$) extracted via DI-SPME from *E. coli* culture samples control (C) and treated with cinnamaldehyde (CA) [Reproduced from Mousavi, F.; Bojko, B.; Bessonneau, V.; Pawliszyn, J. *J. Proteome Res.* **2016**, *15*, 963−975 (ref 225). Copyright (2016) American Chemical Society]. (B) Comparison of extraction efficiency for identified lipid groups by (upper) SPME and (lower) Bligh & Dyer, covering a broad range of class-specific lipids from human hepatocellular carcinoma cell lines [Reprinted from Birjandi, A. P.; Bojko, B.; Ning, Z.; Figeys, D.; Pawliszyn, J. *J. Chromatogr. B* **2017**, *1043*, 12−19 (ref 228). Copyright (2017) with permission from Elsevier].

pathways of the studied living systems, was a driving force for the development of coatings compatible with both LC and GC applications, as described in the section corresponding to Coatings, which have aided in further simplification and uniformity of sample preparation for such procedures.[53]

Despite the fact that cell line studies performed via SPME are not as common in the literature as analyses of other biological matrixes, the range of application is surprisingly broad, thus indicating the flexibility of the method. For instance, an interesting analytical setup was utilized by Wang et al. to compare the VOC profile of three lung cancer cell lines, lung cancer tissues collected from patients, normal lung tissue, and exhaled breath from the aforementioned patients and controls.[395] The authors were able to identify 23 discriminant VOC compounds with areas under curve (AUC) of receiver operating characteristic (ROC) > 0.60 and $p < 0.01$. In a study of human B-cells, the use of HS-SPME showed that the profile of volatile compounds reflects the genotype of specific alleles of human leukocyte antigen (HLA).[402] Although preliminary in nature, the attained results nonetheless highlight the potential of employing relatively simple analytical methods as completely new approaches in the determination of expression of specific HLA sequences. A similar study reported by Lee et al. employed SPME as a means to monitor VOC profile changes of mesenchymal stromal cells related to adipogenic differentiation. Mesenchymal stromal cells are widely used in stem cell-based therapies, as they rely on the regeneration capacity of these cells to differentiate targeted tissue or organ. One of the most critical issues related to such therapy is maintenance of the stemness of the cells, i.e., their potential to differentiate into a desired cell type after transplantation. For this application, cells obtained from bone marrow stromal cells collected from a healthy donor were characterized for their mesenchymal stromal cell properties. The results showed that seven fatty acid methyl esters (FAMEs) were only detected in adipogenic differentiated mesenchymal stromal cells and not in mesenchymal stromal cells before differentiation. This finding was linked with peroxisome proliferator-activated receptors (PPARs) regulating adipogenesis of mesenchymal stromal cells.

In addition to volatile metabolites profiling, recent reports have also demonstrated the applicability of SPME biocompatible coatings for study of various cell lines. To this end, a human hepatocellular carcinoma (HCC) cell line was used as a model in the first ever documented lipid profiling by SPME.[228] In this study, SPME was used in the format of thin film and high throughput for DI extraction. The results of the SPME analysis were then compared with the Bligh & Dyer (B&D) method, the standard extraction approach for lipid analysis (Figure 8B). The attained results revealed that the signal-to-noise ratios attained for several lipids were comparable, despite the fact that SPME is a nonexhaustive method, while the B&D method extracts lipids exhaustively, allowing for better recoveries. This observation could be explained based on the nonexhaustive extraction provided by SPME that enables a lower background noise. Conversely, the use of organic solvent in the B&D method is well-known to lead to the extraction of a

DOI: 10.1021/acs.analchem.7b04502
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much larger amount of media components; in this sense, the nonselectivity of the method, which results in the introduction of all sample constituents into the LC-MS platform, compromises high recovery and sensitivity as well as the precision of the analysis. The comparative lower precision of the B&D method in this instance has also been attributed to the presence of a matrix effect, which was pronounced for B&D and negligible for SPME. In this regard, the pronounced matrix effect observed for B&D can be mostly attributed to the build-up of phospholipids in the instrument, which are heavily extracted with solvents, while only found in low abundance in SPME extracts. The high abundance of certain lipids in B&D extracts was also noted to affect the detection of lipids present in low quantities, while for SPME, balanced coverage enabled observation of a more diverse lipid population, especially in the range of less hydrophobic species. SPME was also used for monitoring of metabolism of repaglinide, an insulin secretagog induced by the human liver microsomes (HLM) fraction.[224] The main goal of the analysis in this case was to determine the applicability of the high-throughput 96-blade thin-film microextraction (TFME) system coupled with LC−MS/MS for such an assay. To that end, the authors monitored the decline in parent drug concentration and the increase of its two main metabolites. Several coatings were tested for their effectiveness, namely, PS-DVB-PAN, PBA-PAN, mixed-mode-PAN, LC-DIOL-PAN, and C18-PAN, with the latter showing the best results and availability. While the use of microsomes permitted the use of relatively large sample volumes (1 mL), cell line studies are hindered by the limited availability of samples, with maximum volumes used for standard cell line assays ranging around 100 μL. The TFME system was also used to determine the presence of avocatin B in cytosolic and mitochondrial fractions of leukemia OCI-AML2 cells.[403] In the study, avocatin B was found to be a biologically active compound of high potential in acute myeloid leukemia treatment, and its cytotoxicity relied on mitochondrial localization as cells withouth the enzyme that facilitates mitochondria lipid transport (CPT1) were insensitive to avocation B. As means to facilitate the analysis of small sample volumes via SPME, various experimental setups are currently being tested with aims of selecting the most appropriate solution for future protein binding, cytotoxicity, pharmaco- and toxicokinetic studies (unpublished work). Among possible solutions, the use of 1 mm length ultrathin coatings has to date been demonstrated as a useful approach, enabling extractions of target analytes at negligible depletion conditions. The use of such devices would allow for determinations of both free and total concentrations, while also enabling minimum disturbance to system equilibria, a particularly challenging feat to accomplish when handling volumes in the order of 100 μL. Furthermore, the utilization of SPME devices of such dimensions for the discussed applications would allow for multiple samplings from the same sample, which certainly eases time-course based studies involving small volumes of cell lines.

The miniaturization of SPME devices has also enabled analysis at the single cell level.[404] In this study, the tip of an acupuncture needle (120 μm diameter) was electrochemically etched to a tip with an approximate diameter of 5 μm, which was subsequently electrochemically coated with PPy. The small coating size and thickness of <5 μm enabled extraction of quercetin from single cells of *Allium cepa* (red-onion) in less than 2 min under static conditions. The method, however, still requires further modifications, such as the anticipated development of nanoSPME tips, as it currently leads to disturbance of system equilibrium and cannot prevent cell damage incurred from the penetration of the membrane or leakage of intracellular components. As expected, the small extraction phase volume and short extraction time used in this study only allowed for the monitoring of the most abundant compounds in said matrix. However, to some extent, this limitation could be addressed by replacing off-line solvent desorption and LC-MS analysis with the direct coupling of an SPME microprobe with mass spectrometer via one of the available interfaces, i.e., nanoESI or open port probe (OPP), as will be discussed in the section on Perspective on Future Directions. The versatility of SPME formats, its applicability to both targeted and untargeted analyses from the HS or via DI into a sample matrix, its adaptability for extraction at equilibrium or pre-equilibrium conditions, as well as its compatibility with small sample volumes all foresee the incredible potential of this technology for bacteria and/or cell-related investigations. As indicated above, SPME can be easily adopted to the high-throughput format routinely used for a range of *in vitro* assays, as well as used to study the profile of metabolites, including lipids, toward biomarker discovery. Undoubtedly, several applications remain to be tested, with further modifications needed to enable more efficient application of SPME toward cell studies, particularly targeting the extrapolation of the technique to *in vivo* conditions. It cannot be argued that the technology opens new door to such research and should be further explored in combination with modern analytical instrumentation.

PERSPECTIVE ON FUTURE DIRECTIONS

Future Paths for SPME Technology. One of the main goals of microextraction technologies, spurring their ongoing development, is to support implementation of Green Chemistry principles in analytical practice. This translates not only to efforts toward the elimination/reduction of organic solvents but also to the on-site implementation of integrated sampling/sample preparation approaches that afford reductions in the consumption of energy and to the overall cost of analysis, in addition to providing rapid information for decision making.[405,406] In this regard, a recent major enabling advance in SPME was the development of matrix-compatible coatings, as previously discussed in the Coatings section in this review. In addition to allowing for the direct sampling of complex matrixes, this strategy enables "balance coverage" of small organic molecules while eliminating large molecular interferences, thus affording clean extractions. In this sense, the elimination of said interferences has not only allowed for a significant reduction in the fouling of coatings, it has also resulted in more reliable quantifying instrument performance. These cleaner extractions, attained via the free form of compounds present in matrixes, have eliminated contamination of SPME devices, making them more robust not only for lab but also on-site applications. It is expected that more research efforts will be directed toward further improvements to these matrix-compatible coatings. Coated polymeric composite materials have also been demonstrated as a suitable alternative to currently used approaches employed in the attainment of cleaner extractions, as such composites have been shown to mask the limitations of other substrates, such as bleeding, while enhancing the overall performance of coatings (e.g., better thermal conductivity). Matrix-compatible coatings are poised to have significant impact on all major areas of applications where on-site analysis capabilities and high-throughput automated performance are critical. In environmental and forensic applications, a number of practical

DOI: 10.1021/acs.analchem.7b04502
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implementations have already been carried out by many groups, as discussed throughout this review.

In food analysis, it can be envisioned that the introduction of new matrix-compatible coatings for direct analysis of food commodities will promote rapid growth in the number of related developed applications and methods, such as the above-reported, hopefully with the consequent implementation of the technique as a standard method by Regulatory Agencies for screening of pesticides and other contaminants, following the same path as the QuEChERS method. In view of their current availability, as well as fast progress being made in matrix-compatible coating technologies, the benefits that DI-SPME provides over HS-SPME can now open new scenarios for untargeted metabolomics and *in vivo* studies of food commodities for assessments of quality and origin.

As previously discussed in this review, a wide variety of targeted and untargeted approaches to investigations involving complex biological matrixes have been successfully demonstrated for a variety of routine bioapplications and in novel investigations, a trend that is expected to continue as new developments in this area continue to unfold. Undoubtedly, a key determinant factor in the implementation of SPME is the availability of cost-effective coating chemistries suitable for different analytical purposes. For instance, the rewarding results exhibited by HLB-PAN coated devices in the determination of a broad range of compounds demand the commercial availability of such SPME extraction phases. The availability of materials is capable of offering selectivity for targeted analysis, improved affinity for polar compounds, and high reproducibility, all while ensuring biocompatibility, will also aid in the further implementation of SPME toward the analysis of biological systems. In addition to the availability of a variety of coating types, the high-throughput feature offered by SPME plays a crucial role in the future development of this microextraction technology. However, future studies should be oriented toward the achievement of shorter analysis times and higher enrichment factors with minimum sample volumes. In addition, the feasibility of incorporating matrix modification techniques (e.g., addition of organic solvent, use of high extraction temperatures, etc.) in analytical workflows as a means of enhancing free analyte concentrations, increasing extraction recoveries, and normalizing relative matrix effects should be further evaluated for the analysis of biological matrixes via SPME and LC-MS.

In terms of untargeted analysis, SPME opens new paths for investigations of biochemical processes. By enabling *in vivo* (or close to *in vivo*) sampling of complex biological systems, SPME streamlines the metabolism quenching step, thus facilitating the capture of unstable metabolites. Unquestionably, a large number of studies could benefit from the complementary information that this microextraction technology can provide in relation to data obtained via traditional sample preparation methodologies. In addition, as *in vivo* SPME enables nonlethal and/or nondestructive sampling, thus allowing for multiple samplings to be carried out from the same animal or sample, time course-based metabolomics studies as well as the attainment of extracts corresponding to true compositions in living systems including unstable species not seen when using *ex vivo* approaches, are also facilitated through employment of this technology. However, further work is necessary in order to fully demonstrate and validate the performance of SPME in untargeted metabolomics investigations. To this end, future outlooks should involve a thorough comparison of SPME versus traditional sample preparation approaches through applications of both workflows to already studied animal models (e.g., control vs diabetes). Such studies will help elucidate the type of information that SPME is able to provide compared to typical extraction approaches and will support further application of this microextraction tool in the metabolomics field. The suitability of SPME for the extraction of a broad range of metabolites also opens new pathways for SPME-based fast profiling applications. Moreover, on the basis of the capabilities of SPME for lipid extraction, combinations of this microextraction technique with shotgun lipidomics strategies present an opportunity for the development of new platforms aimed at facilitating tissue analysis. Other future directions targeted at the integration of SPME in the study of biological systems involve the use of smaller probes for improved spatial resolution, the coupling of SPME with more sensitive and advanced instrumentation, and the development of novel SPME samplers aimed at facilitating SPME operation by personnel from different fields. Owing to its versatility and simplicity, SPME emerges as a promising technology, with a myriad of possible future applications directed at providing new insights into the processes that define biological systems.

Cell lines studies offer a significant pathway toward the reduction of animal use in research. To this end, SPME shows great potential in facilitating further developments in this line of research due to its flexibility and high throughput, which accommodates the methodology in various multiwell plate formats of routinely used in *in vitro* assays. Although the high-throughput coupling of SPME is currently only commercially available in the 96-fiber/blade systems format, the technology can be easily upgraded to the 384-format or otherwise modified to fit 6-, 12-, 24-, or 48-well plates with appropriate adjustments in extraction phase size. The universality and simplicity of SPME protocols enable the application of similar analytical setups to various *in vitro* models, starting from microsomes or supersomes, via enzyme fractions to different cell models. In contrast to traditional cell assays, this approach offers simultaneous untargeted and targeted analysis capabilities when combined with instrumental platforms such as GC-MS and/or LC-MS. This advantage of SPME enables the attainment of an entire spectrum of information regarding the extracellular biochemistry of small molecules, all within one experiment. Although still in development, a definite future is foreseen for SPME-based cell line studies involving exploration of intracellular changes at the single cell level, especially for applications involving direct coupling to MS, which would afford significant enhancements in sensitivity. Nonetheless, such applications still require modifications and further development, particularly pertaining to sample (cell) handling, as well as needed improvements to the low sensitivity currently attained as a consequence of the miniaturization of the device and the small sample volumes employed in such applications. Another very important aspect of using SPME for cell line studies is related to translational medicine, namely, the adaptation of the *in vitro* SPME protocol to *in vivo* studies. Such an approach would eliminate the variability factor related to the use of different standard analytical methods for different matrixes. In other words, SPME may simplify analytical workflows in translational research laboratories and minimize the expenses related to maintaining different equipment and materials.

As demonstrated throughout this review, SPME does not represent a specific method of analysis; rather, SPME should be considered an analysis platform that is based on a variety of

DOI: 10.1021/acs.analchem.7b04502
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Table 3. Representative SPME to MS Couplings in Different Fields of Study and Their Experimental Configurations

ionization mechanism	application	SPME geometry and coating	desorption mechanism	instrumentation	year of introduction and reference(s)
ESI-based technologies	determination of cocaine and diazepam in urine and plasma; voriconazole in plasma and plasma spots, amitriptyline in blood spots, 9 pharmaceuticals in wastewater samples; multiple controlled substances by WADA in plasma and urine	coated blade spray, HLB-PAN and C_{18}-PAN	solvent, substrate-spray source	triple quadrupole	2014[222,404,407,430,431]
	perfluorinated compounds, fluoroquinolone and macrolide antibiotics in water samples	coated wooden-tip probe, customized polymeric coating	solvent, substrate-spray source	triple quadrupole	2014[418,432]
	determination of metoprolol, propranolol in whole blood	coated fiber, C_{18}-SCX-PAN	solvent, modified ESI source	triple quadrupole	2015[433]
	determination of salbutamol, codeine, methadone, and oxycodone in urine, as well as amitriptyline and imatinib in whole blood	coated fiber, C_{18}-SCX-PAN and miniature PPY coated tips	solvent, nano-ESI source	triple quadrupole	2016[152,404]
	imprinting of materials such leafs or fruits on surface	coated flat surface, nylon-6 nanofiber	DESI	linear quadrupole ion trap mass spectrometer	2016[434]
	determination of clenbuterol, fentanyl and buprenorphine in urine; opioid isomers codeine and hydrocodone in plasma	coated fiber, C_{18}-SCX-PAN	solvent, open port probe	triple quadrupole with multistage fragmentation and differential mobility spectrometry	2017[419,428]
	benzodiazepines in plasma	coated fiber, C_{18}-PAN	solvent, microfluidic capillary gap sampler	triple quadrupole	2017[435]
plasma-based technologies	determination of triazine herbicides in environmental waters and orange juice	in-tube SPME, (poly(MAA-EDMA-SWNT)) monolith	solvent, DART	triple quadrupole	2014[436]
	determination of cocaine and diazepam in urine and plasma; multiple pesticides in food matrices and drugs of abuse in oral fluids	coated mesh, HLB-PAN and C_{18}-PAN	thermal, DART	triple quadrupole, Orbitrap and single quadrupole	2014[177,178,437]
	determination of triazine herbicides in environmental waters and orange juice	glass capillary, multiwall carbon nanotube (MWNT) incorporated monolith	laser, DART	time of flight	2015[438]
	determination of phosphoric acid esters in aqueous matrixes	stir bar, PDMS	thermal, DART	Orbitrap	2015[202]
	determination of 2-isobutyl-3-methoxypyrazine, linalool, 3-isobutyl-2-methoxypyrazine and β-damascenone in grape volatiles	coated mesh, PDMS, PDMS/DVB, DVB/Car/PSMS, Car-PDMS	thermal, DART	Orbitrap	2016[421,439]
	determination of pesticides in surface water samples	coated fiber, PDMS/DVB	thermal, DBDI	Orbitrap	2016[420]
	determination of protonated dimethyl methylphosphonate, diethyl ethylphosphonate and pinacolyl methylphosphonic acid in water and urine samples	coated fiber, zeolitic microporous material	thermal, LTP	linear quadrupole ion trap mass spectrometer	2016[440]

DOI: 10.1021/acs.analchem.7b04502
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different sample preparation strategies that have in common SPME principles of extraction. In this sense, SPME is a chameleon technology capable of adapting limitless geometries and extraction phase chemistries based on the needs of a specific application to achieve optimum conditions. For instance, supports made of any material or shape can be coated by appropriate extraction phases, enabling creative new approaches to sampling and sample preparation. New opportunities for SPME applications have also been enabled from the design of optimized "shapes" of supports, as discussed throughout this review, thus resulting in improvements in the kinetics of extraction, with consideration also given to convenience of use in practice. In this regard, SPME implementations are only limited to the imagination of the researcher. In addition, SPME is able to adopt to the emerging needs of the technological revolution, as clearly demonstrated when considering its potential in direct introduction to rapidly developing mass spectrometry instrumentation. To this end, currently introduced advancements in this field have resulted in very powerful hyphenations, as summarized below in detail, which are foreseen to become future standard approaches for on-site analysis.

Direct Coupling of SPME to MS. Among the many benefits imparted by this combination of technologies, the direct coupling of SPME to MS analyzers eliminates the separation step and, as a result, dramatically reduces analytical turnaround times. Owing to the intrinsic features of SPME, such as sample cleanup and analyte molar fraction enrichment, lower matrix-suppression effects can be attained, an advantage that is highly beneficial for detection of trace compounds in complex matrixes when a chromatographic separation is not used. In addition, since the dilution step inherent to SPME-LC applications is removed from the workflow, higher sensitivity can be attained as well.[404,407] The direct coupling of SPME-based devices to MS dates back more than 20 years and is a continuously growing field. While advances in this field have been often interrupted by long pauses over the years, great breakthroughs have been made in the last 5 years, driven in part by the advancing state of the art in mass spectrometry as well as outstanding advances in SPME coating technology.[20,178,408]

SPME-MS technologies can be classified according to either (a) the ionization strategy employed, (b) the analyte desorption strategy used, or (c) the type of interfacing utilized. In the first scenario, inductively coupled plasma (ICP)MS,[409,410] electron impact (EI)-MS,[411−415] and atmospheric pressure ionization (API)-MS, available in either electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) formats, remain the most common approaches to SPME-MS coupling.[416,417] In the second case, pre-enriched analytes can be released from the SPME coating via either liquid,[152,418,419] thermal,[415,420,421] or laser[422−425] desorption. Finally, depending on the degree of "ambience" required for a specific application,[426] the coupling of SPME to stand-alone mass spectrometers (SAMS)[427] can be performed by either (a) desorbing analytes on a desorption chamber,[420,428] (b) interfacing the SPME device between an ambient ionization source and the MS system,[177,429] or (c) without any additional device/instrument other than the SPME device itself (e.g., SPME as substrate-electrospray ionization system).[407,418,430] Among these categories, the latter is perhaps the most comprehensive and, as such, was selected in this review to provide a detailed discussion regarding these approaches. Table 3 summarizes the most recent applications involving the use of diverse SPME to MS coupling approaches.

SPME-SAMS via Desorption Chamber. The first SPME-SAMS technology based on liquid desorption on a chamber was disclosed in 1997 by Möder et al.[441] In this approach, an SPME fiber, used for extraction of acyl carnitines from urine, was statically desorbed on a sealed, custom-made chamber connected to a six-port-valve. Subsequently, by switching the valve, the mechanically pumped solvent carried the desorbed analytes toward the ionization source.[442] Since this first publication, several groups have utilized the concept of liquid desorption on a chamber, followed by ionization of analytes on either ESI or APCI commercial sources, as a mean to provide rapid quantitative analysis.[417,433,443,444] Recently, the use of a nonsealed interface that allows for the rapid transfer of analytes extracted by SPME devices to the ionization source was reported in the literature.[419,428] This interface, known as the Open Port Sampling Interface (OPSI) or Open Port Probe (OPP), was developed by Van Berkel and Kertez at Oak Ridge National Laboratory (ORNL)[445,446] to circumvent the use of high-pressure pumps and injection valves and, as a result, prevent complications typical of most LC applications, such as leaking and carryover. As its name suggests, the OPP is an interface exposed to ambient air, with of a continuous flowing operation mode and a defined "sampling area", known as the "desorption dome" (Figure 9), where SPME fibers can be effortlessly inserted for elution of enriched analytes.[428] This interface, made of two coaxial tubes with well-defined dimensions,[446] can be built on top of the ionization source, enabling the transport of desorbed analytes toward the ionization source through the inner tube by the aspiration force of the nebulizing gas. Although the OPSI was originally intended as a tool for the analysis of multiple types of unprocessed complex samples without sample preparation (e.g., marker inks and vegetable oils),[446] Gómez-Ríos et al. demonstrated that employment of OPSI in combination with biocompatible SPME-fibers was suitable for the quantitation of buprenorphine, clenbuterol, and fentanyl present at low nanogram-per-milliliter levels in urine samples, with processing times of less than 2 min.[428] Furthermore, application of online separation technology, such as differential mobility spectrometry (DMS),[362] has been shown to enable enough selectivity enhancement so as to allow for the quantification of two opioid isomers in human plasma (i.e., codeine and hydrocodone), thus making SPME-OPP a much faster alternative to classical LC-MS/MS based approaches. Indeed, when compared to other SPME direct couplings to MS developed to date,[152,420,433] one of the greatest advantages of the OPP is that it requires no modifications to the conventional ionization source setup employed by most analytical laboratories, enabling the switch between OPP-MS and LC-MS setups to occur in just a few seconds.

The first reported coupling of SPME to a SAMS was performed via thermal desorption in 1996.[447,448] In this approach, SPME devices are desorbed on the injection port of the GC system, where analytes are subsequently moved toward the MS system with the use of carrier gas. Instead of the classical chromatographic process, where separation of analytes occurs on a long coated column, a short and noncoated capillary is used to link the injection port with the MS analyzer.[411,412,449−452] Although this configuration has been mainly used for rapid qualitative analysis (e.g., profiling),[411] Boyacı et al. recently reported its applicability toward quantitative analysis of fluorinated benzoic acids in seawater.[415]

DOI: 10.1021/acs.analchem.7b04502
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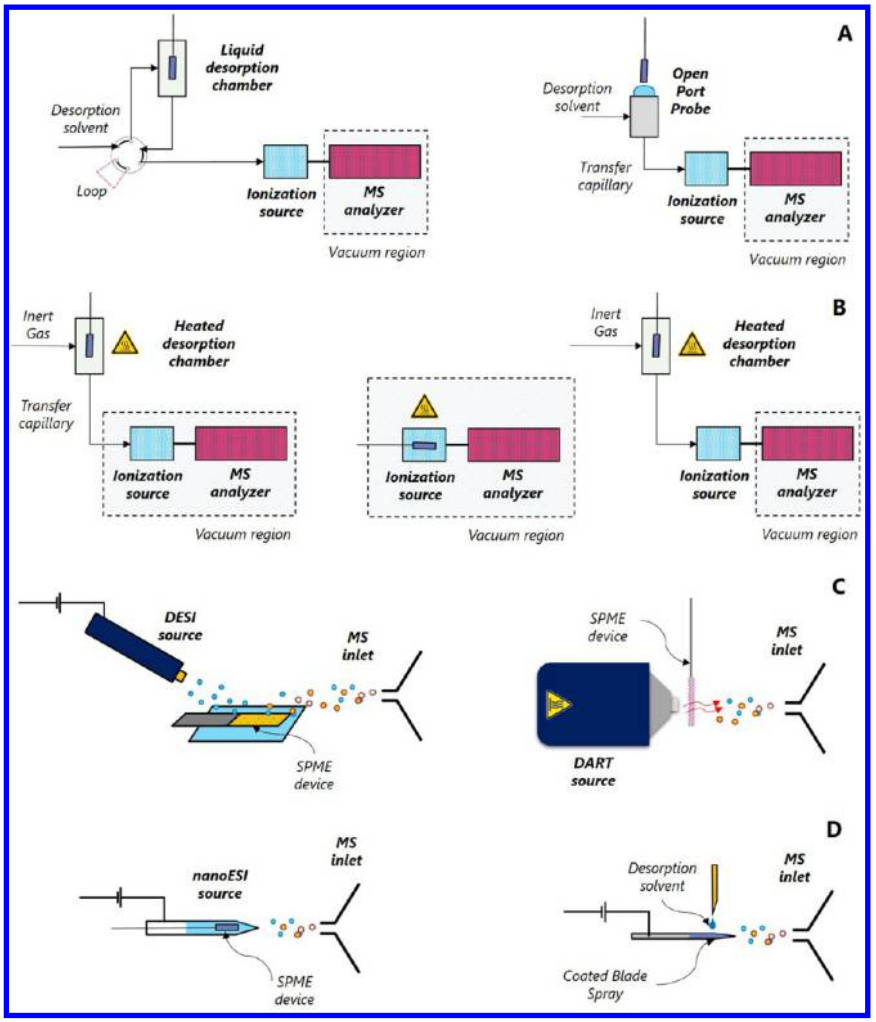

Figure 9. Schematic diagrams of some of the most relevant SPME-MS technologies suitable for analysis of biofluids. (A) SPME-SAMS technologies via liquid desorption, closed chamber (left) and open chamber (right); (B) SPME-SAMS technologies via thermal desorption, closed chamber and vacuum ionization (left), thermal desorption and ionization under vacuum conditions (center), and open chamber and ionization under ambient conditions (right); (C) SPME-SAMS technologies via AMS, DESI (left) and DART (right); (D) SPME-SAMS technologies via SPME-nanoESI (left) and substrate spray device (right).

Aiming to prevent any potential sources of confusion for the reader, it should be clarified at this junction that another Open Probe interface, distinct from the abovementioned, and which can also be used to couple SPME devices to SAMS was developed by Amirav's research group back in 1997.[449] Distinct from the OPSI described above, this interface is based on the thermal desorption of analytes on a custom-made chamber (i.e., without GC-injection port) and allows for rapid coupling to electron ionization mass spectrometry.[450] A second arrangement of SPME-SAMS via thermal desorption consists of circumventing the transfer capillary by performing the desorption of the SPME device directly at the ionization chamber of the mass spectrometer.[413,414,453] While this approach allows for higher sensitivity, its configuration cannot be easily set up without affecting the instrument vacuum. Further, the technique cannot be easily automated nor does it allow for easily reproducible results. It should be noted that there is an additional SPME-SAMS strategy via thermal desorption that does not require gas chromatography hardware. In addition, the ionization step, unlike the two previous strategies, occurs under ambient conditions (i.e., outside the instrument). As shown in Figure 9, thermal desorption takes place on a custom-made chamber, where analytes are driven toward the ionization chamber prior to MS analysis. Analyte ionization can be performed either by ICP,[454] Dielectric Barrier Desorption Ionization (DBDI),[420] or Low Temperature Plasma (LTP),[440,455] among others.[456,457] In the context of these developments, the work by Mirabelli et al. on SPME-DBDI stands out as perhaps the most relevant among them: using SPME fibers traditionally used in GC applications, this coupling offers limits of detection (LOD) in the low picogram-per-milliliter levels for pesticides present in water samples.[420,458]

One of the greatest advantages of SPME-SAMS via a desorption chamber is that it allows for the introduction of all analytes into the MS in a single band or peak (Figure 10).[427,442] This feature affords better signal-to-noise ratios in comparison to substrate-spray methods and, as a result, outstanding sensitivity.[420] Yet, four factors should be kept in mind when selecting SAMS technologies for direct coupling. First of all, the technology should allow for rapid desorption and efficient transmission of the ionized molecules toward the mass spectrometer.[458] Second, depending on the composition of the materials chosen for construction of the device, including materials for the desorption chamber, transfer tubes, and

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

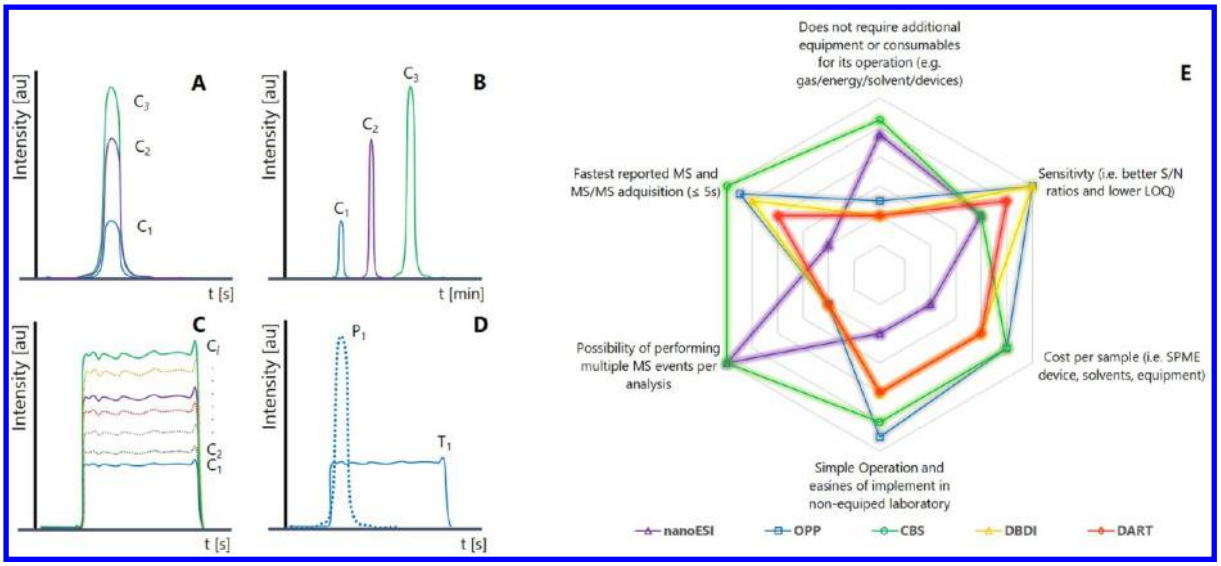

Figure 10. Schematic representation of instrumental signals obtained via SPME-mass spectrometry according to the analytical workflow. (A) Single peak signal obtained via SPME-SAMS desorption in a chamber approach (e.g., OPP and DBDI); (B) multiple peaks obtained via SPME and chromatographic separation; (C) transient signal obtained by employment of the direct-SPME-to-SAMS approach, without a liquid or gas flow pushing the analytes toward the MS inlet (e.g., CBS and nano-ESI); and (D) comparison between transient signal (T1) obtained via SPME-direct-to-SAMS and peak signal (P1) obtained via SPME-SAMS desorption in a chamber approach. (E) Comparison between most relevant SPME-MS technologies developed to date. Letters C_1 to C_i in panels A–C represent different compounds extracted from the same sample.

capillaries that move the analytes toward the MS system, it is possible that analyte carryover may occur as a result of nonspecific attachments. Therefore, if analytes are not efficiently desorbed/transferred, the analyst should wait until the entire system is purged, either by the desorption solvent or the carrier gas, before a second SPME device is coupled to the MS system.[420] Undoubtedly, such an issue might lead to a dramatic reduction in analytical throughput. This problem can be overcome with the use of silanized materials, which are also used in GC and LC to similar effect. The third factor, on the other hand, relies on the inherent ionization weaknesses of each technology.[313,428,458,459] Given that some technologies might be intrinsically unable to ionize certain compounds, this factor must be kept in mind with respect to technique selection. In this line, a fourth factor to consider involves the versatility (i.e., capability to rapidly interchange between ESI or APCI modes) and the simplicity of setup (i.e., rapid installation and operation with minimal modifications to the system) of a given technology. On the basis of the last factor, SPME-OPP certainly stands out as one of the SPME-SAMS technologies with the greatest potential for further development in the upcoming years.

SPME-SAMS via AMS Technologies. The term ambient mass spectrometry (AMS), or ambient ionization mass spectrometry, describes a family of techniques that allow for the generation of ions under ambient conditions from ordinary samples in their native environment.[460,461] Hence, most AMS technologies enable measurement of a given compound(s) in real time, and in proximity to the system under study (e.g., *in vivo* or *in situ* analysis).[462–464] As recently reviewed by Venter et al. and Trimpin et al., over the past decade, more than 40 ambient ionization methods have been introduced for analysis of complex matrixes.[426,465] Given that most AMS approaches seek to record mass spectra with minimal or no sample preparation/analyte preconcentration,[466] the linear dynamic range (e.g., diminished sensitivity by ion suppression[408]) as well as the selectivity of such methods are likely to be sacrificed. Therefore, modifications in the experimental workflow, such as addition of an efficient enrichment step,[437,467,468] are often needed in order to obtain better analyte quantitation. Given the multiple advantages already mentioned and the easiness of its coupling, SPME has aided well-known AMS technologies, such as direct analysis in real time (DART) and desorption electrospray ionization (DESI), in reaching required limits of quantitation.[176–178,380,421,436,439,469]

Undeniably, DESI is one the most successful ambient ionization techniques developed to date.[426,460] DESI's advantage lies in its capability to scrutinize analytes on surfaces, with its high-throughput imaging-MS capabilities being one of its major attractions.[470–472] As suggested by its name, in DESI, analytes present on a given surface are initially desorbed/swept and subsequently ionized.[460] Likewise, DESI is suitable to perform the desorption/ionization of analytes previously concentrated on SPME devices (see Figure 10). Accordingly, the first SPME-DESI applications were disclosed only a few years following the initial publications by Cooks and co-workers that introduced the DESI-MS platform.[473–475] Expectedly, authors reported that SPME fibers greatly improved the quantitation capabilities of DESI toward the analysis of anabolic steroids spiked in raw urine[475] or drugs of abuse (DoA) in real urine samples.[429] In addition, data showed good agreement between the results obtained by DESI and those reported using traditional confirmation methods (i.e., LC-MS/MS and GC-MS protocols).[429] In recent times, Strittmatter et al. reported for the first time the direct coupling of blade geometry to DESI-MS.[469] In this study, devices coated with C_{18} and a strong cation exchanger were used for both targeted and untargeted determinations of pharmaceuticals and personal-care product components in wastewater samples. One of the greatest advantages of the blade-DESI-MS coupling entails the possibility of easily merging two steps of the analytical process, namely, extraction/preconcentration and desorption/ionization, in an automated fashion.[469] In addition, one could foresee in the near future a combination of SPME fibers and DESI-MS/MS for the

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302–360

determination of the spatial distribution of targeted analytes in living samples such as tissues.[462] Likewise, flat SPME devices can be used to perform extraction of compounds present on tissue slides/smears and subsequently "image" the physical distribution of those analytes in a given sample. For instance, Hemalatha et al. recently explored the use of electrospun nanofiber mats made of nylon-6 for rapid imaging of natural compounds present on plant leaf via DESI-MS.[434] Unlike traditional DESI, where imaging is performed directly from a thin tissue attached on a glass slide, molecules present in plant leafs were "imprinted" on the coated substrate and subsequently desorbed/ionized by DESI. While the development of new SPME-DESI applications has been pursued vigorously, fundamental studies are still needed in order to fully understand the desorption/ionization process from particle coatings used on SPME devices as well as to determine ideal experimental conditions such as desorption solvent flow,[471] sprayer position,[476] and coating thickness.

Around the same period that DESI was developed, Cody and collaborators invented DART, an atmospheric pressure chemical ionization (APCI)-based ambient ionization technique.[477] In applications that couple SPME to DART, analytes are first thermally desorbed from the coating surface by a heated gas and subsequently ionized by excited-state species created in the atmosphere proximal to the coating surface.[437,439,478−480] Initial experiments to couple SPME fibers to DART-TOF-MS by Cajka et al. have revealed SPME as a promising tool for determination of chemical profiles that allow for rapid authentication of food commodities.[481] Because of the large flow of heated gas (~3 L/min), necessary precautions need to be taken to secure SPME fibers during exposure to the DART source so as to avoid severe fiber swinging and, consequently, irreproducible desorption/ionization of extracted analytes.[479,480] Recently, Wang et al. reported the coupling of IT-SPME with DART for the determination of trace pesticides in liquid food matrixes.[408] In spite of the great sensitivity attained by this method, the proposed system was very intricate, while also requiring solvent assistance to move analytes from the coating for ionization by the DART stream. Likewise, due to the inherent design of the employed IT-SPME device, samples were required to undergo centrifugation and filtration prior to extraction so as to prevent clogging of the device with fibers or particulates from the matrix. Concomitantly, the first combinations of thin-film SPME with DART-MS/MS were reported for determinations of cocaine and diazepam in urine and whole blood, respectively.[176,380] Essentially, the employed device consisted of a stainless steel mesh coated with a matrix-compatible coating. The idea behind this work was to emulate the transmission mode (TM) configuration reported by the Fernandez group.[482,483] Yet, while the device had the extraction/enrichment features of SPME, the methodology used during the coating process (i.e., brush painting) covered not only the strands but also the mesh openings.[176] Aiming to improve ion transmission, tiny, randomly selected holes were placed on the coated mesh to allow the gas stream to flow through it. In a following work, Gómez-Ríos redesigned the SPME-TM[437] to improve its performance. One distinctive characteristic of the new device is that the mesh is exclusively coated on the strands with a thin-layer of particles (diameter $\leq$ 20 μm).[177,178] Therefore, the stream of gas, consisted of metastable helium atoms, easily flows through the mesh, and efficient desorption and ion transmission can be attained.[439,484] The use of a thinner coating allowed for attainment of faster extraction/enrichment, rapid desorption, and minimal carryover. Although the SPME-TM device was initially developed for the determination of target compounds in biological fluids,[437] Gómez-Ríos et al. also demonstrated its suitability toward the quantitation of pesticides in environmental waters and liquid food samples. The application of SPME-TM (also known as SPME-mesh or SPMESH) was also demonstrated for rapid molecular profiling of milk samples from diverse farming origins via a portable MS system (Waters QDA).[177] Recently, Jastrzembski et al. showed the suitability of the PDMS and PDMS-DVB coated SPME meshes toward the quantitative analysis of grape volatiles (e.g., linalool and 2-isobutyl-3-methoxypyrazine).[421,439] Unlike the original coated mesh device that was envisioned to extract analytes via direct-immersion, the SPMESH developed by Sack's group extracts compounds present on the HS of the vial containing the sample.[421] In this context, the employment of more elaborate coatings, such as PDMS-DVB, allowed for the attainment of better analyte recoveries as well as in the reduced loss of volatiles during the transportation of the mesh to the DART source.[421] A similar approach was also described by Li et al.[485] for the rapid sampling and characterization of smokeless powders of forensic interest via the use of a mesh coated with carbonaceous particles.

SPME-SAMS via SPME Direct-to-MS. Unlike other approaches, direct SPME-to-MS technologies do not require intricate equipment to interface to the MS system. These technologies can be separated into two groups: those using nanoelectrospray (nanoESI) emitters[486] and those operating as substrate spray devices.[487] SPME-nanoESI-MS, first explored by Walles et al.,[486] has been assessed for its qualitative and quantitation capabilities in several publications to date.[152,164,404,488,489] The main goal behind the interfacing of SPME with MS via nanoESI is to desorb devices on a chamber with very small volumes ($V_{des} \leq 10$ μL) so as to attain the best enrichment factor (i.e., highest volume of extraction/volume of desorption) and fully utilize the molar enrichment factor offered by SPME.[152,404] Furthermore, nanoESI not only yields higher ionization efficiency when compared to ESI, it also allows for longer electrospray events that permit a far greater number of MS experiments. For instance, a single nanoESI emitter could be used for targeted analysis (MS^n), high-resolution MS experiments (HRMS and HRMS/MS), as well as for its interface with other online technologies such as ion mobility (IMS).[490,491] However, because of the inner diameter of the emitters (diameter $\leq$ 1000 μm), nanoESI technologies are suitable only for SPME devices with small diameters (diameter $\leq$ 500 μm). Recently, Pawliszyn and collaborators have explored the use of nanoESI as a mean to improve the quantitation capabilities offered by commercial BioSPME fibers as well as miniature devices manufactured in-house.[404] Succinctly, when employed in tandem with nanoESI, SPME is capable of reaching subpart per billion LOQs, even when small sample volumes ($\leq$20 μL) and short extraction times ($\leq$2 min) are used.

Substrate spray technologies based on SPME devices were described prior to the invention of AMS (~1999).[492] Indeed, Prof. Shiea and his group of collaborators were the first to report the use of this technology; by spraying directly from wetted SPME fibers, researchers could detected subppb levels of Triton X-100 in aqueous samples. Surprisingly, after this initial breakthrough, almost 15 years elapsed without major advances in these technologies, until 2014, when novel technologies such as surface coated wooden-tip ESI,[418,432] coated-membrane/paper spray,[493−496] and coated blade spray

DOI: 10.1021/acs.analchem.7b04502
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(CBS)[222,404,407,430,431] were disclosed. Essentially, this group of technologies integrates sample preparation and sample introduction into the MS system in a single device. Thus, such technologies not only simplify the analytical workflow, they also decrease the cost per analysis. Given the material used for its construction (i.e., stainless steel), as well as the geometrical characteristics of the substrate (i.e., ∼350 μm flat sheet, sword-like shape), CBS would appear to be not only the best substrate spray strategy developed to date but also a disrupting technology that may shift the paradigm of direct sample introduction to MS. For instance, Tascon et al. recently developed a CBS-high throughput method for determination of 18 doping compounds in plasma and urine samples using HLB coated blades.[430] This protocol enables total analysis times under 1 min per sample, including sample preparation and MS-time and median LOQs under 1 nanogram per mL for all compounds in both matrixes. Likewise, this methodology can also be employed toward the analysis of drugs that exhibit a narrow therapeutic range, such as voriconazole or tacrolimus, in biofluids.[431] Furthermore, this group of authors also demonstrated the versatility of this technology toward the analysis of target compounds in either small sample volumes, such as biofluid droplets, or large environmental samples, such as wastewater.[222,404]

Comparison of Different SPME-MS Strategies. Most of the SPME to SAMS approaches developed in the last 5 years have been shown to be rapid, simple to operate, deployable, cost-effective, and able to provide results close to real-time, while causing negligible instrument contamination, thus guaranteeing its reliable and long-term operation. In addition to providing biocompatibility and adequate sensitivity, most of the devices herein discussed can be arranged with automated systems to provide high-throughput determinations (i.e., ≥96 samples simultaneously). Furthermore, workflows suitable either for analysis of semisolid samples, such as biological tissues, or liquid matrixes, such as biofluids, can be developed for use of the presented technology. With respect to the analysis of aqueous matrixes, methodologies developed to date afford sampling of volumes that range from microdroplet size ($V \leq 20$ μL) to hundreds of milliliters. Such advances are positioned to have an immediate impact on the speed, precision, and efficiency of biological investigations in drug development and point-of-care (POC) diagnosis. Thus, the strategies herein disclosed can be essentially applied to any field that requires robust, inexpensive, sensitive, and rapid workflows such as military, clinical, toxicological, environmental, food, doping, and forensic sciences.

As shown in Figure 10, CBS[407] stands as one of the most comprehensive SPME-MS technologies introduced to date due to its well-defined benefits over other SPME-MS couplings. Some of these benefits include no gas or heating requirements for the desorption/ionization step,[420,437] low solvent consumption per analysis (≤15 μL),[433] no fluidic requirements (i.e., pumps, valves, syringes or tubes),[428] no need for a desorption chamber,[152,433,444] no need for a sampling vessel when analyzing small sample volumes,[152,433,444] and no requisite of a pumping mechanism during the sample preparation process.[436,444,497] In addition, CBS can be coated with different extractive materials on each side, thus offering numberless experimental opportunities not afforded by other SPME interfaces.[164,436,444,488] For instance, CBS offers introduction of more than one replicate at a time in the MS instrument, simply by independently spraying each side of the sampling device. Likewise, a derivatization reaction could be carried out on only one side of the blade, thus enhancing the selectivity and sensitivity of the method for a specific group of analytes, while the other size can be employed for an untargeted analysis of the system under investigation. Furthermore, in comparison to DBDI or OPP, CBS is capable of quantifying more compounds in a single analysis, since the area under the curve that is used for quantitation lacks the shape of a Gaussian peak, which is limited in width,[411,415,420,428,444] while the electrospray event can be extended with the use of a continuous solvent supply (i.e., analyte is introduced at a given spray rate). The extended electrospray event also allows for multiple MS experiments (i.e., MS/MS, MRM,[3] DMS/IMS, HRMS) to be carried out with a single device. However, it is fair to say that technologies that introduce all extracted analytes into the mass spectrometer within a narrow window of time (i.e., peak or band) allow for higher sensitivity (i.e., higher signal-to-noise ratio, S/N). Two examples of such technologies include SPME-OPP[428] and SPME-DBDI.[420] Unfortunately, sensitivity is attained at the expense of the total number of compounds that can be analyzed, especially when using tandem mass spectrometry, as the number of analyzed compounds is dependent on the amount of transitions chosen per compound (i.e., single reaction monitoring, SRM) and the dwell time selected for each transition. CBS is able to address this limitation by offering an additional feature that enables faster analysis times in comparison to DBDI or OPP. As shown by Tascon et al., spraying times as short as 3 s (or shorter) can be performed for small sets of analytes due to the good spray stability offered by CBS. Essentially, the total analysis time required for a given CBS application hinges on the total number of analytes being targeted for investigation. For example, for a small set of compounds (≤10), CBS can collect an adequate number of data points in 1−2 s when a dwell time of 25 ms is used. Indeed, it would be difficult for technologies that depend on fluidic systems to outperform CBS's speed of analysis while maintaining the low-cost per analysis. Unquestionably, the greatest advantage offered by CBS is that the blade acts as both the extraction device and the ionization source. In summary, among all the technologies herein discussed, CBS is perhaps the SPME-MS approach with the highest chance of shifting the paradigm of direct sample introduction to MS for *ex vivo* applications.

Great advances with respect to the development and application of diverse SPME-MS technologies have been presented in this review. However, because of the novelty of these technologies, several factors still require further investigation and optimization. For instance, the SPME-TM devices herein described were strictly focused on the use of stainless steel meshes. Although the performance of the stainless steel SPME-TM was outstanding for DI analysis, employment of this technology for *in vivo* applications (e.g., road testing) would require the use of biocompatible molded/extruded polymers,[175] biocompatible 3D printed materials,[498] or other alternative substrates.[499] Furthermore, the SPME-TM device herein discussed for DI applications was manufactured by welding a mesh spot on a metal support blade.[437] However, state-of-the-art manufacturing technologies, such as the one employed for the production of CBS (i.e., photochemical etching),[430] can be used for preparation of individual self-supported meshes. Furthermore, high-throughput mesh arrangements, similar to the ones used for liquid chromatography,[385] can be constructed to enhance the manufacturing speed of these devices. In addition, employment of the 96-mesh on a single holder would allow for significant reductions in total analysis time

DOI: 10.1021/acs.analchem.7b04502
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per sample. Undeniably, further work on SPME-TM will also be directed toward the use of novel coating chemistries that utilize smaller particle sizes, and innovative mesh designs that allow for improved ion transmission.[500] Yet, the development of novel geometries and coating characteristics will necessitate further investigations of the desorption and ionization fundamentals related to such devices.[501] For instance, there is need for a deeper understanding of the physical and physicochemical parameters (e.g., proton affinity, Henry's constant, thermal conductivity of the substrate, polymeric phase chemistry affinity, particle size, porosity) that govern instrumental sensitivity. Undeniably, the employment of modeling tools, such as COMSOL, would be quite useful in the optimization of such parameters.[40] Certainly, the availability of such information would enable the tuning of devices to favor the highest possible instrumental response.

With respect to SPME-nanoESI, results reported to date have indicated that further work is needed in relation to the wettability and smoothness of the tested commercial coatings.[152] Such developments would help prevent the formation of droplets inside emitters, which would in turn enable employment of longer electrospray events, further facilitating the employment of this technique toward diverse MS experiments.[152] In regards to the commercial applicability of this technique, the total cost of emitters needs to be reduced in order for employment of this technology to become feasible in commercial applications. To that extent, the implementation of high-throughput analysis that utilizes commercially available automatized nanoESI systems might aid not only in enhancing the speed of analysis but also contribute toward an overall decrease in the total cost per sample.[502,503] Although all related studies to date have focused on targeted studies, employment of nanoESI will fundamentally allow for the attainment of diverse information regarding the system under investigation. Therefore, it is anticipated that in a foreseeable future, combinations of SPME-nanoESI with MS/MS, HRMS, and IMS-MS will facilitate the attainment of maximum amounts of information gathered from a single sample/fiber/emitter.

Certainly, the SPME-OPP results herein presented are just a foreword for a technology with a bright future. As matter of fact, ongoing work is focused on the optimization of desorption conditions (e.g., open chamber dimensions, evaluation of dynamic versus static desorption, effect of pump-flow and capillary inertness on band-broadening) and features of the SPME device (e.g., geometry, dimensions, coating thickness, and coating chemistry). As previously discussed, owing to the inherent operational mechanism of the OPP (i.e., analytes are introduced into the MS system as a peak), this technology shows great potential of becoming one of the most sensitive SPME couplings available to date once all features listed above have been optimized. It is clear, at least for the authors of this review, that SPME-OPP has already found a niche in the implementation of SPME for rapid diagnosis at the surgery room, the clinical setting, or any application that requires the use of small SPME devices while guaranteeing adequate sensitivity (e.g., *in vivo* sampling from brain).[382]

Undeniably, CBS is a technology that has great potential to replace existing direct-to-MS technologies and online SPE-MS approaches for the analysis of complex matrixes. Future work on CBS should be directed toward improving the selectivity of the method, either by implementing on-coating derivatization approaches,[220] through the use of smart materials as coatings (e.g., molecular imprinted polymers or metal organic frameworks),[434] or by addition of nonchromatographic separations such as ion mobility or differential mobility prior to MS detection.[428] In addition, CBS is moving toward fully automated and integrated sample preparation and MS events, allowing for total analysis times of less than 15 s for biofluids. Novel methodologies for determination of drug metabolites will include an enzymatic hydrolysis step in the workflow prior to the enrichment step.[504] This new step will not dramatically affect the total analysis time and will enhance the sensitivity of the method for the target drug. Furthermore, ongoing experiments have shown the potential of CBS for quantitation of target analytes from smaller sample volumes ($\leq$5 μL). Much like other SPME-MS technologies, one can predict the immediate application of CBS as a tool for rapid profiling studies[505,506] that, when used in tandem with portable mass spectrometers, will enable rapid qualitative or semiquantitative on-site analysis.[177]

■ CONCLUDING REMARKS

Owing to SPME's flexibility of design and its easy adaptation to proven analytical approaches, there would appear to be no limits to the evolution of this technology as a superior platform for a variety of diverse applications. It can be conveniently coupled to a variety of instrumentations, as exemplified above in its hyphenation to mass spectrometry. Stable thin films, especially when directly coupled to analytical detection systems, will provide agile and sensitive alternatives to existing point-of-care technologies. Miniaturizations of SPME will enable the monitoring of biological changes at even at the single cell level without disturbances or irreversible damage to the living system. To date, SPME technology has elegantly responded to various challenges in food, environmental, bioanalytical, and clinical fields and will continue to advance to address very specific needs of future emerging fields of applications.

While current SPME applications are limited to the extraction of small molecules, development of very selective coatings designed to eliminate nonspecific binding would allow for the targeting of macromolecules, thus extending the use of SPME toward such applications. To that end, many specific materials developed for purposes other than SPME applications already exist and should be investigated for their suitability in SPME applications. In addition, while the small surface area of typical SPME devices reduces their ability to efficiently extract large molecules such as proteins, this limitation may be overcome with the use of magnetic particles, such as the ones previously discussed in the Coatings section of this review. Within this context, the rapidly increasing performance of analytical instrumentation, including foreseeable improvements in instrumental selectivity, would also facilitate development of SPME technology for applications involving direct coupling to analytical instrumentation other than chromatography and mass spectrometry. Previously published work on hyphenation to spectroscopic and electrochemistry methods, as well as a combination of these techniques, have demonstrated the feasibility of such couplings; considering the convenience and low cost afforded by these approaches, further research aimed at SPME couplings with such instrumentation for on-site implementation is expected in the near future.[447,507−514] Particularly, recent advancements in hyphenation of SPME to Raman techniques introduced interesting modifications, including self-cleaning[515] and self-calibration,[516] as well as the introduction of interesting environmental,[517] food,[518] and point-of-care monitoring applications.

DOI: 10.1021/acs.analchem.7b04502
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Implementation of SPME in combination with rapidly developing technologies associated with communication and e-commerce can also be envisioned in the near future. For example, on-site application can be facilitated by advancements in wireless and drone technologies. Information about the investigated system (associated with environmental, food, health studies) obtained by a remote operating instrument can be wirelessly fed to central offices, allowing for faster decision-making processes and circumventing or minimizing the need for periodic on-site visits. Drones can be used not only to facilitate sampling but also to deliver the small and low cost SPME devices to sampling sites and likewise carry back devices containing samples to central laboratories for analysis.

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Notes

The authors declare no competing financial interest.

Biographies

Nathaly Reyes-Garcés finished her B.Sc. in Chemistry at the Industrial University of Santander (Colombia), and in 2012 and 2017 completed her M.Sc. and Ph.D., respectively, at the University of Waterloo (Canada) under Professor Janusz Pawliszyn's supervision. During her M.Sc. studies, she worked on the application of SPME and needle trap devices for environmental analysis via portable analytical instrumentation. Her doctoral thesis was focused on the application of SPME as a sample preparation tool for targeted and untargeted analysis of various biological samples prior to LC-MS analysis. Currently, she is appointed as a Postdoctoral fellow at the University of Waterloo, where she continues to use SPME in different formats and LC-MS for analysis of drugs and metabolites in various biological systems, including *in vivo* brain studies.

Emanuela Gionfriddo received her B.Sc. (2008) and M.Sc. (2010) in Chemistry and her Ph.D. in Analytical Chemistry (2013) at University of Calabria (Italy). She is currently a Research Associate in Prof. Pawliszyn's research group at the University of Waterloo (ON, Canada). Her research focuses on the development and testing of new matrix compatible SPME coatings that afford compatibility with both gas- and liquid-chromatography applications and suitability for direct immersion in complex matrixes. She is also active in the development of new SPME methods for determination of contaminants at trace levels in various food and environmental matrixes as well as in pharmaceutical supplements by GC-MS, GC × GC-MS, and direct coupling with MS. As of January 2018, she will be an Assistant Professor of Analytical Chemistry with the Department of Chemistry and Biochemistry of University of Toledo (OH).

German Augusto Gómez-Ríos began his academic career at the Industrial University of Santander (Colombia), where he obtained his B.Sc. in Chemistry. After working for more than 2 years at the Colombian National Institute for Legal Medicine and Forensic Sciences, he joined Prof. Janusz Pawliszyn's research group at the University of Waterloo (Canada), where he obtained his M.Sc. and Ph.D. degrees in Analytical Chemistry in 2012 and 2017, respectively. Currently, he is a postdoctoral fellow working in collaboration with thoracic surgeons at the Toronto General Hospital on the application of SPME as a bedside rapid diagnostics tool. His research interests are primary focused on the development of novel technologies based on the direct interface of microextraction devices and mass spectrometry instrumentation, which aim to solve challenging applications of bioanalytical, forensic, environmental, food, or military interest.

Md. Nazmul Alam received his Ph.D. in Analytical Chemistry in 2016 at the University of Waterloo under the supervision of Prof. Janusz Pawliszyn. His doctoral thesis was focused on the development of mathematical models for various types of quantification approaches in solid-phase microextraction (SPME). Dr. Alam gained multidisciplinary research experience through his masters in Inorganic Chemistry at Western University, under the supervision of Prof. Bernie Kraatz, and a postgraduate diploma in Chemical Engineering at the Tokyo Institute of Technology, under the supervision of Prof. Yashiro Nakano. Currently, he is engaged in postdoctoral research at the University of Waterloo. His research interests include the development of fast sampling methods, mathematical modeling, and numerical simulations of mass and momentum transport in chemical analysis.

Ezel Boyaci studied chemistry at the Izmir Institute of Technology, Turkey, where she received her M.Sc. and Ph.D. degrees in Analytical Chemistry in 2008 and 2012, respectively. In 2012, she became a postdoctoral fellow at the University of Waterloo, Canada, in Prof. Janusz Pawliszyn's research group. In 2016, she became a research associate in the same group. As of 2017, she joined the Middle East Technical University, Turkey, as an associate professor. Her research interests focus on bioanalytical and environmental applications of various formats of SPME, development of new coatings for SPME, and toxicokinetic studies in cell lines, metabolomics, and in vivo studies using SPME.

Barbara Bojko studied laboratory medicine at the Medical University of Silesia (Poland), where she received her Master's degree in 2001 and Ph.D. degree in Pharmaceutical Sciences in 2005. The same year, she became an Adjunct Professor at the same university, and in 2009, she joined Prof. Pawliszyn's research group at the University of Waterloo (Canada), initially as a Postdoctoral Fellow and later (2012) as a Research Associate. In 2014, she completed her Habilitation (D.Sc.) at the Medical University of Gdansk (Poland) and became an Associate Professor at Nicolaus Copernicus University (Poland), where she established her research group. Her research is focused on the utilization of microtechnologies in various clinical and pharmaceutical applications, with particular interest in translational medicine and low invasive tissue analysis for oncology and transplantation.

Varoon Singh received his B.Sc. and M.Sc. degrees in Chemistry from the University of Pune, India. He completed his Ph.D. in Analytical Chemistry while working at the Defense Research and Development Establishment (Gwalior, India), from Bharathiar University (India), on the development of polymer coated magnetic materials and sample preparation methods for detection and identification of toxic chemicals via gas chromatography-mass spectrometry. Currently, he works in the Department of Chemistry, University of Waterloo, as a postdoctoral fellow. His research activities focus on the development of coatings for solid phase microextraction and their application in sample preparation. His current research interests are material chemistry, chromatography, mass spectrometry, sample preparation, and method development for trace analysis.

Jonathan Grandy is completing his Ph.D. program at the University of Waterloo (Ontario, Canada). He received his Honours degree in Environmental Chemistry from the Memorial University of Newfoundland and Labrador in 2012 and worked as an on-site water quality analyst for the Bluenose Costal Action Foundation (Nova Scotia, Canada). His current research involves the development and validation of novel SPME sampling devices for on-site

DOI: 10.1021/acs.analchem.7b04502
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environmental analysis, including work on carbon-mesh supported TFME, in-vial standard analyte generating systems, and both diver and remotely operated underwater vehicle (ROV) submersible deep sea SPME samplers.

Janusz Pawliszyn is NSERC Industrial Research Chair and Canada Research Chair in Analytical Methods and Technologies at the University of Waterloo, Canada. The primary focus of his research program is aimed at the elimination of organic solvents from the sample preparation step to facilitate on-site monitoring and *in vivo* analysis. Several alternative techniques to solvent extraction are investigated as part of this program, including the use of coated fibers and other supports for extraction phases, packed needles, membranes, and supercritical fluids. In addition, Professor Pawliszyn is exploring application of computational and modeling techniques to enhance the performance of sample preparation, chromatographic separation, and detection systems. One of his major areas of interest involve the development and application of imaging detection techniques for microcolumn chromatography, capillary electrophoresis, and microchip separation devices. He is the editor-in-chief of *Trends in Analytical Chemistry* and has initiated and currently coordinates a conference, "ExTech", which meets every year in different part of the world and has as a focus new advances in sample preparation and the dissemination of new scientific developments in the area of Analytical Chemistry. He received the 2000 ACS Award in Separation Science for introduction and contributions to commercialization of SPME technology and the 2018 ACS Award in Chromatography for invention of whole column imaging detection technology hyphenated to capillary isoelectric focusing, which is used in antibody characterization and QC in biotechnology applications.

■ ACKNOWLEDGMENTS

The authors of this manuscript thank the financial support provided by the Natural Sciences and Engineering Research Council (NSERC) of Canada.

■ REFERENCES

(1) Azzi-Achkouty, S.; Estephan, N.; Im Ouaini, N.; Rutledge, D. N. *Crit. Rev. Food Sci. Nutr.* **2017**, *57*, 2009.
(2) Xu, J.; Chen, G.; Huang, S.; Qiu, J.; Jiang, R.; Zhu, F.; Ouyang, G. *TrAC, Trends Anal. Chem.* **2016**, *85*, 26−35.
(3) Kenessov, B.; Koziel, J. A.; Bakaikina, N. V.; Orazbayeva, D. *TrAC, Trends Anal. Chem.* **2016**, *85*, 111−122.
(4) Piri-Moghadam, H.; Ahmadi, F.; Pawliszyn, J. *TrAC, Trends Anal. Chem.* **2016**, *85*, 133−143.
(5) Xu, C.-H.; Chen, G.-S.; Xiong, Z.-H.; Fan, Y.-X.; Wang, X.-C.; Liu, Y. *TrAC, Trends Anal. Chem.* **2016**, *80*, 12−29.
(6) Zhang, Q.-H.; Zhou, L.-D.; Chen, H.; Wang, C.-Z.; Xia, Z.-N.; Yuan, C.-S. *TrAC, Trends Anal. Chem.* **2016**, *80*, 57−65.
(7) Bojko, B.; Reyes-Garcés, N.; Bessonneau, V.; Goryński, K.; Mousavi, F.; Souza Silva, E. A.; Pawliszyn, J. *TrAC, Trends Anal. Chem.* **2014**, *61*, 168−180.
(8) Kataoka, H.; Ishizaki, A.; Saito, K. *Anal. Methods* **2016**, *8*, 5773−5788.
(9) Boyaci, E.; Rodriguez-Lafuente, A.; Gorynski, K.; Mirnaghi, F.; Souza-Silva, E. A.; Hein, D.; Pawliszyn, J. *Anal. Chim. Acta* **2015**, *873*, 14−30.
(10) Souza-Silva, É. A.; Jiang, R.; Rodríguez-Lafuente, A.; Gionfriddo, E.; Pawliszyn, J. *TrAC, Trends Anal. Chem.* **2015**, *71*, 224−235.
(11) Souza-Silva, É. A.; Gionfriddo, E.; Pawliszyn, J. *TrAC, Trends Anal. Chem.* **2015**, *71*, 236−248.
(12) Souza-Silva, É. A.; Reyes-Garcés, N.; Gómez-Ríos, G. A.; Boyaci, E.; Bojko, B.; Pawliszyn, J. *TrAC, Trends Anal. Chem.* **2015**, *71*, 249−264.
(13) Mehdinia, A.; Aziz-Zanjani, M. O. *TrAC, Trends Anal. Chem.* **2013**, *51*, 13−22.
(14) Ghaemi, F.; Amiri, A.; Yunus, R. *TrAC, Trends Anal. Chem.* **2014**, *59*, 133−143.
(15) Piri-Moghadam, H.; Alam, M. N.; Pawliszyn, J. *Anal. Chim. Acta* **2017**, *984*, 42.
(16) Rocío-Bautista, P.; Pacheco-Fernandez, I.; Pasan, J.; Pino, V. *Anal. Chim. Acta* **2016**, *939*, 26−41.
(17) Amiri, A. *TrAC, Trends Anal. Chem.* **2016**, *75*, 57−74.
(18) Fernández-Amado, M.; Prieto-Blanco, M. C.; López-Mahía, P.; Muniategui-Lorenzo, S.; Prada-Rodríguez, D. *Anal. Chim. Acta* **2016**, *906*, 41−57.
(19) Deng, J.; Yang, Y.; Wang, X.; Luan, T. *TrAC, Trends Anal. Chem.* **2014**, *55*, 55−67.
(20) Fang, L.; Deng, J.; Yang, Y.; Wang, X.; Chen, B.; Liu, H.; Zhou, H.; Ouyang, G.; Luan, T. *TrAC, Trends Anal. Chem.* **2016**, *85*, 61−72.
(21) Tang, S.; Zhang, H.; Lee, H. K. *Anal. Chem.* **2016**, *88*, 228−249.
(22) *Solid Phase Microextraction*; Ouyang, G., Jiang, R., Eds.; Springer Berlin Heidelberg: Berlin, Heidelberg, Germany, 2017.
(23) Poole, C.; Mester, Z.; Miró, M.; Pedersen-Bjergaard, S.; Pawliszyn, J. *Pure Appl. Chem.* **2016**, *88*, 517−558.
(24) Mirnaghi, F. S.; Goryński, K.; Rodriguez-Lafuente, A.; Boyacı, E.; Bojko, B.; Pawliszyn, J. *J. Chromatogr. A* **2013**, *1316*, 37−43.
(25) Boyacı, E.; Rodríguez-Lafuente, Á.; Gorynski, K.; Mirnaghi, F.; Souza-Silva, É. A.; Hein, D.; Pawliszyn, J. *Anal. Chim. Acta* **2015**, *873*, 14−30.
(26) Pawliszyn, J.; Vuckovic, D.; Risticevic, S. In *Handbook of Solid Phase Microextraction*; Elsevier, 2012; pp. 455−478.
(27) Jiang, R.; Pawliszyn, J. *TrAC, Trends Anal. Chem.* **2012**, *39*, 245−253.
(28) Tena, M. T.; Carrillo, J. D. *TrAC, Trends Anal. Chem.* **2007**, *26*, 206−214.
(29) Piri-Moghadam, H.; Ahmadi, F.; Gómez-Ríos, G. A.; Boyacı, E.; Reyes-Garcés, N.; Aghakhani, A.; Bojko, B.; Pawliszyn, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 7510.
(30) Alam, M. N.; Ricardez-Sandoval, L.; Pawliszyn, J. *Ind. Eng. Chem. Res.* **2017**, *56*, 3679−3686.
(31) Ouyang, G.; Vuckovic, D.; Pawliszyn, J. *Chem. Rev.* **2011**, *111*, 2784−2814.
(32) Ouyang, G.; Pawliszyn, J. *Anal. Chim. Acta* **2008**, *627*, 184−197.
(33) Bartkow, M. E.; Booij, K.; Kennedy, K. E.; Müller, J. F.; Hawker, D. W. *Chemosphere* **2005**, *60*, 170−176.
(34) Louch, D.; Motlagh, S.; Pawliszyn, J. *Anal. Chem.* **1992**, *64*, 1187−1199.
(35) Koziel, J.; Jia, M.; Pawliszyn, J. *Anal. Chem.* **2000**, *72*, 5178−5186.
(36) Ouyang, G.; Pawliszyn, J. *J. Chromatogr. A* **2007**, *1168*, 226−235.
(37) Mao, Y. F.; Li, Z.; He, Y. L.; Tao, W. Q. *Int. J. Heat Mass Transfer* **2016**, *99*, 613−621.
(38) Liang, Y.; Xu, Y. *Atmos. Environ.* **2015**, *103*, 147−155.
(39) Sigurdson, M.; Wang, D.; Meinhart, C. D. *Lab Chip* **2005**, *5*, 1366.
(40) Alam, M. N.; Pawliszyn, J. *Anal. Chem.* **2016**, *88*, 8632−8639.
(41) Chen, Y.; Koziel, J. A.; Pawliszyn, J. *Anal. Chem.* **2003**, *75*, 6485−6493.
(42) Ouyang, G.; Oakes, K. D.; Bragg, L.; Wang, S.; Liu, H.; Cui, S.; Servos, M. R.; Dixon, D. G.; Pawliszyn, J. *Environ. Sci. Technol.* **2011**, *45*, 7792−7798.
(43) Khaled, A.; Pawliszyn, J. *J. Chromatogr. A* **2000**, *892*, 455−467.
(44) Ahmadi, F.; Sparham, C.; Boyacı, E.; Pawliszyn, J. *Environ. Sci. Technol.* **2017**, *51*, 3929−3937.
(45) Ai, J. *Anal. Chem.* **1997**, *69*, 1230−1236.
(46) Chen, Y.; Pawliszyn, J. *Anal. Chem.* **2004**, *76*, 5807−5815.
(47) Chen, Y.; Pawliszyn, J. *Anal. Chem.* **2004**, *76*, 5807−5815.
(48) Zhao, W.; Ouyang, G.; Alaee, M.; Pawliszyn, J. *J. Chromatogr. A* **2006**, *1124*, 112−120.
(49) Zhang, X.; Oakes, K. D.; Luong, D.; Metcalfe, C. D.; Pawliszyn, J.; Servos, M. R. *Anal. Chem.* **2011**, *83*, 2371−2377.
(50) Wang, Y.; O'Reilly, J.; Chen, Y.; Pawliszyn, J. *J. Chromatogr. A* **2005**, *1072*, 13−17.

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

(51) Souza-Silva, É. A.; Gionfriddo, E.; Shirey, R.; Sidisky, L.; Pawliszyn, J. *Anal. Chim. Acta* **2016**, *920*, 54−62.
(52) Risticevic, S.; Pawliszyn, J. *Anal. Chem.* **2013**, *85*, 8987−8995.
(53) Gionfriddo, E.; Boyaci, E.; Pawliszyn, J. *Anal. Chem.* **2017**, *89*, 4046−4054.
(54) Mirnaghi, F. S.; Mousavi, F.; Rocha, S. M.; Pawliszyn, J. *J. Chromatogr. A* **2013**, *1276*, 12−19.
(55) Mousavi, F.; Gionfriddo, E.; Carasek, E.; Souza-Silva, E. A.; Pawliszyn, J. *Metabolomics* **2016**, *12*, 169.
(56) Nilsson, L. B. *Bioanalysis* **2013**, *5*, 3033−3050.
(57) Pawliszyn, J. *Handbook of Solid Phase Microextraction*; Chemical Industry Press: Beijing, 2009.
(58) Sarafraz-Yazdi, A.; Rounaghi, G.; Vatani, H.; Razavipanah, I.; Amiri, A. *Microchim. Acta* **2015**, *182*, 217−225.
(59) Ai, Y.; Wu, M.; Li, L.; Zhao, F.; Zeng, B. *J. Chromatogr. A* **2016**, *1437*, 1−7.
(60) Wu, M.; Wang, L.; Zeng, B.; Zhao, F. *J. Chromatogr. A* **2016**, *1444*, 42−49.
(61) Ghorbani, M.; Chamsaz, M.; Rounaghi, G. H. *Anal. Bioanal. Chem.* **2016**, *408*, 4247−4256.
(62) Abbasian, M.; Balali-Mood, M.; Mozaffari, S. A.; Amoli, H. S. *J. Sep. Sci.* **2016**, *39*, 4449−4457.
(63) Sun, Y.; Chen, J.; Qi, H.; Shi, Y. *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* **2015**, *1004*, 53−59.
(64) Wu, T.; Wang, J.; Liang, W.; Zang, X.; Wang, C.; Wu, Q.; Wang, Z. *Microchim. Acta* **2017**, *184*, 2171−2180.
(65) Xu, N.; Wang, Y.; Rong, M.; Ye, Z.; Deng, Z.; Chen, X. *J. Chromatogr. A* **2014**, *1364*, 53−58.
(66) Fu, M.; Xing, H.; Chen, X.; Zhao, R.; Zhi, C.; Wu, C. L. *Anal. Bioanal. Chem.* **2014**, *406*, 5751−5754.
(67) Chang, N.; Gu, Z. Y.; Wang, H. F.; Yan, X. P. *Anal. Chem.* **2011**, *83*, 7094−7101.
(68) Yu, L.-Q.; Yan, X.-P. *Chem. Commun.* **2013**, *49*, 2142.
(69) Zhang, S.; Yang, Q.; Li, Z.; Wang, W.; Wang, C.; Wang, Z. *Analyst* **2016**, *141*, 1127−1135.
(70) Zhang, S.; Du, Z.; Li, G. *Talanta* **2013**, *115*, 32−39.
(71) Zheng, J.; Li, S.; Wang, Y.; Li, L.; Su, C.; Liu, H.; Zhu, F.; Jiang, R.; Ouyang, G. *Anal. Chim. Acta* **2014**, *829*, 22−27.
(72) Huo, S.-H.; Yu, J.; Fu, Y.-Y.; Zhou, P.-X. *RSC Adv.* **2016**, *6*, 14042−14048.
(73) Bagheri, H.; Javanmardi, H.; Abbasi, A.; Banihashemi, S. *J. Chromatogr. A* **2016**, *1431*, 27−35.
(74) Saraji, M.; Shahvar, A. *Anal. Chim. Acta* **2017**, *973*, 51−58.
(75) Liu, S.; Xie, L.; Hu, Q.; Yang, H.; Pan, G.; Zhu, F.; Yang, S.; Ouyang, G. *Anal. Chim. Acta* **2017**, *987*, 38−46.
(76) Li, J.; Liu, Y.; Su, H.; Elaine Wong, Y. L.; Chen, X.; Dominic Chan, T. W.; Chen, Q. *Microchim. Acta* **2017**, *184*, 3809−3815.
(77) Hashemi-Moghaddam, H.; Hagigatgoo, M. *Chromatographia* **2015**, *78*, 1263−1270.
(78) Jin, Y.; Li, Z.; Yang, L.; Xu, J.; Zhao, L.; Li, Z.; Niu, J. *Anal. Chem.* **2017**, *89*, 1290−1298.
(79) Wu, M.; Chen, G.; Liu, P.; Zhou, W.; Jia, Q. *Analyst* **2016**, *141*, 243−250.
(80) Zhang, S.; Yang, Q.; Li, Z.; Wang, W.; Wang, C.; Wang, Z. *Anal. Bioanal. Chem.* **2017**, *409*, 3429−3439.
(81) Wu, M.; Chen, G.; Liu, P.; Zhou, W.; Jia, Q. *J. Chromatogr. A* **2016**, *1456*, 34−41.
(82) Wang, W.; Wang, J.; Zhang, S.; Cui, P.; Wang, C.; Wang, Z. *Talanta* **2016**, *161*, 22−30.
(83) Du, F.; Alam, M. N.; Pawliszyn, J. *Anal. Chim. Acta* **2014**, *845*, 45−52.
(84) Liu, H.; Gan, N.; Chen, Y.; Li, T.; Cao, Y. *RSC Adv.* **2017**, *7*, 6800−6808.
(85) Pei, M.; Zhang, Z.; Huang, X.; Wu, Y. *Talanta* **2017**, *165*, 152−160.
(86) Cagliero, C.; Ho, T. D.; Zhang, C.; Bicchi, C.; Anderson, J. L. *J. Chromatogr. A* **2016**, *1449*, 2−7.
(87) Nacham, O.; Clark, K. D.; Varona, M.; Anderson, J. L. *Anal. Chem.* **2017**, *89*, 10661−10666.
(88) Chen, G.; Qiu, J.; Xu, J.; Fang, X.; Liu, Y.; Liu, S.; Wei, S.; Jiang, R.; Luan, T.; Zeng, F.; Zhu, F.; Ouyang, G. *Chem. Sci.* **2016**, *7*, 1487−1495.
(89) Asensio-Ramos, M.; Herrera-Herrera, A.; Rodríguez-Delgado, M. À.; Fanali, S.; Hernández-Borges, J. *LCGC N. Am.* **2013**, *31*, 882−892.
(90) Masoumi, V.; Mohammadi, A.; Khoshayand, M. R.; Ansari, M. *J. Anal. Chem.* **2017**, *72*, 264−271.
(91) Ghiasvand, A.; Dowlatshah, S.; Nouraei, N.; Heidari, N.; Yazdankhah, F. *J. Chromatogr. A* **2015**, *1406*, 87−93.
(92) Kazemipour, M.; Behzadi, M.; Ahmadi, R. *Microchem. J.* **2016**, *128*, 258−266.
(93) Saraji, M.; Jafari, M. T.; Mossaddegh, M. *J. Chromatogr. A* **2016**, *1429*, 30−39.
(94) Tang, Z.; Hou, W.; Liu, X.; Wang, M.; Duan, Y. *J. Chromatogr. A* **2016**, *1461*, 18−26.
(95) Song, X. L.; Chen, Y.; Yuan, J. P.; Qin, Y. J.; Zhao, R. S.; Wang, X. *J. Chromatogr. A* **2016**, *1468*, 17−22.
(96) Wu, M.; Wang, L.; Zhao, F.; Zeng, B. *RSC Adv.* **2015**, *5*, 99483−99490.
(97) Abbasian, M.; Balali-Mood, M.; Salar Amoli, H.; Masoumi, A. J. *J. Sol-Gel Sci. Technol.* **2017**, *81*, 247−260.
(98) Li, L.; Wu, M.; Feng, Y.; Zhao, F.; Zeng, B. *Anal. Chim. Acta* **2016**, *948*, 48−54.
(99) Akhlaghi, H.; Ghorbani, M.; Lahoori, N. A.; Shams, A.; Seyedin, O. *J. Anal. Chem.* **2016**, *71*, 641−647.
(100) Golberg, D.; Bando, Y.; Tang, C. C.; Zhi, C. Y. *Adv. Mater.* **2007**, *19*, 2413−2432.
(101) Lei, W.; Portehault, D.; Liu, D.; Qin, S.; Chen, Y. *Nat. Commun.* **2013**, *4*, 1777.
(102) Xie, L.; Liu, S.; Han, Z.; Jiang, R.; Liu, H.; Zhu, F.; Zeng, F.; Su, C.; Ouyang, G. *Anal. Chim. Acta* **2015**, *853*, 303−310.
(103) Zang, X.; Zhang, G.; Chang, Q.; Zhang, X.; Wang, C.; Wang, Z. *Anal. Methods* **2015**, *7*, 918−923.
(104) Lv, F.; Gan, N.; Huang, J.; Hu, F.; Cao, Y.; Zhou, Y.; Dong, Y.; Zhang, L.; Jiang, S. *Microchim. Acta* **2017**, *184*, 2561−2568.
(105) Xie, L.; Liu, S.; Han, Z.; Jiang, R.; Zhu, F.; Xu, W.; Su, C.; Ouyang, G. *Anal. Bioanal. Chem.* **2017**, *409*, 5239.
(106) Zhang, X.; Zang, X. H.; Wang, J. T.; Wang, C.; Wu, Q. H.; Wang, Z. *Microchim. Acta* **2015**, *182*, 2353−2359.
(107) Li, Q. L.; Wang, X.; Chen, X. F.; Wang, M. L.; Zhao, R. S. *J. Chromatogr. A* **2015**, *1415*, 11−19.
(108) Abolghasemi, M. M.; Yousefi, V.; Piryaei, M. *J. Sep. Sci.* **2015**, *38*, 1187−1193.
(109) Zhang, S.; Yang, Q.; Wang, W.; Wang, C.; Wang, Z. *J. Agric. Food Chem.* **2016**, *64*, 2792−2801.
(110) Wang, G.; Lei, Y.; Song, H. *Talanta* **2015**, *144*, 369−374.
(111) Wang, G. H.; Lei, Y. Q. *Bull. Environ. Contam. Toxicol.* **2017**, *99*, 270−275.
(112) Niu, J.; Li, Z.; Yang, H.; Ye, C.; Chen, C.; Li, D.; Xu, J.; Fan, L. *J. Chromatogr. A* **2016**, *1441*, 16−23.
(113) Lan, H.; Pan, D.; Sun, Y.; Guo, Y.; Wu, Z. *Anal. Chim. Acta* **2016**, *937*, 53−60.
(114) Gao, J.; Huang, C.; Lin, Y.; Tong, P.; Zhang, L. *J. Chromatogr. A* **2016**, *1436*, 1−8.
(115) Zang, X.; Zhang, X.; Chang, Q.; Li, S.; Wang, C.; Wang, Z. *J. Sep. Sci.* **2016**, *39*, 2770−2776.
(116) Liang, W.; Wang, J.; Zang, X.; Wang, C.; Wang, Z. *J. Sep. Sci.* **2016**, *39*, 1331−1338.
(117) Chen, B.; Yang, Z.; Zhu, Y.; Xia, Y. *J. Mater. Chem. A* **2014**, *2*, 16811−16831.
(118) Pimentel, B. R.; Parulkar, A.; Zhou, E. K.; Brunelli, N. A.; Lively, R. P. *ChemSusChem* **2014**, *7*, 3202−3240.
(119) Huang, J.; Ou, C.; Lv, F.; Cao, Y.; Tang, H.; Zhou, Y.; Gan, N. *Talanta* **2017**, *165*, 326−331.
(120) Zhang, J.; Zhang, W.; Bao, T.; Chen, Z. *J. Chromatogr. A* **2015**, *1388*, 9−16.

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

(121) Lan, H.; Rönkkö, T.; Parshintsev, J.; Hartonen, K.; Gan, N.; Sakeye, M.; Sarfraz, J.; Riekkola, M. L. *J. Chromatogr. A* **2017**, *1486*, 76−85.
(122) Diercks, C. S.; Yaghi, O. M. *Science (Washington, DC, U. S.)* **2017**, *355*, eaal1585.
(123) Bisbey, R. P.; Dichtel, W. R. *ACS Cent. Sci.* **2017**, *3*, 533−543.
(124) Pan, J.; Jia, S.; Li, G.; Hu, Y. *Anal. Chem.* **2015**, *87*, 3373−3381.
(125) Wu, M.; Chen, G.; Ma, J.; Liu, P.; Jia, Q. *Talanta* **2016**, *161*, 350−358.
(126) Huang, Z.; Liu, S.; Xu, J.; Yin, L.; Zheng, J.; Zhou, N.; Ouyang, G. *Anal. Chim. Acta* **2017**, *989*, 21−28.
(127) Mu, L.; Hu, X.; Wen, J.; Zhou, Q. *J. Chromatogr. A* **2013**, *1279*, 7−12.
(128) Guo, X.; Ye, T.; Liu, L.; Hu, X. *J. Sep. Sci.* **2016**, *39*, 1533−1541.
(129) Koster, E. H. M.; Crescenzi, C.; Den Hoedt, W.; Ensing, K.; De Jong, G. J. *Anal. Chem.* **2001**, *73*, 3140−3145.
(130) Terzopoulou, Z.; Papageorgiou, M.; Kyzas, G. Z.; Bikiaris, D. N.; Lambropoulou, D. A. *Anal. Chim. Acta* **2016**, *913*, 63−75.
(131) Mirzajani, R.; Kardani, F. *J. Pharm. Biomed. Anal.* **2016**, *122*, 98−109.
(132) Gao, D.; Wang, D. D.; Zhang, Q.; Yang, F. Q.; Xia, Z. N.; Zhang, Q. H.; Yuan, C. S. *J. Agric. Food Chem.* **2017**, *65*, 1158−1166.
(133) Zhu, J.; Chen, D.; Ai, Y.; Dang, X.; Huang, J.; Chen, H. *Microchim. Acta* **2017**, *184*, 1161−1167.
(134) Hashemi-Moghaddam, H.; Jedi, D. J. *Int. J. Environ. Anal. Chem.* **2015**, *95*, 33−44.
(135) Díaz-Álvarez, M.; Smith, S. P.; Spivak, D. A.; Martín-Esteban, A. *J. Sep. Sci.* **2016**, *39*, 552−558.
(136) Moein, M. M.; Javanbakht, M.; Karimi, M.; Akbari-Adergani, B. *Talanta* **2015**, *134*, 340−347.
(137) Hashemi-Moghaddam, H.; Ahmadifard, M. *Talanta* **2016**, *150*, 148−154.
(138) Li, J. W.; Wang, Y. L.; Yan, S.; Li, X. J.; Pan, S. Y. *Food Chem.* **2016**, *192*, 260−267.
(139) Pebdani, A. A.; Shabani, A. M. H.; Dadfarnia, S.; Khodadoust, S. *Spectrochim. Acta, Part A* **2015**, *147*, 26−30.
(140) Guan, X.; Cheng, T.; Wang, S.; Liu, X.; Zhang, H. *Anal. Bioanal. Chem.* **2017**, *409*, 3127−3133.
(141) Guan, X.; Zhu, X.; Yu, B.; Zhao, T.; Zhang, H. *RSC Adv.* **2015**, *5*, 91716−91722.
(142) Tamayo, F. G.; Turiel, E.; Martín-Esteban, A. *J. Chromatogr. A* **2007**, *1152*, 32−40.
(143) Ho, T. D.; Canestraro, A. J.; Anderson, J. L. *Anal. Chim. Acta* **2011**, *695*, 18−43.
(144) Clark, K. D.; Emaus, M. N.; Varona, M.; Bowers, A. N.; Anderson, J. L. *J. Sep. Sci.* **2017**, DOI: 10.1002/jssc.201700864.
(145) Tang, Z.; Duan, Y. *Talanta* **2017**, *172*, 45−52.
(146) Trujillo-Rodriguez, M. J.; Pino, V.; Psillakis, E.; Anderson, J. L.; Ayala, J. H.; Yiantzi, E.; Afonso, A. M. *Anal. Chim. Acta* **2017**, *962*, 41−51.
(147) Chen, L.; Huang, X. *Analyst* **2017**, *142*, 4039.
(148) Cagliero, C.; Nan, H.; Bicchi, C.; Anderson, J. L. *J. Chromatogr. A* **2016**, *1459*, 17−23.
(149) Sun, M.; Bu, Y.; Feng, J.; Luo, C. *J. Sep. Sci.* **2016**, *39*, 375−382.
(150) Musteata, M. L.; Musteata, F. M.; Pawliszyn, J. *Anal. Chem.* **2007**, *79*, 6903−6911.
(151) Yeung, J. C. Y.; de Lannoy, I.; Gien, B.; Vuckovic, D.; Yang, Y.; Bojko, B.; Pawliszyn, J. *Anal. Chim. Acta* **2012**, *742*, 37−44.
(152) Gómez-Ríos, G. A.; Reyes-Garcés, N.; Bojko, B.; Pawliszyn, J. *Anal. Chem.* **2016**, *88*, 1259−1265.
(153) Ahmad, S.; Tucker, M.; Spooner, N.; Murnane, D.; Gerhard, U. *Anal. Chem.* **2015**, *87*, 754−759.
(154) Souza-Silva, É. A.; Gionfriddo, E.; Alam, M. N.; Pawliszyn, J. *Anal. Chem.* **2017**, *89*, 2978−2985.
(155) Setkova, L.; Risticevic, S.; Linton, C. M.; Ouyang, G.; Bragg, L. M.; Pawliszyn, J. *Anal. Chim. Acta* **2007**, *581*, 221−231.
(156) Risticevic, S.; Souza-Silva, E. A.; DeEll, J. R.; Cochran, J.; Pawliszyn, J. *Anal. Chem.* **2016**, *88*, 1266−1274.
(157) Risticevic, S.; Chen, Y.; Kudlejova, L.; Vatinno, R.; Baltensperger, B.; Stuff, J. R.; Hein, D.; Pawliszyn, J. *Nat. Protoc.* **2010**, *5*, 162−176.
(158) Risticevic, S.; DeEll, J. R.; Pawliszyn, J. *J. Chromatogr. A* **2012**, *1251*, 208−218.
(159) Risticevic, S.; Lord, H.; Górecki, T.; Arthur, C. L.; Pawliszyn, J. *Nat. Protoc.* **2010**, *5*, 122−139.
(160) Bai, Z.; Pilote, A.; Sarker, P. K.; Vandenberg, G.; Pawliszyn, J. *Anal. Chem.* **2013**, *85*, 2328−2332.
(161) Kremser, A.; Jochmann, M. A.; Schmidt, T. C. *Anal. Bioanal. Chem.* **2016**, *408*, 943−952.
(162) Helin, A.; Rönkkö, T.; Parshintsev, J.; Hartonen, K.; Schilling, B.; Läubli, T.; Riekkola, M.-L. *J. Chromatogr. A* **2015**, *1426*, 56−63.
(163) Poole, J. J.; Grandy, J. J.; Yu, M.; Boyaci, E.; Gómez-Ríos, G. A.; Reyes-Garcés, N.; Bojko, B.; Heide, H. Vander; Pawliszyn, J. *Anal. Chem.* **2017**, *89*, 8021−8026.
(164) Deng, J.; Yang, Y.; Xu, M.; Wang, X.; Lin, L.; Yao, Z. P.; Luan, T. *Anal. Chem.* **2015**, *87*, 9923−9930.
(165) Wu, Q.; Wu, D.; Guan, Y. *J. Chromatogr. A* **2014**, *1342*, 16−23.
(166) Qiu, J.; Chen, G.; Zhu, F.; Ouyang, G. *J. Chromatogr. A* **2016**, *1455*, 20−27.
(167) Bruheim, I.; Liu, X.; Pawliszyn, J. *Anal. Chem.* **2003**, *75*, 1002−1010.
(168) Jiang, R.; Cudjoe, E.; Bojko, B.; Abaffy, T.; Pawliszyn, J. *Anal. Chim. Acta* **2013**, *804*, 111−119.
(169) Riazi Kermani, F.; Pawliszyn, J. *Anal. Chem.* **2012**, *84*, 8990−8995.
(170) Grandy, J. J.; Boyaci, E.; Pawliszyn, J. *Anal. Chem.* **2016**, *88*, 1760−1767.
(171) Piri-Moghadam, H.; Gionfriddo, E.; Rodriguez-Lafuente, A.; Grandy, J. J.; Lord, H. L.; Obal, T.; Pawliszyn, J. *Anal. Chim. Acta* **2017**, *964*, 74−84.
(172) Cudjoe, E.; Vuckovic, D.; Hein, D.; Pawliszyn, J. *Anal. Chem.* **2009**, *81*, 4226−4232.
(173) Mirnaghi, F. S.; Chen, Y.; Sidisky, L. M.; Pawliszyn, J. *Anal. Chem.* **2011**, *83*, 6018−6025.
(174) Gómez-Ríos, G. A.; Tascon, M.; Reyes-Garcés, N.; Boyacı, E.; Poole, J. J.; Pawliszyn, J. *Anal. Chim. Acta* **2017**, DOI: 10.1016/j.aca.2017.10.016.
(175) Reyes-Garcés, N.; Bojko, B.; Hein, D.; Pawliszyn, J. *Anal. Chem.* **2015**, *87*, 9722−9730.
(176) Rodriguez-Lafuente, A.; Mirnaghi, F. S.; Pawliszyn, J. *Anal. Bioanal. Chem.* **2013**, *405*, 9723−9727.
(177) Gómez-Ríos, G. A.; Vasiljevic, T.; Gionfriddo, E.; Yu, M.; Pawliszyn, J. *Analyst* **2017**, *142*, 2928−2935.
(178) Gómez-Ríos, G. A.; Gionfriddo, E.; Poole, J.; Pawliszyn, J. *Anal. Chem.* **2017**, *89*, 7240−7248.
(179) Boyacı, E.; Gorynski, K.; Rodriguez-Lafuente, A.; Bojko, B.; Pawliszyn, J. *Anal. Chim. Acta* **2014**, *809*, 69−81.
(180) Boyacı, E.; Sparham, C.; Pawliszyn, J. *Anal. Bioanal. Chem.* **2014**, *406*, 409−420.
(181) Boyaci, E.; Pawliszyn, J. *Anal. Chem.* **2014**, *86*, 8916−8921.
(182) Boyacı, E.; Goryński, K.; Viteri, C. R.; Pawliszyn, J. *J. Chromatogr. A* **2016**, *1436*, 51−58.
(183) Togunde, O. P.; Oakes, K. D.; Servos, M. R.; Pawliszyn, J. *Environ. Sci. Technol.* **2012**, *46*, 5302−5309.
(184) Mousavi, F.; Bojko, B.; Pawliszyn, J. *Anal. Chim. Acta* **2015**, *892*, 95−104.
(185) Ríos, Á.; Zougagh, M. *TrAC, Trends Anal. Chem.* **2016**, *84*, 72−83.
(186) Kaewsaneha, C.; Tangboriboonrat, P.; Polpanich, D.; Elaissari, A. *ACS Appl. Mater. Interfaces* **2015**, *7*, 23373−23386.
(187) González-Sálamo, J.; Herrera-Herrera, A. V.; Fanali, C.; Hernández-Borges, J. *LC-GC Eur.* **2016**, *29*, 180−193.
(188) Ghorbani, M.; Chamsaz, M.; Rounaghi, G. H. *J. Sep. Sci.* **2016**, *39*, 1082−1089.
(189) Wondracek, M. H. P.; Oliveira Jorgetto, A.; Silva, A. C. P.; Ivassechen, J. do R.; Schneider, J. F.; Castro, G. R.; Saeki, M. J.;

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

Pedrosa, V. A.; Yoshito, W. K.; Colauto, F.; Ortiz, W. A. *Appl. Surf. Sci.* **2016**, *367*, 533−541.
(190) Baghban, N.; Yilmaz, E.; Soylak, M. *Microchim. Acta* **2017**, *184*, 3969−3976.
(191) Kazemi, E.; Dadfarnia, S.; Shabani, A. M. H. *Talanta* **2015**, *141*, 273−278.
(192) Wang, H.; Chen, B.; Zhu, S.; Yu, X.; He, M.; Hu, B. *Anal. Chem.* **2016**, *88*, 796−802.
(193) Mills, D. G. A.; Dean, D. J. R.; Pawliszyn, P. J.; Qin, Z.; Bragg, L.; Ouyang, G.; Pawliszyn, J. *J. Chromatogr. A* **2008**, *1196*, 89−95.
(194) Aparicio, I.; Martín, J.; Santos, J. L.; Malvar, J. L.; Alonso, E. *J. Chromatogr. A* **2017**, *1500*, 43−52.
(195) Baltussen, E.; Sandra, P.; David, F.; Cramers, C. *J. Microcolumn Sep.* **1999**, *11*, 737−747.
(196) Gilart, N.; Marcé, R. M.; Borrull, F.; Fontanals, N. *TrAC, Trends Anal. Chem.* **2014**, *54*, 11−23.
(197) Speltini, A.; Scalabrini, A.; Maraschi, F.; Sturini, M.; Profumo, A. *Anal. Chim. Acta* **2017**, *974*, 1−26.
(198) Abdulra'Uf, L. B.; Tan, G. H. *Chromatographia* **2014**, *77*, 15−24.
(199) Camino-Sánchez, F. J.; Rodríguez-Gómez, R.; Zafra-Gómez, A.; Santos-Fandila, J. L. V. *Talanta* **2014**, *130*, 388−399.
(200) Kawaguchi, M.; Takatsu, A.; Ito, R.; Nakazawa, H. *TrAC, Trends Anal. Chem.* **2013**, *45*, 280−293.
(201) Ochiai, N.; Sasamoto, K.; Ieda, T.; David, F.; Sandra, P. *J. Chromatogr. A* **2013**, *1315*, 70−79.
(202) Bridoux, M. C.; Malandain, H.; Leprince, F.; Progent, F.; Machuron-Mandard, X. *Anal. Chim. Acta* **2015**, *869*, 1−10.
(203) Zhang, Z.; Zhang, W.; Bao, T.; Chen, Z. *J. Chromatogr. A* **2015**, *1407*, 1−10.
(204) Benedé, J. L.; Chisvert, A.; Giokas, D. L.; Salvador, A. *J. Chromatogr. A* **2014**, *1362*, 25−33.
(205) Gilart, N.; Cormack, P. A. G.; Marcé, R. M.; Borrull, F.; Fontanals, N. *J. Chromatogr. A* **2013**, *1295*, 42−47.
(206) Mao, X.; He, M.; Chen, B.; Hu, B. *J. Chromatogr. A* **2016**, *1472*, 27−34.
(207) Li, J.; Wang, Y.-B.; Li, K.-Y.; Cao, Y.-Q.; Wu, S.; Wu, L. *TrAC, Trends Anal. Chem.* **2015**, *72*, 141−152.
(208) Souza-Silva, É. A.; Pawliszyn, J. Recent Advances in Solid-Phase Microextraction for Contaminant Analysis in Food Matrices. In *Green Extraction Techniques: Principles, Advances and Applications*; Comprehensive Analytical Chemistry, Vol. *76*, Elsevier, 2017; p 483, DOI: 10.1016/bs.coac.2017.03.002.
(209) Sanchis, Y.; Yusà, V.; Coscollà, C. *J. Chromatogr. A* **2017**, *1490*, 22−46.
(210) Kataoka, H.; Lord, H. L.; Pawliszyn, J. *J. Chromatogr. A* **2000**, *880*, 35−62.
(211) Garwolińska, D.; Hewelt-Belka, W.; Namieśnik, J.; Kot-Wasik, A. *J. Proteome Res.* **2017**, *16*, 3200−3208.
(212) Alberdi-Cedeño, J.; Ibargoitia, M. L.; Cristillo, G.; Sopelana, P.; Guillén, M. D. *Food Chem.* **2017**, *221*, 1135−1144.
(213) De Lima, P. F.; Furlan, M. F.; De Lima Ribeiro, F. A.; Pascholati, S. F.; Augusto, F. *J. Sep. Sci.* **2015**, *38*, 1924−1932.
(214) Souza-Silva, É. A.; Pawliszyn, J. *J. Agric. Food Chem.* **2015**, *63*, 4464−4477.
(215) De Grazia, S.; Gionfriddo, E.; Pawliszyn, J. *Talanta* **2017**, *167*, 754−760.
(216) Silveira, G. O.; Loddi, S.; de Oliveira, C. D. R.; Zucoloto, A. D.; Fruchtengarten, L. V. G.; Yonamine, M. *Forensic Toxicol.* **2017**, *35*, 125−132.
(217) Andrade, M. A.; Lanças, F. M. *J. Chromatogr. A* **2017**, *1493*, 41−48.
(218) Rodriguez-Lafuente, A.; Piri-Moghadam, H.; Lord, H. L.; Obal, T.; Pawliszyn, J. *Water Qual. Res. J. Can.* **2016**, *51*, 331−343.
(219) Jiang, R.; Pawliszyn, J. *Anal. Chem.* **2014**, *86*, 403−410.
(220) Poole, J. J.; Grandy, J. J.; Gómez-Ríos, G. A.; Gionfriddo, E.; Pawliszyn, J. *Anal. Chem.* **2016**, *88*, 6859−6866.
(221) Xu, S.; Shuai, Q.; Pawliszyn, J. *Anal. Chem.* **2016**, *88*, 8936−8941.
(222) Poole, J. J.; Gomez-Rios, G. A.; Boyaci, E.; Reyes-Garcés, N.; Pawliszyn, J. *Environ. Sci. Technol.* **2017**, *51*, 12566.
(223) Antonucci, A.; Vitali, M.; Avino, P.; Manigrasso, M.; Protano, C. *Anal. Bioanal. Chem.* **2016**, *408*, 5789−5800.
(224) Simões, R. A.; Bonato, P. S.; Mirnaghi, F. S.; Bojko, B.; Pawliszyn, J. *Bioanalysis* **2015**, *7*, 65−77.
(225) Mousavi, F.; Bojko, B.; Bessonneau, V.; Pawliszyn, J. *J. Proteome Res.* **2016**, *15*, 963−975.
(226) Silva, C. L.; Perestrelo, R.; Silva, P.; Tomás, H.; Câmara, J. S. *Sci. Rep.* **2017**, *7*, 43969.
(227) Wang, C.; Feng, Y.; Wang, M.; Pi, X.; Tong, H.; Wang, Y.; Zhu, L.; Li, E. *Sci. Rep.* **2015**, *5*, 2−10.
(228) Birjandi, A. P.; Bojko, B.; Ning, Z.; Figeys, D.; Pawliszyn, J. *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* **2017**, *1043*, 12−19.
(229) Jiang, H.-P.; Qi, C.-B.; Chu, J.-M.; Yuan, B.-F.; Feng, Y.-Q. *Sci. Rep.* **2015**, *5*, 7785.
(230) Gionfriddo, E.; Souza-Silva, E. A.; Pawliszyn, J. *Anal. Chem.* **2015**, *87*, 8448−8456.
(231) Contini, M.; Esti, M. *Food Chem.* **2006**, *94*, 143−150.
(232) Roberts, D. D.; Pollien, P.; Milo, C. *J. Agric. Food Chem.* **2000**, *48*, 2430−2437.
(233) Abdulra'uf, L. B.; Tan, G. H. *Food Chem.* **2015**, *177*, 267−273.
(234) Sang, Z. Y.; Wang, Y. T.; Tsoi, Y. K.; Leung, K. S. Y. *Food Chem.* **2013**, *136*, 710−717.
(235) Jafari, M. T.; Saraji, M.; Sherafatmand, H. *Anal. Chim. Acta* **2014**, *814*, 69−78.
(236) Saraji, M.; Rezaei, B.; Boroujeni, M. K.; Bidgoli, A. A. H. *J. Chromatogr. A* **2013**, *1279*, 20−26.
(237) Melo, A.; Aguiar, A.; Mansilha, C.; Pinho, O.; Ferreira, I. M. P. L. V. O. *Food Chem.* **2012**, *130*, 1090−1097.
(238) Aresta, A.; Zambonin, C. *J. Pharm. Biomed. Anal.* **2016**, *121*, 63−68.
(239) Mirzajani, R.; Ramezani, Z.; Kardani, F. *Microchem. J.* **2017**, *130*, 93−101.
(240) Ye, D.; Wu, S.; Xu, J.; Jiang, R.; Zhu, F.; Ouyang, G. *J. Chromatogr. Sci.* **2016**, *54*, 112−118.
(241) Jiang, R.; Xu, J.; Zhu, F.; Luan, T.; Zeng, F.; Shen, Y.; Ouyang, G. *J. Chromatogr. A* **2015**, *1411*, 34−40.
(242) Xu, J.; He, S.; Jiang, R.; Zhu, F.; Ruan, J.; Liu, H.; Luan, T.; Ouyang, G. *Anal. Methods* **2014**, *6*, 4895−4900.
(243) Souza Silva, É. A.; Pawliszyn, J. *Anal. Chem.* **2012**, *84*, 6933−6938.
(244) De Jager, L. S.; Perfetti, G. A.; Diachenko, G. W. *Food Chem.* **2008**, *107*, 1701−1709.
(245) Stenerson, K. K.; Young, T.; Shirey, R.; Chen, Y.; Sidisky, L. M. *LCGC N. Am.* **2016**, *34*, 500−509.
(246) Souza-Silva, É. A.; Lopez-Avila, V.; Pawliszyn, J. *J. Chromatogr. A* **2013**, *1313*, 139−146.
(247) Naccarato, A.; Pawliszyn, J. *Food Chem.* **2016**, *206*, 67−73.
(248) Stenerson, K.; Young, T. *Reporter* **2016**, *34.3*, 15−19.
(249) Altaki, M. S.; Santos, F. J.; Puignou, L.; Galceran, M. T. *Food Addit. Contam., Part A* **2017**, *0*, 1−12.
(250) García-Reyes, J. F.; Ferrer, C.; Gómez-Ramos, M. J.; Fernández-Alba, A. R.; Molina-Díaz, A. *TrAC, Trends Anal. Chem.* **2007**, *26*, 239−251.
(251) Nieva-Echevarría, B.; Goicoechea, E.; Guillén, M. D. *Food Res. Int.* **2017**, *97*, 104−115.
(252) Nieva-Echevarría, B.; Goicoechea, E.; Manzanos, M. J.; Guillén, M. D. *Food Res. Int.* **2017**, *91*, 171−182.
(253) Nieva-Echevarría, B.; Goicoechea, E.; Guillén, M. D. *Food Chem.* **2017**, *232*, 733−743.
(254) Purcaro, G.; Picardo, M.; Barp, L.; Moret, S.; Conte, L. S. *J. Chromatogr. A* **2013**, *1307*, 166−171.
(255) Argyri, A. A.; Mallouchos, A.; Panagou, E. Z.; Nychas, G. J. E. *Int. J. Food Microbiol.* **2015**, *193*, 51−58.
(256) Met, A.; Şahin Yeşilçubuk, N. *Food Anal. Methods* **2017**, *10*, 2311−2324.
(257) Jiang, Y.; Ni, Y. *J. Sep. Sci.* **2015**, *38*, 418−425.
(258) Canellas, E.; Vera, P.; Nerín, C. *Food Chem.* **2016**, *197*, 24−29.

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

(259) Moreira, M. A.; André, L. C.; Cardeal, Z. D. L. *Food Chem.* **2015**, *178*, 195−200.
(260) Togunde, O. P.; Oakes, K. D.; Servos, M. R.; Pawliszyn, J. *J. Chromatogr. A* **2012**, *1261*, 99−106.
(261) Huang, S.; Xu, J.; Wu, J.; Hong, H.; Chen, G.; Jiang, R.; Zhu, F.; Liu, Y.; Ouyang, G. *Talanta* **2017**, *168*, 263−268.
(262) Chen, L.; Qiu, J.; Tang, Y.; Xu, J.; Huang, S.; Liu, Y.; Ouyang, G. *Talanta* **2017**, *171*, 179−184.
(263) Alizadeh, N.; Kamalabadi, M.; Mohammadi, A. *Food Anal. Methods* **2017**, *10*, 3001−3008.
(264) Delvaux Júnior, N. A.; de Queiroz, M. E. L. R.; Neves, A. A.; Oliveira, A. F.; da Silva, M. R. F.; Faroni, L. R. A.; Heleno, F. F. *Microchem. J.* **2017**, *133*, 539−544.
(265) Zhang, Y.; Guo, W.; Yue, Z.; Lin, L.; Zhao, F.; Chen, P.; Wu, W.; Zhu, H.; Yang, B.; Kuang, Y.; Wang, J. *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* **2017**, *1051*, 41−53.
(266) Huang, J.; Gan, N.; Lv, F.; Cao, Y.; Ou, C.; Tang, H. *J. Sep. Sci.* **2016**, *39*, 4384−4390.
(267) Togunde, O. P.; Lord, H.; Oakes, K. D.; Servos, M. R.; Pawliszyn, J. *J. Sep. Sci.* **2013**, *36*, 219−223.
(268) Xu, J.; Huang, S.; Wu, R.; Jiang, R.; Zhu, F.; Wang, J.; Ouyang, G. *Anal. Chem.* **2015**, *87*, 3453−3459.
(269) Bessonneau, V.; Ings, J.; McMaster, M.; Smith, R.; Bragg, L.; Servos, M.; Pawliszyn, J. *Sci. Rep.* **2017**, *7*, 44038.
(270) Bessonneau, V.; Ings, J.; McMaster, M.; Smith, R.; Bragg, L.; Servos, M.; Pawliszyn, J. *Environ. Res.* **2016**, *151*, 216−223.
(271) Chen, L.; Huang, X. *J. Agric. Food Chem.* **2016**, *64*, 8684−8693.
(272) Merib, J.; Nardini, G.; Carasek, E. *Anal. Methods* **2014**, *6*, 3254−3260.
(273) de Oliveira Silveira, G.; Loddi, S.; Dizioli Rodrigues de Oliveira, C.; Zucoloto, A. D.; Gimenez Fruchtengarten, L. V.; Yonamine, M. *Forensic Toxicol.* **2017**, *35*, 125−132.
(274) Lin, W.; Wei, S.; Jiang, R.; Zhu, F.; Ouyang, G. *Anal. Chim. Acta* **2016**, *933*, 117−123.
(275) Zhang, X.; Oakes, K. D.; Hoque, M. E.; Luong, D.; Metcalfe, C. D.; Pawliszyn, J.; Servos, M. R. *Anal. Chem.* **2011**, *83*, 3365−3370.
(276) Psillakis, E.; Yiantzi, E.; Sanchez-Prado, L.; Kalogerakis, N. *Anal. Chim. Acta* **2012**, *742*, 30−36.
(277) Psillakis, E. *Anal. Chim. Acta* **2017**, *986*, 12−24.
(278) Fernandez, M. E.; Palacio, M. A.; Labaque, M. C. *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* **2017**, *1044−1045*, 39−46.
(279) Li, X.; Yang, R.; Lin, S.; Ye, H.; Chen, F. *J. Food Meas. Charact.* **2017**, *11*, 1118−1127.
(280) Naddaf, E.; Ebrahimi, M.; Es'haghi, Z.; Akhlaghi, H. *Anal. Methods* **2015**, *7*, 7831−7839.
(281) Wang, H.; Geppert, H.; Fischer, T.; Wieprecht, W.; Moller, D. *J. Chromatogr. Sci.* **2015**, *53*, 1427−1431.
(282) Al-Alam, J.; Fajloun, Z.; Chbani, A.; Millet, M. *Anal. Bioanal. Chem.* **2017**, *409*, 5157−5169.
(283) Cifuentes, A. *J. Chromatogr. A* **2009**, *1216*, 7109.
(284) Cuadros-Rodríguez, L.; Ruiz-Samblás, C.; Valverde-Som, L.; Pérez-Castaño, E.; González-Casado, A. *Anal. Chim. Acta* **2016**, *909*, 9−23.
(285) Oliveira, L. F.; Braga, S. C. G. N.; Augusto, F.; Hashimoto, J. C.; Efraim, P.; Poppi, R. J. *Food Res. Int.* **2016**, *90*, 133−138.
(286) Jiang, Y.; Zhao, L.; Yuan, M.; Fu, A. *J. Food Biochem.* **2017**, *41*, e12375.
(287) Silva, P.; Freitas, J.; Silva, C. L.; Perestrelo, R.; Nunes, F. M.; Câmara, J. S. *Food Control* **2017**, *73*, 1176−1188.
(288) Chmiel, T.; Kupska, M.; Wardencki, W.; Namieśnik, J. *Food Chem.* **2017**, *221*, 1041−1056.
(289) Beema Shafreen, R.; Dymerski, T.; Namieśnik, J.; Jastrzębski, Z.; Vearasilp, S.; Gorinstein, S. *Food Hydrocolloids* **2017**, *72*, 297−303.
(290) Fontanive, F. C.; Souza-Silva, É. A.; Caramao, E.; Zini, C. A.; Pawliszyn, J.; Sidisky, L. M.; Buchanan, M. D.; Vitkuske, D. *Reporter* **2016**, *34.1*, 3−7.
(291) Lee, C. W.; Tabor, D. G.; Cowen, K. A. *J. Mater. Cycles Waste Manage.* **2008**, *10*, 38−45.
(292) Grandy, J. J.; Gómez-Ríos, G. A.; Pawliszyn, J. *J. Chromatogr. A* **2015**, *1410*, 1−8.
(293) Pawliszyn, J. *Handbook of Solid Phase Microextraction*; Chemical Industry Press: Beijing, 2009.
(294) Belardi, R. P.; Pawliszyn, J. B. *Water Qual. Res. J. Canada* **1989**, *24*, 179−191.
(295) Arthur, C. L.; Pawliszyn, J. *Anal. Chem.* **1990**, *62*, 2145−2148.
(296) Gałuszka, A.; Migaszewski, Z. M.; Konieczka, P.; Namieśnik, J. *TrAC, Trends Anal. Chem.* **2012**, *37*, 61−72.
(297) Lord, H. L.; Zhan, W.; Pawliszyn, J. *Compr. Sampl. Sample Prep.* **2012**, *2*, 677−697.
(298) Gómez-Ríos, G. A.; Reyes-Garcés, N.; Pawliszyn, J. *J. Sep. Sci.* **2013**, *36*, 2939−2945.
(299) Xie, X.; Truong, T. V.; Murray, J. A.; Contreras, J. A.; Tolley, H. D.; Lee, M. L. *Anal. Methods* **2013**, *5*, 6312.
(300) Pawliszyn, J. B.; Grandy, J. J.; Gomez-Rios, G. A. *Standard Analyte Generator*. U.S. Patent 9,625,426, April 18, 2017.
(301) Gionfriddo, E.; Passarini, A.; Pawliszyn, J. *J. Chromatogr. A* **2016**, *1457*, 22−28.
(302) Jia, M.; Koziel, J.; Pawliszyn, J. *Field Anal. Chem. Technol.* **2000**, *4*, 73−84.
(303) Grandy, J.; Asl-Hariri, S.; Pawliszyn, J. In *Comprehensive Analytical Chemistry*; Elsevier: Amsterdam, The Netherlands, 2015; pp 209−235.
(304) Lord, H. L.; Zhan, W.; Pawliszyn, J. *Anal. Chim. Acta* **2010**, *677*, 3−18.
(305) Cheng, W.-H.; Zhan, W.; Pawliszyn, J. *J. Chin. Chem. Soc.* **2013**, *60*, 1027−1032.
(306) Cheng, W. H.; Jiang, J. R.; Lin, C.; Liou, J. J.; Wu, Z. H.; Hsu, Y. H.; Yang, Z. Y. *J. Air Waste Manage. Assoc.* **2014**, *64*, 488−493.
(307) Saito, Y.; Ueta, I.; Ogawa, M.; Jinno, K. In *Comprehensive Sampling and Sample Preparation*; Pawliszyn, J., Ed.; Elsevier, 2012; pp 927−942.
(308) Kędziora, K.; Wasiak, W. *J. Chromatogr. A* **2017**, *1505*, 1−17.
(309) Reyes-Garcés, N.; Gómez-Ríos, G. A.; Souza-Silva, É. A.; Pawliszyn, J. *J. Chromatogr. A* **2013**, *1300*, 193−198.
(310) Azari, M. R.; Barkhordari, A.; Zendehdel, R.; Heidari, M. *Microchem. J.* **2017**, *134*, 270−276.
(311) Baktash, M. Y.; Bagheri, H. *Microchim. Acta* **2017**, *184*, 2151−2156.
(312) Vallecillos, L.; Borrull, F.; Sanchez, J. M.; Pocurull, E. *Talanta* **2015**, *132*, 548−556.
(313) Kleeblatt, J.; Stengel, B.; Radischat, C.; Passig, J.; Streibel, T.; Sippula, O.; Rabe, R.; Harndorf, H.; Zimmermann, R. *Anal. Methods* **2015**, *7*, 3608−3617.
(314) Heidari, M.; Attari, S. G.; Rafieiemam, M. *Anal. Chim. Acta* **2016**, *918*, 43−49.
(315) Xie, X.; Tolley, D. H.; Lee, M. L. *J. Chromatogr. A* **2017**, *1502*, 1−7.
(316) Peruga, A.; Beltrán, J.; López, F.; Hernández, F. *Anal. Bioanal. Chem.* **2014**, *406*, 5271−5282.
(317) Yegemova, S.; Bakaikina, N. V.; Kenessov, B.; Koziel, J. A.; Nauryzbayev, M. *Talanta* **2015**, *143*, 226−233.
(318) Djurovic-Pejcev, R.; Djordjevic, T.; Bursic, V. *J. Serb. Chem. Soc.* **2016**, *81*, 923−934.
(319) Ghiasvand, A. R.; Hajipour, S.; Heidari, N. *TrAC, Trends Anal. Chem.* **2016**, *77*, 54−65.
(320) Menezes, H. C.; De Lourdes Cardeal, Z. *J. Chromatogr. A* **2011**, *1218*, 3300−3305.
(321) Dias, C. M.; Menezes, H. C.; Cardeal, Z. L. *Anal. Bioanal. Chem.* **2017**, *409*, 2821−2828.
(322) Memarian, E.; Hosseiny Davarani, S. S.; Nojavan, S.; Movahed, S. K. *Anal. Chim. Acta* **2016**, *935*, 151−160.
(323) Contreras, J. A.; Murray, J. A.; Tolley, S. E.; Oliphant, J. L.; Tolley, H. D.; Lammert, S. A.; Lee, E. D.; Later, D. W.; Lee, M. L. *J. Am. Soc. Mass Spectrom.* **2008**, *19*, 1425−1434.
(324) Ouyang, Z.; Cooks, R. G. *Annu. Rev. Anal. Chem.* **2009**, *2*, 187−214.

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

(325) Smith, P. A.; Lepage, C. R. J.; Savage, P. B.; Bowerbank, C. R.; Lee, E. D.; Lukacs, M. J. *Anal. Chim. Acta* **2011**, *690*, 215−220.
(326) Smith, P. A.; Lepage, C. J.; Lukacs, M.; Martin, N.; Shufutinsky, A.; Savage, P. B. *Int. J. Mass Spectrom.* **2010**, *295*, 113−118.
(327) Smith, P. A.; Roe, M. T. A.; Sadowski, C.; Lee, E. D. *J. Occup. Environ. Hyg.* **2011**, *8*, 129−138.
(328) Snyder, D. T.; Pulliam, C. J.; Ouyang, Z.; Cooks, R. G. *Anal. Chem.* **2016**, *88*, 2−29.
(329) Zhang, M.; Kruse, N. A.; Bowman, J. R.; Jackson, G. P. *Appl. Spectrosc.* **2016**, *70*, 785−793.
(330) Visotin, A.; Lennard, C. *Aust. J. Forensic Sci.* **2016**, *48*, 203−221.
(331) de la Mata, A. P.; McQueen, R. H.; Nam, S. L.; Harynuk, J. J. *Anal. Bioanal. Chem.* **2017**, *409*, 1905−1913.
(332) Couto, M.; Barbosa, C.; Silva, D.; Rudnitskaya, A.; Delgado, L.; Moreira, A.; Rocha, S. M. *Pediatr. Allergy Immunol.* **2017**, *28*, 452−457.
(333) Ahmed, I.; Greenwood, R.; de Costello, B. L.; Ratcliffe, N. M.; Probert, C. S. *PLoS One* **2013**, *8*, e58204.
(334) Lamani, X.; Horst, S.; Zimmermann, T.; Schmidt, T. C. *Anal. Bioanal. Chem.* **2015**, *407*, 241−252.
(335) Kwon, S.-M.; Shin, H.-S. *J. Chromatogr. A* **2015**, *1407*, 216−221.
(336) Mochalski, P.; Wzorek, B.; Sliwka, I.; Amann, A. *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* **2009**, *877*, 189−196.
(337) Song, H.-N.; Kim, C. H.; Lee, W.-Y.; Cho, S.-H. *Rapid Commun. Mass Spectrom.* **2017**, *31*, 613−622.
(338) Koureas, M.; Karagkouni, F.; Rakitskii, V.; Hadjichristodoulou, C.; Tsatsakis, A.; Tsakalof, A. *Environ. Res.* **2016**, *148*, 318−321.
(339) Meyer-Monath, M.; Beaumont, J.; Morel, I.; Rouget, F.; Tack, K.; Lestremau, F. *Anal. Bioanal. Chem.* **2014**, *406*, 4481−4490.
(340) Rahman, G. M. M.; Wolle, M. M.; Fahrenholz, T.; Kingston, H. M. S.; Pamuku, M. *Anal. Chem.* **2014**, *86*, 6130−6137.
(341) Sommer, Y. L.; Verdon, C. P.; Fresquez, M. R.; Ward, C. D.; Wood, E. B.; Pan, Y.; Caldwell, K. L.; Jones, R. L. *Anal. Bioanal. Chem.* **2014**, *406*, 5039−5047.
(342) Ali, S. E.; Farag, M. A.; Holvoet, P.; Hanafi, R. S.; Gad, M. Z. *Sci. Rep.* **2016**, *6*, 36359.
(343) Wang, C.; Li, P.; Lian, A.; Sun, B.; Wang, X.; Guo, L.; Chi, C.; Liu, S.; Zhao, W.; Luo, S.; Guo, Z.; Zhang, Y.; Ke, C.; Ye, G.; Xu, G.; Zhang, F.; Li, E. *Cancer Biol. Ther.* **2014**, *15*, 200−206.
(344) Mochalski, P.; King, J.; Klieber, M.; Unterkofler, K.; Hinterhuber, H.; Baumann, M.; Amann, A. *Analyst* **2013**, *138*, 2134−2145.
(345) De Filippis, F.; Vannini, L.; La Storia, A.; Laghi, L.; Piombino, P.; Stellato, G.; Serrazanetti, D. I.; Gozzi, G.; Turroni, S.; Ferrocino, I.; Lazzi, C.; Di Cagno, R.; Gobbetti, M.; Ercolini, D. *PLoS One* **2014**, *9*, e112373.
(346) Monteiro, M.; Moreira, N.; Pinto, J.; Pires-Luís, A. S.; Henrique, R.; Jerónimo, C.; Bastos, M. de L.; Gil, A. M.; Carvalho, M.; Guedes de Pinho, P. *J. Cell. Mol. Med.* **2017**, *21*, 2092−2105.
(347) Calejo, I.; Moreira, N.; Araújo, A. M.; Carvalho, M.; De Lourdes Bastos, M.; De Pinho, P. G. *Talanta* **2016**, *148*, 486−493.
(348) Cozzolino, R.; De Magistris, L.; Saggese, P.; Stocchero, M.; Martignetti, A.; Di Stasio, M.; Malorni, A.; Marotta, R.; Boscaino, F.; Malorni, L. *Anal. Bioanal. Chem.* **2014**, *406*, 4649−4662.
(349) Zhang, S.; Liu, L.; Steffen, D.; Ye, T.; Raftery, D. *Metabolomics* **2012**, *8*, 323−334.
(350) Wang, C.; Feng, Y.; Wang, M.; Pi, X.; Tong, H.; Wang, Y.; Zhu, L.; Li, E. *Sci. Rep.* **2015**, *5*, 14744.
(351) De Angelis, M.; Montemurno, E.; Piccolo, M.; Vannini, L.; Lauriero, G.; Maranzano, V.; Gozzi, G.; Serrazanetti, D.; Dalfino, G.; Gobbetti, M.; Gesualdo, L. *PLoS One* **2014**, *9*, e99006.
(352) De Angelis, M.; Piccolo, M.; Vannini, L.; Siragusa, S.; De Giacomo, A.; Serrazzanetti, D. I.; Cristofori, F.; Guerzoni, M. E.; Gobbetti, M.; Francavilla, R. *PLoS One* **2013**, *8*, e76993.
(353) Khatib, S.; Finberg, J. P. M.; Artoul, F.; Lavner, Y.; Mahmood, S.; Tisch, U.; Haick, H.; Aluf, Y.; Vaya, J. *Neurochem. Int.* **2014**, *76*, 82−90.
(354) Bouhlel, J.; Ratel, J.; Abouelkaram, S.; Mercier, F.; Travel, A.; Baéza, E.; Jondreville, C.; Dervilly-Pinel, G.; Marchand, P.; Le Bizec, B.; Dubreil, E.; Mompelat, S.; Verdon, E.; Inthavong, C.; Guérin, T.; Rutledge, D. N.; Engel, E. *J. Chromatogr. A* **2017**, *1497*, 9−18.
(355) Naccarato, A.; Gionfriddo, E.; Sindona, G.; Tagarelli, A. *J. Chromatogr. A* **2014**, *1338*, 164−173.
(356) Naccarato, A.; Gionfriddo, E.; Sindona, G.; Tagarelli, A. *Anal. Chim. Acta* **2014**, *810*, 17−24.
(357) Hardy, E. M.; Duca, R. C.; Salquebre, G.; Appenzeller, B. M. R. *Forensic Sci. Int.* **2015**, *249*, 6−19.
(358) Sun, Y.-P.; Chen, J.; Qi, H.-Y.; Shi, Y.-P. *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* **2015**, *1004*, 53−59.
(359) Abedi, H.; Ebrahimzadeh, H.; Ghasemi, J. B. *Microchim. Acta* **2015**, *182*, 633−641.
(360) Banitaba, M. H.; Davarani, S. S. H.; Ahmar, H.; Movahed, S. K. *J. Sep. Sci* **2014**, *37*, 1162−1169.
(361) Rajabi Khorrami, A.; Rashidpur, A. *Anal. Chim. Acta* **2012**, *727*, 20−25.
(362) Jia, J.; Xu, L.; Wang, S.; Wang, L.; Liu, X. *Anal. Bioanal. Chem.* **2014**, *406*, 3209−3217.
(363) Rezazadeh, M.; Yamini, Y.; Seidi, S.; Ebrahimpour, B. *J. Chromatogr. A* **2013**, *1280*, 16−22.
(364) Rezazadeh, M.; Yamini, Y.; Seidi, S. *J. Chromatogr. A* **2015**, *1396*, 1−6.
(365) Shamsayei, M.; Yamini, Y.; Asiabi, H.; Rezazadeh, M.; Seidi, S. *Microchim. Acta* **2017**, *184*, 2697−2705.
(366) Mohammadkhani, E.; Yamini, Y.; Rezazadeh, M.; Seidi, S. *J. Chromatogr. A* **2016**, *1443*, 75−82.
(367) Souza-Silva, É. a.; Reyes-Garcés, N.; Gómez-Ríos, G. a.; Boyacı, E.; Bojko, B.; Pawliszyn, J.; Boyaci, E.; Bojko, B.; Pawliszyn, J. *TrAC, Trends Anal. Chem.* **2015**, *71*, 249−264.
(368) Piri-Moghadam, H.; Alam, M. N.; Pawliszyn, J. *Anal. Chim. Acta* **2017**, *984*, 42−65.
(369) Bojko, B.; Vuckovic, D.; Cudjoe, E.; Hoque, M. E.; Mirnaghi, F.; Wąsowicz, M.; Jerath, A.; Pawliszyn, J. *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* **2011**, *879*, 3781−3787.
(370) Birjandi, A. P.; Mirnaghi, F. S.; Bojko, B.; Wąsowicz, M.; Pawliszyn, J. *Anal. Chem.* **2014**, *86*, 12022−12029.
(371) Vuckovic, D.; Pawliszyn, J. *Anal. Chem.* **2011**, *83*, 1944−1954.
(372) Bojko, B.; Wąsowicz, M.; Pawliszyn, J. *J. Pharm. Anal.* **2014**, *4*, 6−13.
(373) Ouyang, G.; Vuckovic, D.; Pawliszyn, J. *Chem. Rev.* **2011**, *111*, 2784−2814.
(374) Cudjoe, E.; Bojko, B.; Togunde, P.; Pawliszyn, J. *Bioanalysis* **2012**, *4*, 2605−2619.
(375) Musteata, F. M.; Musteata, M. L.; Pawliszyn, J. *Clin. Chem.* **2006**, *52*, 708−715.
(376) Vuckovic, D.; De Lannoy, I.; Gien, B.; Yang, Y.; Musteata, F. M.; Shirey, R.; Sidisky, L.; Pawliszyn, J. *J. Chromatogr. A* **2011**, *1218*, 3367−3375.
(377) Lord, H. L.; Zhang, X.; Musteata, F. M.; Vuckovic, D.; Pawliszyn, J. *Nat. Protoc.* **2011**, *6*, 896−924.
(378) Vuckovic, D.; De Lannoy, I.; Gien, B.; Shirey, R. E.; Sidisky, L. M.; Dutta, S.; Pawliszyn, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5344−5348.
(379) Vuckovic, D.; Risticevic, S.; Pawliszyn, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5618−5628.
(380) Mirnaghi, F. S.; Pawliszyn, J. *Anal. Chem.* **2012**, *84*, 8301−8309.
(381) Bojko, B.; Gorynski, K.; Gomez-Rios, G. A.; Knaak, J. M.; Machuca, T.; Spetzler, V. N.; Cudjoe, E.; Hsin, M.; Cypel, M.; Selzner, M.; Liu, M.; Keshavjee, S.; Pawliszyn, J. *Anal. Chim. Acta* **2013**, *803*, 75−81.
(382) Cudjoe, E.; Bojko, B.; de Lannoy, I.; Saldivia, V.; Pawliszyn, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12124−12126.
(383) Bojko, B.; Gorynski, K.; Gomez-Rios, G. A.; Knaak, J. M.; Machuca, T.; Cudjoe, E.; Spetzler, V. N.; Hsin, M.; Cypel, M.; Selzner, M.; Liu, M.; Keshjavee, S.; Pawliszyn, J. *Lab. Invest.* **2014**, *94*, 586−594.

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

(384) Boyacı, E.; Gorynski, K.; Rodriguez-Lafuente, A.; Bojko, B.; Pawliszyn, J. *Anal. Chim. Acta* **2014**, *809*, 69−81.
(385) Reyes-Garcés, N.; Bojko, B.; Pawliszyn, J. *J. Chromatogr. A* **2014**, *1374*, 40−49.
(386) Gorynski, K.; Bojko, B.; Kluger, M.; Jerath, A.; Wąsowicz, M.; Pawliszyn, J. *J. Pharm. Biomed. Anal.* **2014**, *92*, 183−192.
(387) Bessonneau, V.; Boyaci, E.; Maciazek-Jurczyk, M.; Pawliszyn, J. *Anal. Chim. Acta* **2015**, *856*, 35−45.
(388) Mousavi, F.; Bojko, B.; Pawliszyn, J. *Anal. Chim. Acta* **2015**, *892*, 95−104.
(389) Yang, Q. J. J.; Kluger, M.; Goryński, K.; Pawliszyn, J.; Bojko, B.; Yu, A. M. M.; Noh, K.; Selzner, M.; Jerath, A.; McCluskey, S.; Pang, K. S. S.; Wąsowicz, M. *Biopharm. Drug Dispos.* **2017**, *38*, 326−339.
(390) Shamsayei, M.; Yamini, Y.; Asiabi, H. *J. Chromatogr. A* **2016**, *1475*, 8−17.
(391) Wang, C.; Zhou, W.; Liao, X.; Zhang, W.; Chen, Z. *Microchim. Acta* **2017**, *184*, 2715−2721.
(392) Wu, S.; Cai, C.; Cheng, J.; Cheng, M.; Zhou, H.; Deng, J. *Anal. Chim. Acta* **2016**, *935*, 113−120.
(393) Jiang, H. P.; Chu, J. M.; Lan, M. D.; Liu, P.; Yang, N.; Zheng, F.; Yuan, B. F.; Feng, Y. Q. *J. Chromatogr. A* **2016**, *1462*, 90−99.
(394) Filipiak, W.; Mochalski, P.; Filipiak, A.; Ager, C.; Cumeras, R.; Davis, C. E.; Agapiou, A.; Unterkofler, K.; Troppmair, J. *Curr. Med. Chem.* **2016**, *23*, 2112−2131.
(395) Wang, Y.; Hu, Y.; Wang, D.; Yu, K.; Wang, L. *Cancer Biomark.* **2012**, *11*, 129−137.
(396) Hossain, S. M. Z.; Bojko, B.; Pawliszyn, J. *Anal. Chim. Acta* **2013**, *776*, 41−49.
(397) Bean, H. D.; Dimandja, J.-M. D.; Hill, J. E. *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* **2012**, *901*, 41−46.
(398) Tang, H.; Lu, Y.; Zhang, L.; Wu, Z.; Hou, X.; Xia, H. *Biosci. Rep.* **2017**, *37*, BSR20170106.
(399) Li, J. H.; Xu, H. *Talanta* **2017**, *167*, 623−629.
(400) Pyo, J. S.; Ju, H. K.; Park, J. H.; Kwon, S. W. *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.* **2008**, *876*, 170−174.
(401) Mousavi, F.; Gionfriddo, E.; Carasek, E.; Souza-Silva, E. A.; Pawliszyn, J. *Metabolomics* **2016**, DOI: 10.1007/s11306-016-1111-9.
(402) Aksenov, A. A.; Gojova, A.; Zhao, W.; Morgan, J. T.; Sankaran, S.; Sandrock, C. E.; Davis, C. E. *ChemBioChem* **2012**, *13*, 1053−1059.
(403) Lee, E. A.; Angka, L.; Rota, S. G.; Hanlon, T.; Mitchell, A.; Hurren, R.; Wang, X. M.; Gronda, M.; Boyaci, E.; Bojko, B.; Minden, M.; Sriskanthadevan, S.; Datti, A.; Wrana, J. L.; Edginton, A.; Pawliszyn, J.; Joseph, J. W.; Quadrilatero, J.; Schimmer, A. D.; Spagnuolo, P. A. *Cancer Res.* **2015**, *75*, 2478−2488.
(404) Piri-Moghadam, H.; Ahmadi, F.; Gómez-Ríos, G. A.; Boyaci, E.; Reyes-Garcés, N.; Aghakhani, A.; Bojko, B.; Pawliszyn, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 7510−7514.
(405) Pawliszyn, J. *J. High Resolut. Chromatogr.* **1993**, *16* (10), 565−565.
(406) Zhang, Z.; Yang, M. J.; Pawliszyn, J. *Anal. Chem.* **1994**, *66*, 844A−853A.
(407) Gómez-Ríos, G. A.; Pawliszyn, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 14503−14507.
(408) Deng, J.; Yang, Y.; Wang, X.; Luan, T. *TrAC, Trends Anal. Chem.* **2014**, *55*, 55−67.
(409) Mester, Z.; Lam, J.; Sturgeon, R.; Pawliszyn, J. *J. Anal. At. Spectrom.* **2000**, *15*, 837−842.
(410) Zheng, F.; Hu, B. *Talanta* **2011**, *85*, 1166−1173.
(411) Liberto, E.; Ruosi, M. R.; Cordero, C.; Rubiolo, P.; Bicchi, C.; Sgorbini, B. *J. Agric. Food Chem.* **2013**, *61*, 1652−1660.
(412) Bicchi, C.; Ruosi, M. R.; Cagliero, C.; Cordero, C.; Liberto, E.; Rubiolo, P.; Sgorbini, B. *J. Chromatogr. A* **2011**, *1218*, 753−762.
(413) Meurer, E. C.; Tomazela, D. M.; Silva, R. C.; Augusto, F.; Eberlin, M. N. *Anal. Chem.* **2002**, *74*, 5688−5692.
(414) da Silva, R. C.; Zuin, V. G.; Yariwake, J. H.; Eberlin, M. N.; Augusto, F. *J. Mass Spectrom.* **2007**, *42*, 1358−1362.
(415) Boyacı, E.; Goryński, K.; Viteri, C. R.; Pawliszyn, J. *J. Chromatogr. A* **2016**, *1436*, 51−58.
(416) Lord, H. L.; Möder, M.; Popp, P.; Pawliszyn, J. B. *Analyst* **2004**, *129*, 107−108.
(417) van Hout, M. W. J.; Jas, V.; Niederländer, H. A. G.; de Zeeuw, R. A.; de Jong, G. J. *Analyst* **2002**, *127*, 355−359.
(418) Deng, J.; Yu, T.; Yao, Y.; Peng, Q.; Luo, L.; Chen, B.; Wang, X.; Yang, Y.; Luan, T. *Anal. Chim. Acta* **2017**, *954*, 52−59.
(419) Liu, C.; Gómez-Ríos, G. A.; Schneider, B. B.; Le Blanc, J. C. Y.; Reyes-Garcés, N.; Arnold, D. W.; Covey, T. R.; Pawliszyn, J. *Anal. Chim. Acta* **2017**, *991*, 89−94.
(420) Mirabelli, M. F.; Wolf, J.-C.; Zenobi, R. *Anal. Chem.* **2016**, *88*, 7252−7258.
(421) Jastrzembski, J. A.; Bee, M. Y.; Sacks, G. L. *J. Agric. Food Chem.* **2017**, *65*, 9353.
(422) Tong, H.; Sze, N.; Thomson, B.; Nacson, S.; Pawliszyn, J. *Analyst* **2002**, *127*, 1207−1210.
(423) Wang, Y.; Walles, M.; Thomson, B.; Nacson, S.; Pawliszyn, J. *Rapid Commun. Mass Spectrom.* **2004**, *18*, 157−162.
(424) Wang, Y.; Schneider, B. B.; Covey, T. R.; Pawliszyn, J. *Anal. Chem.* **2005**, *77*, 8095−8101.
(425) Huang, S.; Xu, J.; Tao, X.; Chen, X.; Zhu, F.; Wang, Y.; Jiang, R.; Ouyang, G. *Talanta* **2017**, *172*, 155−161.
(426) Javanshad, R.; Venter, A. R. *Anal. Methods* **2017**, *9*, 4896−4907.
(427) Nanita, S. C.; Kaldon, L. G. *Anal. Bioanal. Chem.* **2016**, *408*, 23−33.
(428) Gómez-Ríos, G. A.; Liu, C.; Tascon, M.; Reyes-Garcés, N.; Arnold, D. W.; Covey, T. R.; Pawliszyn, J. *Anal. Chem.* **2017**, *89*, 3805−3809.
(429) Kennedy, J. H.; Aurand, C.; Shirey, R.; Laughlin, B. C.; Wiseman, J. M. *Anal. Chem.* **2010**, *82*, 7502−7508.
(430) Tascon, M.; Gómez-Ríos, G. A.; Reyes-Garcés, N.; Poole, J.; Boyacı, E.; Pawliszyn, J. *Anal. Chem.* **2017**, *89*, 8421−8428.
(431) Tascon, M.; Gómez-Ríos, G. A.; Reyes-Garcés, N.; Poole, J.; Boyacı, E.; Pawliszyn, J. *J. Pharm. Biomed. Anal.* **2017**, *144*, 106−111.
(432) Deng, J.; Yang, Y.; Fang, L.; Lin, L.; Zhou, H.; Luan, T. *Anal. Chem.* **2014**, *86*, 11159−11166.
(433) Ahmad, S.; Tucker, M.; Spooner, N.; Murnane, D.; Gerhard, U. *Anal. Chem.* **2015**, *87*, 754−759.
(434) Hemalatha, R. G.; Ganayee, M. A.; Pradeep, T. *Anal. Chem.* **2016**, *88*, 5710−5717.
(435) Ghiasikhou, S.; da Silva, M. F.; Zhu, Y.; Zenobi, R. *Anal. Bioanal. Chem.* **2017**, *409*, 6873−6883.
(436) Wang, X.; Li, X.; Li, Z.; Zhang, Y.; Bai, Y.; Liu, H. *Anal. Chem.* **2014**, *86*, 4739−4747.
(437) Gómez-Ríos, G. A.; Pawliszyn, J. *Chem. Commun.* **2014**, *50*, 12937−12940.
(438) Wang, X.; Li, X.; Bai, Y.; Liu, H. *Chem. Commun. (Cambridge, U. K.)* **2015**, *51*, 4615−4618.
(439) Jastrzembski, J. A.; Sacks, G. L. *Anal. Chem.* **2016**, *88*, 8617−8623.
(440) Dumlao, M. C.; Jeffress, L. E.; Gooding, J. J.; Donald, W. A. *Analyst* **2016**, *141*, 3714−3721.
(441) Möder, M.; Löster, H.; Herzschuh, R.; Popp, P. *J. Mass Spectrom.* **1997**, *32*, 1195−1204.
(442) Lord, H. L. *J. Chromatogr. A* **2007**, *1152*, 2−13.
(443) McCooeye, M. A.; Mester, Z.; Ells, B.; Barnett, D. A.; Purves, R. W.; Guevremont, R. *Anal. Chem.* **2002**, *74*, 3071−3075.
(444) Piri-Moghadam, H.; Lendor, S.; Pawliszyn, J. *Anal. Chem.* **2016**, *88*, 12188−12195.
(445) Van Berkel, G. J.; Kertesz, V. *Rapid Commun. Mass Spectrom.* **2015**, *29*, 1749−1756.
(446) Van Berkel, G. J.; Kertesz, V. *Rapid Commun. Mass Spectrom.* **2017**, *31*, 281−291.
(447) Guo, F.; Górecki, T.; Irish, D.; Pawliszyn, J. *Anal. Commun.* **1996**, *33*, 361.
(448) Górecki, T.; Pawliszyn, J.; Belkin, M.; Caruso, J. *Anal. Commun.* **1997**, *34*, 275−278.
(449) Amirav, A.; Dagan, S. *Eur. Mass Spectrom.* **1997**, *3*, 105.

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

(450) Poliak, M.; Gordin, A.; Amirav, A. *Anal. Chem.* **2010**, *82*, 5777−5782.
(451) Pérès, C.; Viallon, C.; Berdagué, J. L. *Anal. Chem.* **2001**, *73*, 1030−1036.
(452) Marsili, R. T. *J. Agric. Food Chem.* **1999**, *47*, 648−654.
(453) Riter, L. S.; Meurer, E. C.; Cotte-Rodriguez, I.; Eberlin, M. N.; Cooks, R. G. *Analyst* **2003**, *128*, 1119.
(454) Mester, Z.; Sturgeon, R. E.; Lam, J. W.; Tian, L.-C.; Sandra, P. *J. Anal. At. Spectrom.* **2000**, *15*, 1461−1465.
(455) Almasian, M. R.; Yang, C.; Xing, Z.; Zhang, S.; Zhang, X. *Rapid Commun. Mass Spectrom.* **2010**, *24*, 742−748.
(456) Chou, J. *Multiple Solid Phase Microextraction (m-SPME) Coupled with Thermal Desorption Electrospray Ionization Mass Spectrometry (TD-ESI/MS) for Quantifying Emerging Pollutants and Abused Drugs*. National Sun Yat-Sen University, Taiwan, 2014.
(457) Shiea, J.; Huang, M.; Chou, J. *Multiple Solid Phase Micro-Extraction Thermal Desorption Ionization Device, Mass Spectrometer and Analytical Method for Mass Spectrometry*. U.S. Patent Application 20150144777, May 28, 2015.
(458) Mirabelli, M. F.; Wolf, J. C.; Zenobi, R. *Anal. Bioanal. Chem.* **2016**, *408*, 3425−3434.
(459) Kruth, C.; Czech, H.; Sklorz, M.; Passig, J.; Ehlert, S.; Cappiello, A.; Zimmermann, R. *Anal. Chem.* **2017**, *89*, 10917−10923.
(460) Takáts, Z.; Wiseman, J. M.; Gologan, B.; Cooks, R. G. *Anal. Chem.* **2004**, *76*, 4050−4058.
(461) Cooks, R. G.; Ouyang, Z.; Takats, Z.; Wiseman, J. M. *Science* **2006**, *311*, 1566−1570.
(462) St John, E. R.; Rossi, M.; Pruski, P.; Darzi, A.; Takats, Z. *TrAC, Trends Anal. Chem.* **2016**, *85*, 2−9.
(463) Ferreira, C. R.; Yannell, K. E.; Jarmusch, A. K.; Pirro, V.; Ouyang, Z.; Cooks, R. G. *Clin. Chem.* **2016**, *62*, 99−110.
(464) Zhang, J.; Rector, J.; Lin, J. Q.; Young, J. H.; Sans, M.; Katta, N.; Giese, N.; Yu, W.; Nagi, C.; Suliburk, J.; Liu, J.; Bensussan, A.; DeHoog, R. J.; Garza, K. Y.; Ludolph, B.; Sorace, A. G.; Syed, A.; Zahedivash, A.; Milner, T. E.; Eberlin, L. S. *Sci. Transl. Med.* **2017**, *9*, eaan3968.
(465) Peacock, P. M.; Zhang, W.-J.; Trimpin, S. *Anal. Chem.* **2017**, *89*, 372−388.
(466) Badu-Tawiah, A. K.; Eberlin, L. S.; Ouyang, Z.; Cooks, R. G. *Annu. Rev. Phys. Chem.* **2013**, *64*, 481−505.
(467) Hajslova, J.; Cajka, T.; Vaclavik, L. *TrAC, Trends Anal. Chem.* **2011**, *30*, 204−218.
(468) Guo, T.; Fang, P.; Jiang, J.; Zhang, F.; Yong, W.; Liu, J.; Dong, Y. *J. Chromatogr. A* **2016**, *1471*, 27−33.
(469) Strittmatter, N.; Düring, R.-A.; Takáts, Z. *Analyst* **2012**, *137*, 4037−4044.
(470) Jarmusch, A. K.; Pirro, V.; Baird, Z.; Hattab, E. M.; Cohen-Gadol, A. A.; Cooks, R. G. *Proc. Natl. Acad. Sci. U. S. A.* **2016**, *113*, 1486−1491.
(471) Pruski, P.; MacIntyre, D. A.; Lewis, H. V.; Inglese, P.; Correia, G. D. S.; Hansel, T. T.; Bennett, P. R.; Holmes, E.; Takats, Z. *Anal. Chem.* **2017**, *89*, 1540−1550.
(472) Inglese, P.; McKenzie, J. S.; Mroz, A.; Kinross, J.; Veselkov, K.; Holmes, E.; Takats, Z.; Nicholson, J. K.; Glen, R. C. *Chem. Sci.* **2017**, *8*, 3500−3511.
(473) Wiseman, J. M.; Ifa, D. R.; Song, Q.; Cooks, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7188−7192.
(474) D'Agostino, P. A.; Hancock, J. R.; Chenier, C. L.; Lepage, C. R. J. *J. Chromatogr. A* **2006**, *1110*, 86−94.
(475) Huang, G.; Chen, H.; Zhang, X.; Cooks, R. G.; Ouyang, Z. *Anal. Chem.* **2007**, *79*, 8327−8332.
(476) Tillner, J.; McKenzie, J. S.; Jones, E. A.; Speller, A. V. M.; Walsh, J. L.; Veselkov, K. A.; Bunch, J.; Takats, Z.; Gilmore, I. S. *Anal. Chem.* **2016**, *88*, 4808−4816.
(477) Cody, R. B.; Laramée, J. A.; Durst, H. D. *Anal. Chem.* **2005**, *77*, 2297−2302.
(478) Li, X.; Li, Z.; Wang, X.; Nie, H.; Zhang, Y.; Bai, Y.; Liu, H. *Analyst* **2016**, *141*, 4947−4952.
(479) LaPointe, J.; Musselman, B.; O'Neill, T.; Shepard, J. R. E. *J. Am. Soc. Mass Spectrom.* **2015**, *26*, 159−165.
(480) Wu, M.; Wang, H.; Dong, G.; Musselman, B. D.; Liu, C. C.; Guo, Y. *Chin. J. Chem.* **2015**, *33*, 213−219.
(481) Cajka, T.; Riddellova, K.; Tomaniova, M.; Hajslova, J. *J. Chromatogr. A* **2010**, *1217*, 4195−4203.
(482) Pérez, J. J.; Harris, G. A.; Chipuk, J. E.; Brodbelt, J. S.; Green, M. D.; Hampton, C. Y.; Fernández, F. M. *Analyst* **2010**, *135*, 712−719.
(483) Jones, C. M.; Fernández, F. M. *Rapid Commun. Mass Spectrom.* **2013**, *27*, 1311−1318.
(484) Gross, J. H. *Anal. Bioanal. Chem.* **2014**, *406*, 63−80.
(485) Li, F.; Tice, J.; Musselman, B. D.; Hall, A. B. *Sci. Justice* **2016**, *56*, 321−328.
(486) Walles, M.; Gu, Y.; Dartiguenave, C.; Musteata, F. M.; Waldron, K.; Lubda, D.; Pawliszyn, J. *J. Chromatogr. A* **2005**, *1067*, 197−205.
(487) Venter, A. R.; Douglass, K. A.; Shelley, J. T.; Hasman, G.; Honarvar, E. *Anal. Chem.* **2014**, *86*, 233−249.
(488) Zhao, Y.; Gong, X.; Si, X.; Wei, Z.; Yang, C.; Zhang, S.; Zhang, X. *Analyst* **2015**, *140*, 2599−2602.
(489) Yang, B.-C.; Fang, S.-F.; Wan, X.-J.; Luo, Y.; Zhou, J.-Y.; Li, Y.; Li, Y.-J.; Wang, F.; Huang, O.-P. *Anal. Chim. Acta* **2017**, *973*, 68−74.
(490) Zheng, Y.; Wang, Q.; Wang, X.; Chen, Y.; Wang, X.; Zhang, X.; Bai, Z.; Han, X.; Zhang, Z. *Anal. Chem.* **2016**, *88*, 7005−7013.
(491) Deng, L.; Webb, I. K.; Garimella, S. V. B.; Hamid, A. M.; Zheng, X.; Norheim, R. V.; Prost, S. A.; Anderson, G. A.; Sandoval, J. A.; Baker, E. S.; Ibrahim, Y. M.; Smith, R. D. *Anal. Chem.* **2017**, *89*, 4628−4634.
(492) Kuo, C. P.; Shiea, J. *Anal. Chem.* **1999**, *71*, 4413−4417.
(493) Li, T.; Fan, L.; Wang, Y.; Huang, X.; Xu, J.; Lu, J.; Zhang, M.; Xu, W. *Anal. Chem.* **2017**, *89*, 1453−1458.
(494) Zhang, M.; Lin, F.; Xu, J.; Xu, W. *Anal. Chem.* **2015**, *87*, 3123−3128.
(495) Mendes, T. P. P.; Pereira, I.; Ferreira, M. R.; Chaves, A. R.; Vaz, B. G. *Anal. Methods* **2017**, *9*, 6117.
(496) Pereira, I.; Ferreira Rodrigues, M.; Rodriguez Chaves, A.; Gontijo Vaz, B. *Talanta* **2018**, *178*, 507−514.
(497) Chang, Q.; Peng, Y.; Yun, L.; Zhu, Q.; Hu, S.; Shuai, Q. *Anal. Chem.* **2017**, *89*, 4147.
(498) Macdonald, N. P.; Zhu, F.; Hall, C. J.; Reboud, J.; Crosier, P. S.; Patton, E. E.; Wlodkowic, D.; Cooper, J. M. *Lab Chip* **2016**, *16*, 291−297.
(499) Gross, B. C.; Erkal, J. L.; Lockwood, S. Y.; Chen, C.; Spence, D. M. *Anal. Chem.* **2014**, *86*, 3240−3253.
(500) Chipuk, J. E.; Brodbelt, J. S. *J. Am. Soc. Mass Spectrom.* **2008**, *19*, 1612−1620.
(501) Harris, G. A.; Fernández, F. M. *Anal. Chem.* **2009**, *81*, 322−329.
(502) Eikel, D.; Henion, J. *Rapid Commun. Mass Spectrom.* **2011**, *25*, 2345−2354.
(503) Chekmeneva, E.; Correia, G.; Dénes, J.; Gómez-Romero, M.; Wijeyesekera, A.; Perenyi, D. R.; Koot, Y.; Boomsma, C.; Want, E. J.; Dixon, P. H.; Macklon, N. S.; Chan, Q.; Takáts, Z.; Nicholson, J. K.; Holmes, E. *Anal. Methods* **2015**, *7*, 5122−5133.
(504) Thevis, M.; Kuuranne, T.; Walpurgis, K.; Geyer, H.; Schänzer, W. *Drug Test. Anal.* **2016**, *8*, 7−29.
(505) Balog, J.; Perenyi, D.; Guallar-Hoyas, C.; Egri, A.; Pringle, S. D.; Stead, S.; Chevallier, O. P.; Elliott, C. T.; Takats, Z. *J. Agric. Food Chem.* **2016**, *64*, 4793−4800.
(506) Black, C.; Chevallier, O. P.; Elliott, C. T. *TrAC, Trends Anal. Chem.* **2016**, *82*, 268−278.
(507) Wittkamp, B. L.; Tilotta, D. C. *Anal. Chem.* **1995**, *67*, 600−605.
(508) Odziemkowski, M.; Koziel, J. A.; Irish, D. E.; Pawliszyn, J. *Anal. Chem.* **2001**, *73*, 3131−3139.
(509) Barnes, J. A.; Brown, R. S.; Cheung, A. H.; Dreher, M. A.; Mackey, G.; Loock, H. P. *Sens. Actuators, B* **2010**, *148*, 221−226.
(510) Nwaneshiudu, I. C.; Nwaneshiudu, C. A.; Schwartz, D. T. *Appl. Spectrosc.* **2014**, *68*, 1254−1259.

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360

(511) Yuan, Y.; Li, H.; Han, S.; Hu, L.; Xu, G. *Talanta* **2011**, *84*, 49−52.
(512) Bian, W.; Zhu, S.; Qi, M.; Xiao, L.; Liu, Z.; Zhan, J. *Anal. Methods* **2017**, *9*, 459−464.
(513) Abedi, H.; Ebrahimzadeh, H. *J. Sep. Sci.* **2015**, *38*, 1358−1364.
(514) Anjum, S.; Aziz-Ur-Rehman; Hu, L.; Majeed, S.; Qi, W.; Zhao, J.; Xu, G. *Sens. Actuators, B* **2015**, *210*, 137−143.
(515) Li, B.; Shi, Y. E.; Cui, J.; Liu, Z.; Zhang, X.; Zhan, J. *Anal. Chim. Acta* **2016**, *923*, 66−73.
(516) Sun, L.; Zhang, M.; Natarajan, V.; Yu, X.; Zhang, X.; Zhan, J. *RSC Adv.* **2017**, *7*, 23866−23874.
(517) Deng, J.; Yang, Y.; Xu, M.; Wang, X.; Lin, L.; Yao, Z.-P.; Luan, T. *Anal. Chem.* **2015**, *87*, 9923−9930.
(518) Liu, C.; Zhang, X.; Li, L.; Cui, J.; Shi, Y.; Wang, L.; Zhan, J. *Analyst* **2015**, *140*, 4668−4675.

DOI: 10.1021/acs.analchem.7b04502
Anal. Chem. 2018, 90, 302−360