Analytical methods for determination of cork-taint compounds in wine

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Cork taint is considered a major organoleptic defect in wine, producing a moldy aroma. Haloanisoles are the main compounds responsible, although there are other analytes that cause the same problem. Occurrence of cork taint deteriorates the quality and the acceptability of wines, causing significant financial loss to the wine industry.

The taste and odor thresholds of taint compounds in wine are very low, but the concentration causing a problem depends on the characteristics and the composition of the wine. Many efforts have been made to provide a highly-sensitive, selective analytical method for the determination of cork-taint compounds. Since the concentration of these analytes in wine is usually low, it is necessary to count on highly efficient preconcentration procedures for their estimation by instrumental techniques.

This review summarizes the most recent analytical developments in sample-preparation techniques for the determination of cork-taint compounds in wine, including different modes of liquid-phase microextraction, Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS), solid-phase microextraction, stir-bar sorptive extraction and microextraction in packed syringe.

Furthermore, we explain instrumental techniques used for separating and identifying cork-taint compounds. Recovery rates, detection limits, matrix effects and specific parameters of each method have all been considered and discussed.

Keywords: Cork taint; Gas chromatography (GC); Haloanisole; Liquid-phase microextraction (LPME); Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS); Sample preparation; Sorptive microextraction; Wine; Wine quality; 2,4,6-Trichloroanisole

Abbreviations: AED, Atomic emission detector; BERA, Bioelectric Recognition Assay; DVB/CAR/PDMS, Divinylbenzene/Carboxen/polydimethylsiloxane; DI, Direct immersion; DLLME, Dispersive liquid-liquid microextraction; DSPE, Dispersive solid-phase extraction; ECD, Electron-capture detector; ELISA, Enzyme-linked immunosorbent assay; EF, Enrichment factor; GC, Gas chromatography; HS, Headspace; [Hmim][NTf_2], 1-hexyl-3-methylimidazolium bis(trifluoromethylsulfonyl)-imide; IMS, Ion-mobility spectrometry; IL, Ionic liquid; LD, Liquid desorption; LPME, Liquid-phase microextraction; LLE, Liquid-liquid extraction; MS, Mass spectrometry; MS/MS, Tandem mass spectrometry; MDMP, 2-methoxy-3,5-dimethylpyrazine; MIB, 2-methylisoborneol; MSTFA, *N*-methyl-*N*-trimethylsilyltrifluoroacetamide; MEPS, Microextraction in packed syringe; MCC, Multicapillary column; O, Olfactometry; PCA, Pentachloroanisole; PCP, Pentachlorophenol; PDMS, Polydimethylsiloxane; PA, Polyacrylate; PSA, Primary secondary amine; PT, Purge and trap; SBSE, Stir-bar sorptive extraction; SDME, Single-drop microextraction; SPE, Solid-phase extraction; SPME, Solid-phase microextraction; TeCA, Tetrachloroanisole; TeCP, Tetrachlorophenol; TBA, Tribromoanisole; TD, Thermal desorption; TCA, Trichloroanisole; USAEME, Ultrasound-assisted emulsification microextraction; USA-DLLME, Ultrasound-assisted dispersive liquid-liquid microextraction

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1. Introduction

An unacceptable flavor is one of the most common reasons for consumers rejecting a particular food product, and, every year, the food industry receives complaints from consumers concerning off flavors or taints in fresh, processed and packaged foods [1]. Basically, a taint or off flavor is any flavor that is not normally associated with the food, frequently caused by trace amounts of volatile organic compounds not usually present in that food.

Cork taint is one of the major organoleptic defects in wine, and it is commonly associated with a musty or moldy aroma [2]. Cork taint affects the quality of wines, causing financial loss to wineries, and, thus, damaging their reputation so that their products would always be rejected by the consumer.

Haloanisoles are known to cause off flavor in food and beverages. Under certain conditions (i.e. mold growth, environmental contamination or hypochlorite bleaching), chloroanisoles could be produced by

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microbiological methylation of chlorophenols, and, thus, be found in the cork and transferred to wine [3]. Besides, wood pollution in wine-making procedures (e.g., washing oak barrels) or transportation, storage and handling of wine or packing materials could also increase the cork-taint concentration in the final product [4].

The manufacture of cork stoppers for wine bottles involves several stages, including cork ripening. In this step, the cork is exposed to the environment and is susceptible to the proliferation of fungi and bacteria that can cause its deterioration. To minimize this problem, wood preservatives are added to the cork. The most efficient wood preservatives are based on halophenols, particularly chlorophenols. However, these compounds are biomethylated by fungi present in the cork, yielding their respective haloanisoles, which are the main cause of cork taint in wines. Furthermore, the chlorination of lignin-degradation products in the presence of free chlorine or anionic species containing chlorine also produces different chlorophenols, which suffer the same microbiological degradation [2,3]. The chloroanisoles present in the cork, oak barrels or packing materials could then be transferred to the wines, thereby affecting their quality.

Cork taint in bottled wines of individual wineries is highly variable. However, monitoring haloanisoles in wines is important as an integral component of product quality control before sending the wine to market.

1.1. Cork-taint compounds in wine

Due to its particularly low sensory threshold, the main compound responsible for cork taint in wines is 2,4,6-trichloroanisole (2,4,6-TCA). It has long been associated with musty taint in foodstuffs and was identified by Buser et al. [5] as the major compound causing cork taint in wines.

Besides 2,4,6-TCA, several anisole compounds are frequently related to the same taint aroma, including 2,4,6-tribromoanisole (2,4,6-TBA), 2,3,4,6-tetrachloroanisole (2,3,4,6-TeCA) and pentachloroanisole (PCA). All the analytes mentioned are characterized by their musty-moldy odor, with a perception threshold in the range 0.03–50 ng/L.

Table 1 summarizes the chemical characteristics of the cork-taint compounds reviewed, their odor thresholds and their taint description in wines. As was mentioned, haloanisoles are formed by *O*-methylation of chlorophenols mediated by different microbial species. In this sense, it can be assumed that the direct precursors of chloroanisoles are the chlorophenols – 2,4,6-trichlorophenol (TCP), 2,3,4,6-tetrachlorophenol (TeCP) and pentachlorophenol (PCP). Chlorophenolic products used in cellars, during manufacture of cork stoppers or in cleaning oak barrels, can also be potential sources of cork taint.

There are other minor compounds causing cork taint in wines that are not included in the haloanisole or halophenol families. These analytes include 2-methoxy-3,5-dimethylpyrazine (MDMP), geosmin, 2-methylisoborneol (MIB), 1-octen-3-one, 1-octen-3-ol and guaiacol (2- methoxyphenol) [2] (see Table 1). MDMP is described as a fungal must by winery panelists, with a perception threshold of 2 ng/L. Tasters considered it to be the second most important cork taint after 2,4,6-TCA [6], but there are few works reporting its determination in wines.

The origin of MDMP in corks is unknown, but is not necessarily bacterial, as it has long been recognized that certain aroma-intense microbial metabolites occurring in foods and beverages can be produced by different types of microflora [2].

Geosmin and MIB are also responsible for some unwanted aromas in wine, producing a muddy-earthy odor at relatively higher concentrations than chloroanisoles (see Table 1); also, they are considered mold metabolites. Geosmin is least likely to cause serious cork taint in wine because it is chemically unstable in wine [2].

1-Octen-3-one and 1-octen-3-ol are also mold metabolites arising from the degradation of lipids [7]. Guaiacol is a lignin-degradation product, commonly found in oak-barrel-aged wines and may also be derived from corks [8]. The detection threshold of this compound was 65–75 μg/L, whereas other authors reported a lower detection level, nearer to 20 μg/L.

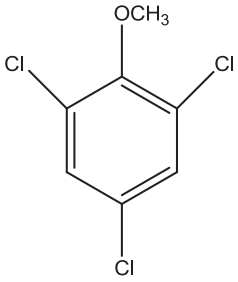
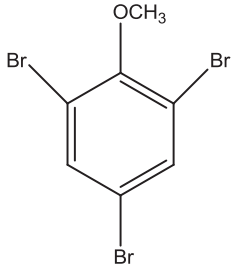
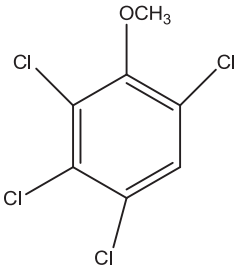
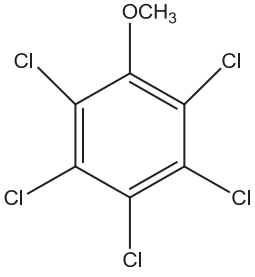
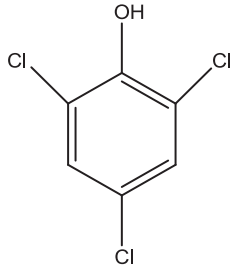
1.2. Analytical methods

Sample preparation plays a central role in the determination of cork-taint compounds due to the complexity of the wine matrix and the low concentration of the analytes. Highly selective and sensitive analytical techniques are therefore required for unequivocal identification and determination. In this sense, considering the physicochemical properties of these compounds, gas chromatography (GC)-based techniques have been the choice for analysis. Different detectors [e.g., mass spectrometry (MS), electron-capture (ECD), atomic emission (AED) and olfactometry (O)] have been reported for the analysis of compounds of interest.

Since the concentrations of chloroanisoles and some related cork-taint compounds in wine are usually low, it is necessary to have highly efficient extraction or preconcentration techniques for their evaluation. Thus, with the developing interest in miniaturization in analytical chemistry to save solvents and samples, some newer miniaturized techniques were successfully applied for odor analysis in wines. Also, novel immunoanalytical systems have also been explored for direct determination of some odors in wines.

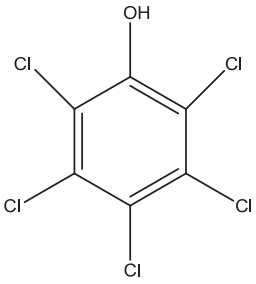
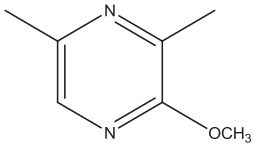
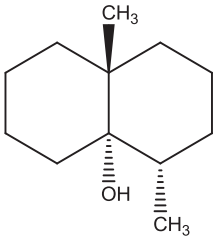
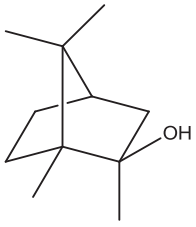
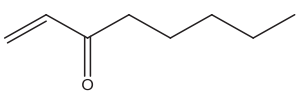
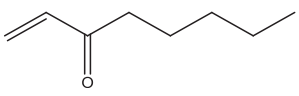
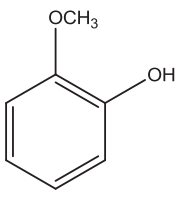
This article presents an overview of the different methodologies reported for cork-taint analysis of wine, published in the past decade, focusing on sample-preparation strategies and instrumentation reported for the determination of these compounds in bottled wines. Thus also critically discuss the limitations and the

Table 1. Chemical characteristics of cork-taint compounds, odor thresholds and taint description

Compound	Abbreviation	Chemical Structure	Molecular weight (g/mol)	Boiling point (°C)	Taint aroma	Odor thresholds (ng/L)
2,4,6-Trichloroanisole CAS: 87-40-1	2,4,6-TCA		211.47	140	Mold	0.03–50
2,4,6-Tribromoanisole CAS: 607-99-8	2,4,6-TBA		344.83	298	Mold	3.4–7.9
2,3,4,6-Tetrachloroanisole CAS: 6936-40-9	2,3,4,6-TeCA		245.92	289	Mold-dust	5–15
Pentachloroanisole CAS: 1825-21-4	PCA		280.36	289	Dust	10,000
2,4,6-Trichlorophenol CAS: 88-06-2	2,4,6-TCP		197.45	246	Phenolic	n.a.

(*continued on next page*)

Table 1 (*continued*)

Compound	Abbreviation	Chemical Structure	Molecular weight (g/mol)	Boiling point (°C)	Taint aroma	Odor thresholds (ng/L)
Pentachlorophenol CAS: 87-86-5	PCP		266.34	310	Phenolic	n.a.
2-Methoxy-3, 5-dimethylpyrazin CAS: n.a.	MDMP		138.087	177.7	Fungal must	2
Geosmin CAS: 19700-21-1	–		182.30	270	Muddy-earthy	80–90
2-Methylisoborneol CAS: 2371-42-8	MIB		168.28	208	Muddy-earthy	30
1-Octen-3-one CAS: 4312-99-6	–		126.20	178	Fungus	70
1-Octen-3-ol CAS: 3391-86-4	–		128.21	174	Fungus	40,000
Guaiacol CAS: 90-05-1	–		124.14	205	Smoky	50,000

n.a.: not available.

Table 2. Reported LPME techniques for determining cork-taint compounds in wines

LPME	Analytes	Solvent	Extraction solvent volume (μL)	Extraction time (min)	Sample volume (mL)	Separation/ detection	LOD (ng/L)	Linear range (ng/L)	RSDs (%)	Recovery (%)	Ref.
DLLME	2,4,6-TCA; 2,4,6-TBA; 2,3,4,6-TeCA; PCA	Chloroform	173	Few seconds	5	GC-MS/MS	5–12	10–500	4.3–11.0	90.3–97.9	[13]
DLLME	2,4,6-TCA; 2,4,6-TBA; 2,3,4,6-TeCA; PCA; 2,4,6-TCP; 2,3,4,6-TeCP; 2,4,6-TBP and PCP	Carbon tetrachloride	150	Few seconds	5	GC-ECD	2.2–5.3	10–500	9.0–9.9	84–97	[12]
DLLME	2,4,6-TCA; 2,4,6-TBA; 2,3,4,6-TeCA; PCA; 2,4,6-TCP; 2,3,4,6-TeCP and PCP	Carbon tetrachloride	30	Few seconds	5	GC-MS	4–108	n.i.	2.5–13.2	81.4–119.0	[14]
USAEME	2,4,6-TCA	Trichloroethylene	25	5	5	GC-MS/MS	0.6–0.7	5–1000	10.5–11.3	80–88	[17]
USA-DLLME	Geosmin and MIB	Tetrachloroethylene	8	3	12	GC-MS	2–9	10–1000 50–1000	10.1–10.4	70–87	[18]
HS-SDME	2,4,6-TCA and 2,4,6-TBA	1-Octanol	2	25	20	GC-ECD	6.1–8.1	20–1000	12.4–16.7	60.1–99.5	[21]
HS-IL-SDME	2,4,6-TCA	[Hmim][NTf_2]	2	30	2	IMS	0.01	0.05–25	6	n.i.	[23]
SPE-HS-IL-SDME	2,4,6-TCA	[Hmim][NTf_2]	2	40	2	IMS	0.2	0.66–100	3	95–104	[22]

n.i.: no information.

potential of the methods with the aim of improving the determination of cork-taint compounds in this complex matrix.

2. Sample-preparation techniques

2.1. Liquid-phase microextraction (LPME)

In the past few years, interest has grown in new extraction techniques, especially in the microextraction category. Efforts have been made to miniaturize liquid-liquid extraction (LLE) by greatly reducing the amount of organic solvent required.

In liquid-phase microextraction (LPME), only a few microliters of solvent is needed to extract analytes from liquid samples. Microextraction techniques are fast, simple, inexpensive, environmentally friendly and compatible with many analytical instruments. Several types of LPME have been developed and thoroughly reviewed in previous works [9,10].

For cork-taint compounds, there are some novel applications exploring the advantages of LPME for complex samples (e.g., wine). This section discusses LPME approaches reported so far for the extraction or preconcentration of cork-taint compounds in wines.

Table 2 summarizes the analytical and practical characteristics of the LPME techniques reported for the analysis of the compounds of interest.

2.1.1. Dispersive liquid-liquid microextraction. Recently, a novel technique, called dispersive liquid-liquid microextraction (DLLME), was reported for extracting and/or preconcentrating target analytes from aqueous samples [11]. DLLME employs a mixture of a high-density, non-polar, water-immiscible solvent (extraction solvent) and a polar, water-miscible solvent (disperser solvent). The disperser solvent is used for dispersing the extraction solvent as very fine droplets into the aqueous bulk and for increasing contact with the extraction solvent. An efficient dispersion of extraction solvent favors the mass-transfer process between the two immiscible phases. After a short contact time, the dispersed phase is separated by centrifugation and the extracted analytes can be determined by conventional analytical techniques. DLLME has high preconcentration capabilities in a very short time with little solvent consumption.

Pizarro et al. [12,13] applied DLLME for the extraction and preconcentration of the main compounds causing cork taint in wine samples prior to GC-MS/MS or GC-ECD analysis. The first methodology reported was employed for the simultaneous extraction and preconcentration of haloanisoles and halophenols. As is well known, for polar and non-volatile analytes, which are unsuitable for GC analysis, a derivatization step is necessary to increase analyte volatility. In this way, Pizarro et al. [12] proposed a novel *in-situ* derivatization of halophenols in

wine matrix using acetic anhydride as the derivatization reagent. In this method, a mixture of acetone as disperser solvent, CCl_4 as extraction solvent and acetic anhydride as derivatization reagent was rapidly injected into the sample, and formed a cloudy solution. As a result, halophenols reacted with acetic anhydride to form the corresponding acetyl derivatives and were further extracted together with haloanisoles into dispersed fine droplets of CCl_4. Afterwards, the organic phase remaining on the bottom was analyzed using GC-ECD.

The same authors developed another DLLME technique for the analysis of haloanisoles [13]. In this recent approach, acetone and chloroform were used as disperser and extraction solvents, respectively.

The analytical performances of both DLLME methodologies were similar with LODs of 2.2–12 ng/L for haloanisoles and 3.9–5.3 ng/L for halophenols. These LODs confirmed the suitability of DLLME for the determination of cork-taint compounds at concentrations lower than their respective olfactory thresholds with satisfactory precision and recovery.

Campillo et al. [14] proposed a DLLME technique similar to that reported by Pizarro et al. [12] for the one-step derivatization and extraction of chlorophenols and haloanisoles prior to their determination by GC-MS/MS. The method reported showed LODs of 9–95 ng/L, which could be considered relatively higher than the other DLLME methods described. The LODs showed higher values for chlorophenols, which could be related to reduced efficiency of the derivatization step.

It is important to comment that the application of DLLME coupled with the *in-situ* derivatization reaction provides a one-step derivatization and extraction/preconcentration technique, particularly for polar chlorophenols, thereby simplifying the operability and shortening the total analysis time. Also, it is possible to determine the two groups of cork-taint compounds most commonly found in defective wines, so improving the applicability of the technique.

2.1.2. Ultrasound-assisted emulsification microextraction. Recently, a novel microextraction technique, named ultrasound-assisted emulsification-microextraction (USAEME), was developed by Regueiro et al. [15]. It uses US radiation to accelerate emulsification. During the sonication step, the solution becomes turbid due to the dispersion of fine extraction-solvent droplets into the aqueous bulk. The fine dispersion favors the mass-transfer process of the analytes from the aqueous bulk into the organic phase, leading to an increase in extraction efficiency in minimum of time [16].

The versatility of USAEME was apparent in a variety of applications in many areas reported. In this sense, it was recently proposed for simultaneously extracting and preconcentrating 2,4,6-TCA from wine samples prior to GC-MS/MS analysis [17]. The technique reported used trichloroethylene as extraction solvent. The mixture was shaken and afterwards sonicated to a cloudy state, due to the dispersion of fine trichloroethylene droplets into the sample. After a centrifugation step, the extraction solvent remained at the bottom of the tube and an aliquot was injected into the GC-MS/MS. The application of the methodology proved to be effective for the determination of 2,4,6-TCA in white and red wines by GC-MS/MS at concentrations considered to produce a defect. Under optimized conditions, high enrichment factors (EFs) were obtained to reach LODs of the order of low ng/L with acceptable precision, which were suitable for analysis of real samples of white and red wines. White wines had a relatively lower matrix effect than red wines, showing the need to use matrix-matched calibration curves specifically for white and red wines.

Geosmin and 2-methylisoborneol (MIB) were recently quantified by GC-MS after a fast, simple, environmentally friendly technique named ultrasound-assisted dispersive liquid-liquid microextraction (USA-DLLME) developed by Cortada et al. [18]. The technique included a single extraction/preconcentration step using a small volume of tetrachloroethylene as extraction solvent, followed by sonication of the mixture and subsequent centrifugation. The analytical performance of the technique showed satisfactory results in terms of sensitivity and reproducibility. The LODs obtained satisfied the requirements for these analytes in wine samples. However, the recoveries obtained were relatively low (70%) in red wines, showing a moderate matrix effect in real samples.

2.1.3. Single-drop microextraction. SDME was first introduced by Jeannot and Cantwell in 1996 [19]. In this technique, the acceptor phase is a drop of a water-immiscible solvent (volume: 1–3 μL) suspended in the needle tip of a microsyringe or a small PTFE tubing, which can be in direct contact (direct immersion) (DI-SDME) with the sample or in the headspace (HS-SDME). After a certain extraction time, the solvent microdrop is retracted back into the microsyringe and transferred into the instrumental system for further analysis. As for SPME, in SDME, the extraction and preconcentration steps occur simultaneously, providing a fast, inexpensive technique using simple equipment. Due to its simplicity and low cost, SDME has become one of the most successful microextraction techniques, being hundreds of applications reported in the past decade for the determination of a wide variety of analytes [9]. Also, their versatility permits use of alternative solvents [e.g., surfactants and ionic liquids (ILs)] in place of traditional organic solvents, when better for the analytical-chemistry process [20].

SDME has been applied to sample preparation of cork-taint compounds. Martendal et al. reported a novel analytical method for the determination of 2,4,6-TCA and 2,4,6-TBA in wine samples based on an HS-SDME

technique combined with separation and detection by GC-ECD [21]. The authors optimized the variables affecting the procedure by a fractional factorial experimental design and subsequent Box-Behnken design to obtain satisfactory results. The final procedure involved sample extraction in HS mode with 2 μL of 1-octanol during 25 min at 48°C. The method reported showed interference in the release of analytes from red wines as a consequence of sample matrix. The authors therefore diluted the sample to minimize matrix interference and increase recovery, at the cost of some loss of sensitivity. However, the method reported low LODs with RSD values a bit higher, compared with other reported LPME techniques (see Table 2). For white wines, the authors did not report significant matrix effects. The lower reproducibility of the technique could be related to evaporation of the solvent microdrop during the HS-extraction step. This SDME approach represented the first application of LPME techniques in the analysis of haloanisole compounds in wines, showing analytical figures of merits compatible with their analysis in contaminated samples.

Recently, Márquez-Sillero et al. [22,23] reported the use of IL-based SDME (IL-SDME) and ion-mobility spectrometry (IMS) for the determination of 2,4,6-TCA in water and wine samples. Taking into account both its affinity for the analyte and its insignificant response in the detector, the authors selected an imidazolium-based IL as extracting solvent.

In both reported methods, SDME was performed by exposing a 2-μL drop of 1-hexyl-3-methylimidazolium bis(trifluoromethylsulfonyl)-imide ([Hmim][NTf_2]) IL to the HS of the vial. After extraction, the [Hmim][NTf_2] drop was retracted and directly introduced into the injection unit, the IL being retained in a glass-wool bed, while the 2,4,6-TCA was transferred to the IMS detector for direct fast response. One of the approaches developed [22] reported the interference of some compounds present in the wine matrix (mostly ethanol) in the ion-mobility spectra. The determination of 2,4,6-TCA was hindered by analyte signal overlapping with the ethanol peak. The authors therefore included a solid-phase extraction (SPE) step to avoid these interferences, and showed a marked reduction of the interfering peak during IMS detection.

As can be seen, the authors avoided the disadvantages of organic solvents commonly used in SDME (e.g., low viscosity and a tendency to high evaporation, resulting in drop instability and low reproducibility). The use of ILs as alternatives to conventional solvents increased the drop stability as their viscosity was higher and facilitated the formation of drops of larger volume. Also, the lower vapor pressure of ILs minimizes drop evaporation, resulting in better reproducibility of the measurements. Thus, the RSDs obtained by the HS-IL-SDME were considerably lower than those obtained in conventional HS-SDME, thereby proving the effectiveness of these alternatives to chlorinated solvents. Probably, future trends expanding these techniques to the extraction of several analytes could give a wide range of techniques for cork-taint evaluation.

2.1.4. Critical comparison of LPME techniques. The analytical performance and experimental data shown in Table 2, could give rise to some comparative remarks.

In terms of sensitivity, HS-IL-SDME-IMS presented the lowest LOD. For the other LPME methods reported, the LODs were higher but also compatible with the determination of cork-taint compounds at their detection-threshold levels in wines. The DLLME methods appear better options, especially those determining haloanisole and halophenol families simultaneously, by coupling novel one-step extraction and *in-situ* derivatization [12,14]. These approaches have the advantages of having been proved to extract a wide range of cork-taint compounds, reduced sample extraction time and excellent analytical figures of merit. SDME requires 25–40 min for extraction of analytes, compared with the few seconds required in DLLME-based techniques. This speed improves the sample throughput of the analytical methodology, as desired in modern applications of analytical chemistry.

Another drawback of SDME is reduced reproducibility due to instability of the microdrop. However, the utilization of alternative non-volatile solvents {e.g., [Hmim][NTf_2] by Márquez-Sillero et al. [22,23]} minimized this problem and appeared a good option for the future. Also, SDME benefits from use of lower volumes of solvents than the other reported LPME techniques and also utilizes non-chlorinated solvents, which are much more toxic and environmentally unfriendly.

USAEME appeared a good option for DLLME because it avoided the use of disperser solvent. However, in the future, a wide range of cork-taint compounds needs to be explored in order to improve its applicability.

In terms of the prospects for LPME automation, SDME seems the most advanced and developed for this purpose in the different existing reported methods, where a modified autosampler can perform all steps of DI-SDME and HS-SDME with good accuracy and reproducibility [24]. In DLLME and USAEME, the combination of automation and on-line analytical instruments seems to be very difficult. In this sense, the automation of LPME has not been applied to cork-taint determination.

2.2. Sorptive microextraction

2.2.1. Solid-phase microextraction. SPME has been the most commonly reported sample-preparation technique for extraction or preconcentration of cork-taint compounds in wines. It has advantages over other techniques, in that it is solvent free and can be easily automated. In this section, we discuss the different SPME

Table 3. Reported sorptive microextraction-based methodologies for the determination of cork-taint compounds in wines

Methodology	Analytes	Fibre/sorbent	Extraction time (min)	LOD (ng/L)	RSDs (%)	Recovery (%)	Ref.
HS-SPME-GC-MS	2,4,6-TCA	PDMS	30	2.9	3–8	n.i.	[25]
D-HS-SPME-GC-ECD	2,4,6-TCA; 2,3,4,6-TCA; PCA; 2,4,6-TCP; 2,3,4,6-TCP and PCP	DVB/CAR/PDMS	75	1–12	2.7–9.5	90.3–98.4	[29]
HS-SPME-GC-AED	2,4,6-TCA; 2,3,4,6-TCA; PCA and 2,4,6-TBA	DVB/CAR/PDMS	60	1.2–2.6	2.7–5.8	98.4	[30]
MHS-SPME-GC-MS/MS	2,4,6-TCA; 2,3,4,6-TCA; PCA and 2,4,6-TBA	DVB/CAR/PDMS	60	10–70	2.4–9.7	93.8–101.3	[33]
HS-SPME-GC-MS	2,4,6-TCA; 2,3,4,6-TCA; PCA; 2,4,6-TBA; 1-octen-3-ol; geosmin; MIB; MDMP and guaiacol	DVB/CAR/PDMS	60	0.95–1.14	1.3–9.6	81.1–115.6	[26]
HS-SPME-GC-HRMS	2,4,6-TCA; 2,3,4,6-TCA; PCA; 2,4,6-TBA and MIB	DVB/CAR/PDMS	30	0.2–0.4	<12	78–93	[27]
HS-SPME-GC-MS	2,4,6-TCA and geosmin	PDMS	40	<0.5	3.1–3.6	⩾ 74.3	[39]
HS-SPME-GC-ECD	2,4,6-TCA	DVB/CAR/PDMS	70	0.3	6.5–15.5	72.5–124.8	[28]
HS-SPME-GC-ECD	2,4,6-TCA	PDMS	30	0.18–0.37	1.5–6.7	92.2–109.2	[34]
HS-SPME-GC-ECD	2,4,6-TCA	PDMS	20	1.0–5.4	2.5–13.4	83–113	[4]
HS-SPME-GC-ECD	2,4,6-TCA	PDMS	30	1	2–7	90–109	[35]
HS-SPME-GC-ECD	2,4,6-TCA; 2,3,4,6-TCA and PCA	DVB/CAR/PDMS	60	1.3–2.5	2.6–9.5	n.i.	[31]
D-HS-SPME-GC-ECD	2,4,6-TCA; 2,3,4,6-TCA; PCA; 2,4,6-TBA; 2,4,6-TCP; 2,3,4,6-TCP; PCP and 2,4,6-TBP	PA	30	0.3–3.8	4.1–8.9	90.5–99.3	[40]
HS-SPME-GC-HRMS	2,4,6-TCA and 2,4,6-TBA	PDMS	30	0.03	3.5–41.6	n.i.	[36]
HS-SPME-GC-ECD	2,4,6-TCA; 2,4,6-TBA and PCA	NiTi-ZrO_2	25	6.8–8.0	3.3–7.0	77.4–118.0	[58]
HS-SPME-GC-MS	2,4,6-TCA; 2,3,4,6-TCA and PCA	PDMS	30	0.06–0.18	3.8–8.4	96.2–108.0	[38]
MHS-SPME-GC-MS/MS	2,4,6-TCA and 2,4,6-TBA	DVB/CAR/PDMS	35	4–5	5–9	92–104	[32]
HS-SPME-GC-MS/MS	2,4,6-TCA; 2,3,4,6-TCA; PCA; 2,4,6-TBA; 2,4,6-TCP; 2,3,4,6-TCP and 2,4,6-TBP	PDMS	60	0.17–243.1	0.5–10.7	n.i.	[43]
SBSE-GC-MS	2,4,6-TCA; 2,3,4,6-TCA; PCA; 2,4,6-TCP; 2,3,4,6-TCP and PCP	PDMS	60	0.006–0.062	1.4–3.1	n.i.	[59]
SBSE-GC-MS	Guaiacol	PDMS	90	38930	0.4	n.i.	[60]
SBSE-GC-MS	2,4,6-TCA; 2,3,4,6-TCA; PCA; 2,4,6-TBA and geosmin	PDMS	60	0.1–3.3	1.8–4.0	93–143	[42]
SBSE-GC-MS/MS	2,4,6-TCA; 2,3,4,6-TCA; PCA; 2,4,6-TBA; 2,4,6-TCP; 2,3,4,6-TCP and 2,4,6-TBP	PDMS	60	0.01–0.71	0.2–13.3	n.i.	[43]
MEPS-GC-HRMS	2,4,6-TCA and 2,4,6-TBA	C_{18}	n.i.	0.22–0.75	2–11	64–95	[45]

D: derivatization; MHS: multiple headspace.
n.i.: no information.

approaches applied for the analysis of cork-taint compounds in wines. Table 3 summarizes the published SPME-based methodologies used for their determination.

There are various approaches to SPME combined with different detectors for the determination of the compounds of interest. The first applications focused only on the determination of 2,4,6-TCA, reporting time evolution to several analytes, including innovative on-fiber derivatization steps with the aim to expand its applicability to polar, non-GC-amenable halophenols.

HS-SPME was the most widespread technique used to extract these compounds. The DI mode of putting SPME fibers into the wine showed reduced sensitivity and would increase contamination of the injector system; and shorten the lifetime of the SPME fibers and analytical GC column [25]. However, DI achieved similar extraction efficiencies to HS in less time.

Since the fiber coating is the ''heart'' of the extraction, it is very important to select the right fibers for the desired application. In this sense, the non-polar polydimethylsiloxane (PDMS) and the combined adsorbent capacity of divinylbenzene/Carboxen/polydimethylsiloxane (DVB/CAR/PDMS) were the most used for extracting cork-taint compounds from wine samples. Also, polyacrylate (PA) fibers were used with good performance. The DVB/CAR/PDMS fibers were more utilized in the analysis of a wide range of cork-taint compounds, including haloanisoles, halophenols, MDMP, MIB, 1-Octen-3-one, 1-Octen-3-ol, geosmin and guaiacol [26–33]. Meanwhile, PDMS was used more for the analysis of

haloanisoles [4,34–39]. Based on the reported methods, DVB/CAR/PDMS-based SPME techniques showed increased extraction efficiency (50–100%) compared with PDMS [28,35]. However, some authors reported lower reproducibility for DVB/CAR/PDMS fibers [35], thereby justifying their selection of PDMS as coating. Generally, with carefully optimized extraction parameters, both fibers showed similar efficiencies and either may be used.

The first SPME method reported was developed by Fischer et al. [25], who proposed the HS-SPME technique to avoid sample matrix obtained during DI-SPME. Despite 2,4,6-TCA being most responsible for cork-taint defects in bottled wines, other compounds contribute to the problem (see Table 1). In this sense, several authors expanded the capacity of SPME technique (by introducing novel derivatization steps that permitted analysis of polar phenols).

Pizarro et al. [40] first proposed the on-fiber derivatization of halophenols after preconcentration on an SPME fiber coated with PA. The analytes were derivatized using *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA) and then determined by GC-ECD.

The same authors [29] proposed a simplified derivatization step before HS-SPME, using acetic anhydride as reagent. The halophenols were converted into their corresponding acetyl derivatives and efficiently extracted into DVB/CAR/PDMS fiber in the HS mode prior to instrumental analysis. Both methods described showed good analytical performance compared with the other methodologies reported, having the advantage of analyzing the two most relevant families of cork-taint compounds. However, they required additional time due to the derivatization step.

Boutou et al. [26] developed a wide-ranging SPME technique for the extraction and preconcentration of several analytes, including haloanisoles, MDMP, MIB, 1-octen-3-ol, geosmin and guaiacol. This is the only technique published for the determination of these compounds together with the haloanisole family. However, it does not apply to halophenol precursors of haloanisoles, and that could be considered a major drawback.

In view of these SPME techniques, more efforts should be made to develop methods able to extract and to preconcentrate all cork-taint compounds, including halophenols. Previously reported derivatization methods will probably be the starting point for several non-GC-amenable cork-taint compounds in new methods, thereby achieving more reliable characterization of defective wines.

One of the most important aspects of SPME is the possibility of completely automating the analytical process, so as to increase the reproducibility, improve the accuracy of the results, reduce analysis time for both routine analysis and method development, and increase the sample throughput. So far, there are no automated SPME methods for cork-taint analysis in wines, so more effort should be devoted to explaining the capabilities of SPME for these compounds.

2.2.2. Stir-bar sorptive extraction. In SBSE methods, analytes are extracted from a liquid phase of an aqueous matrix into a magnetic stir-bar covered with a polymeric phase. In contrast to extraction with adsorbents, whereby the analytes interact with active sites on a surface, in SBSE, the solutes migrate into the sorbent phase. Following the extraction, the desorption step can be thermal desorption (TD), or liquid desorption (LD) if back extraction with an organic solvent is used.

SBSE has much greater amount of sorbent available than SPME, and that results in higher sample capacity and better sensitivity. Nevertheless, it appears that the primary advantage of SBSE using the sorbent will also be its greatest disadvantage. The non-selective sorptive capability of the PDMS sorbent co-concentrates undesirable matrix components from the sample. SBSE accumulates analytes in the sorbent but there is not ever sample clean-up [41].

There are many works applying SBSE to preconcentration of cork-taint compounds, as summarized in Table 3. The methods reported showed good analytical performance in terms of sensitivity and reproducibility. SBSE obtained the lowest LODs for haloanisole compounds, when compared with other proposed techniques. However, some authors found excessively high recoveries for some of the cork-taint compounds analyzed [42], which could be due to interferences between the target analytes and high molecular-weight compounds or other substances present in the wine.

Maggi et al. [43] made an interesting comparison between SBSE and SPME using DI and HS modes, in order to evaluate the most rapid, suitable and efficient extraction technique for the analysis of haloanisoles and halophenols. The authors pointed out that SBSE analysis of halophenols and haloanisoles showed better sensitivity than SPME (DI-SPME and HS-SPME), especially if compared with the HS mode. The SBSE and DI-SPME methods described could determine such compounds at the ng/L level.

However, SPME had some advantages over SBSE (e.g., increased LODs for halophenols). SBSE offered limited capability for enriching polar compounds. In this sense, some derivatization approaches {e.g., as described by Pizarro et al. [29,40] for SPME techniques} should be evaluated in the future for SBSE applications.

Automation of SBSE appears difficult because operations (e.g., removing the stir bar from the sample, rinsing, drying and liquid desorption) are usually performed manually and automation of these steps could increase the cost and complexity of the hardware involved. There are therefore no reported automated SBSE methods for cork-taint analysis.

2.2.3. Microextraction in packed syringe. MEPS was recently developed as a novel method for sample preparation, being a miniaturization of the conventional SPE technique, with the sample volume and extraction and washing solvents volumes being greatly reduced compared to SPE. Also, conventional SPE would not be expected to be a suitable technique for volatile compounds because it is prone to analyte losses. By contrast, MEPS is carried out in a closed system, so avoiding analyte losses.

In MEPS, a small amount of sorbent is packed into a syringe. Once the sorbent has been pre-conditioned, the syringe is connected to the instrument autosampler. The sample is slowly withdrawn through the sorbent and analytes are adsorbed onto the material. A washing step is introduced to eliminate potential interferences. Then, analytes are eluted with an organic solvent, directly into the injector of the instrument [44]. MEPS opened the way for on-line coupling to GC or LC, allowing sample preparation and analysis without any modification of the chromatographic system. This approach to sample preparation is very promising for many reasons, as it is an easy-to-use, rapid, fully automated, on-line procedure that reduces the volumes of solvent and sample. Thus, the cost of analysis is minimal compared to conventional SPE.

Recently, there was a report of the development of a MEPS-based method in combination with GC-MS for the analysis of 2,4,6-TCA and 2,4,6-TBA in wine [45]. The authors proposed use of standard MEPS containing 4 mg of C_{18} sorbent and eluting it with 10 μL of toluene. MEPS proved to be very specific, obtaining eluted extracts free of matrix interferences. No further clean-up of the MEPS solid phase was necessary. The analytical performance of the methodology showed good reproducibility, probably increased by using an internal standard (2,3,6-TCA) for quantification. Furthermore, the possibility of total automation of extraction, separation and detection could increase the sample throughput of the methodology and also the reproducibility. Reproducibility is an important advantage of LPME techniques, allowing full automation of the analytical process. To date, there is no automated application of MEPS for cork-taint analysis, but it appears promising for the future. An additional trend of MEPS is that its cost of analysis is potentially lower than that of SPME or SBSE. In MEPS, a small amount of sorbent is used in place of higher cost SPME fibers or SBSE twists.

2.3. QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe)

QuEChERS was recently introduced by Anastassiades et al. [46] as a simple, fast and inexpensive technique used for the determination of several analytes in foods. The original QuEChERS technique is characterized by single-phase solvent extraction using polar organic solvents and phase separation after salting out and centrifuging the mixture [46]. Afterwards, a simple, rapid clean-up step, known as dispersive solid-phase extraction (DSPE), is applied. DSPE is based on adding the sorbent material into the extract to remove the matrix co-extractives. Then, the sorbent is separated from the extract bulk by centrifugation. In this way, DSPE avoids passing the extract through an SPE column, using smaller quantity of sorbent and solvent. Also, in DSPE, all sorbent particles interact equally with the matrix components, leading to larger sorbent capacity per gram of sorbent [46]. QuEChERS is a convenient alternative to traditional LLE because it uses smaller volumes of organic solvents in a single extraction stage. Therefore, it does not involve a solvent-evaporation step to concentrate the analytes further in the final extract prior to analysis. QuEChERS has been successfully applied to determine several analytes with a variety of chemical properties using different chromatographic techniques.

Recently, a modified QuEChERS technique was developed and validated for the determination of 2,4,6-TCA in wine by GC-MS with time-of-flight and MS/MS detectors [47]. In the reported method, wine sample was extracted with toluene and phase separation was achieved by salting out in the presence of $MgSO_4$ and NaCl. Toluene was selected because it showed the highest extraction efficiency for 2,4,6-TCA. Clean-up of the toluene phase was performed by DSPE with a mixture of $CaCl_2$, primary secondary amine (PSA) and $MgSO_4$ at low temperature, effectively minimizing sample interferences and matrix effects. The matrix interference by co-extracted fatty acids originated from wine makes identification of target compounds ambiguous [48]. Thus, the inclusion of PSA resulted in significant reduction in the peak area of the remaining fatty acids and other co-extractives after $CaCl_2$ treatment. The authors pointed out that application of the optimized one-step clean up improved the peak purity of 2,4,6-TCA, lowering the limit of detection (LOD) of the technique. Besides an LOD of 8.3 ng/L, there were good recoveries and precision compatible with the analysis of cork-tainted samples. Hence, as a consequence of the different extents of matrix effects obtained, it was recommended to prepare separate matrix-matched standards for white and red wines to perform quantification of positive samples. The applicability of the method was proved by analyzing naturally incurred samples showing recoveries of 92–108%. Moreover, the method had advantages in terms of reduced input cost and short analysis time, and is a promising choice for sample preparation of wine samples. However, it should probably be studied for the analysis of a large number of compounds to increase evaluation of wine defects.

With respect to automation, QuEChERS is a relatively new sample-preparation technique and there are no reported innovations in this field. However, based on their extraction and clean-up characteristics, it could be

difficult to achieve complete automation of the process and efforts should focus on avoiding some steps during the extraction process (i.e. centrifugation).

3. Identification and quantification techniques

3.1. Gas chromatography coupled to different detectors

Considering the physicochemical properties of these semi-volatile compounds and the derivatized halophenols, GC-based techniques have been the choice for their analysis. Different detectors included MS, MS/MS, high-resolution (HR) MS, ECD, AED and O.

GC-MS has the advantage of unequivocal identification, particularly when MS/MS is used. Due to the close retention-time values, some co-elution of haloanisoles and halophenols could occur. Thus, the selection of MS/MS methods, unique for each analyte, avoids ambiguous identification of compounds [43]. Also, MS/MS methods could avoid some matrix interferences remaining after the sample-preparation step, increasing the selectivity and the sensitivity of the analytical methodology. The reported MS/MS methods for cork-taint compounds showed lower LODs than MS methods.

GC-HRMS was reported by Jönsson et al. [36,45] for the determination of 2,4,6-TCA and 2,4,6-TBA with high selectivity. This technique showed sensitivity similar to MS/MS methods, but has the disadvantages of high purchase price and high cost of maintenance.

GC-ECD was another common option for cork-taint determination, reporting several applications with sensitivity and selectivity similar to GC-MS/MS (see Table 3). Its relatively low purchase price and maintenance cost, combined with its relatively good sensitivity are the primary reasons for its selection. However, ECD is suitable for only halogenated cork-taint compounds, this being the principal disadvantage compared to GC-MS, which is used most. In this sense, the group of compounds is reduced and it is impossible to determine other minor or less common cork-taint analytes.

GC-O detection is based on sensory evaluation of the eluate from the chromatographic column and aims to discern the active odor compounds present in some sample [49]. This establishes whether a given compound is sensory active at a given concentration (i.e. whether it appears in the sample at a higher level than the sensory detection threshold). The determination of the analyte odor is possible due to the presence of a special attachment, the olfactometric port, connected in parallel to conventional detectors (e.g., MS). The flow of the eluate is split so that the analytes reach both detectors simultaneously, so that both signals can be compared. The combination of the O detector with MS is particularly advantageous, allowing not only evaluation of the odor compounds, but also identification with MS information [50].

AED is a selective, sensitive detection method. It is easier to operate than MS methods and the resulting chromatograms can be interpreted by semi-skilled analysts. By contrast, the high cost of maintenance is a disadvantage of AED. Campillo et al. [51] reported a method based on purge-and-trap (PT) method coupled to AED, which showed a good performance for the determination of 2,4,6-TCA. The LODs obtained were comparable to those reported for GC-ECD or GC-MS/MS methods, proving its applicability for these analytes.

3.2. Other separation and detection techniques

Ion-mobility spectrometry (IMS) characterizes molecules by their gas-phase mobility [52]. This analytical technique offers high sensitivity, instrumental simplicity, low cost, analytical flexibility and real-time monitoring [52]. These advantages make IMS a suitable option for the detection of volatile compounds in different fields of analytical chemistry. However, it has limited selectivity, which has been overcame by separating the analytes using gas capillary chromatographic (GCC) columns or multicapillary columns (MCCs) [53]. Márquez-Sillero et al. [22] proposed utilization of IMS for the determination of 2,4,6-TCA. They utilized an MCC to increase the selectivity of IMS detection by reducing the interference of the ethanol present in wines. Also, the use of IMS in negative-ionization mode to detect chlorine atoms reached high levels of sensitivity.

Interesting detection techniques that appear promising involve immunoanalytical technologies, involving a specific antibody raised against the analyte. These analytical tests are based on the specific interaction between the antibody and the antigen. Because of their high sensitivity and selectivity, immunoassays have been successfully used for both qualitative and quantitative analysis of several compounds at trace levels.

Sanvicens et al. [54] were the first to report an immunoassay technique for 2,4,6-TCA using an enzyme-linked immunosorbent assay (ELISA). Moore et al. [55] described the development of an immunoamperometric technique based on an ELISA method and an electrochemical technique. Both authors reported LODs insufficient for direct analysis of wine samples, considering the low sensory levels for 2,4,6-TCA in this matrix. Also, the time for the assay was extensive and additional sample-preparation steps could be required to avoid interferences in the analysis of real wine samples.

To avoid sample interferences, Sanvicens et al. [56] developed a high-throughput screening immunochemical method to control the presence of 2,4,6-TCA and 2,4,6-TBA. The method involved a selective SPE based on an antibody-antigen reaction, followed by ELISA determination. The LODs obtained (200–400 ng/L) were better than the previously reported immunoanalytical methods. However, it showed interference by ethanol,

and samples needed to be diluted prior to immunosorbent SPE.

Varelas et al. [57] developed a rapid, novel biosensor system based on the Bioelectric Recognition Assay (BERA). This approach responded more selectively to 10^7 ng/L 2,4,6-TCA than the other haloanisoles and halophenols (at the same concentration), which could be also present in wine samples. The method LOD was 1.02 ng/L, but the authors reported that the absolute response values of the sensor against various concentrations of TCA in wine differed from the response against TCA in standard solutions, demonstrating a considerable matrix effect. This technique was the most sensitive of all reported immunochemical methods, representing a new generation of analytical tools for determination of cork-taint compounds.

4. Conclusions

Generally, chemical analysis uses reagents or organic solvents. Recently, the concept of ''green chemistry'' has been extended to ''green analytical chemistry'', so analytical chemists have tried to change the application of existing analytical methodologies and looked for new ones that could use smaller amounts of toxic solvents and reagents.

In analysis of cork-taint compounds in wine samples, progress was mainly in reducing or completely eliminating solvents from sample-preparation procedures. All LPME techniques can effectively be utilized for the extraction of target analytes. The main advantages of the miniaturized systems are high speed of analysis with good extraction efficiencies, environmentally-friendly operation due to minimal solvent consumption and highly selective analysis by systems designed for particular applications. Also, there is increasing utilization of new solvents more attractive than conventional organic solvents, including ILs or surfactants that enhance the sustainability of the process.

The SPME technique has wide application for cork-taint analysis, as it is very simple and is the only real solventless sample-preparation technique reported for cork-taint compounds. Robust, it has been applied in HS mode for several cork-taint analytes.

Biosensor analysis is a convenient alternative for the analysis of the analytes of interest, but it has several matrix effects that affecting its LODs adversely. Hence, more effort should be given to eliminate matrix interferences before sensor determination.

Although all the techniques reviewed are well established and can be successfully applied for the analysis of cork-taint compounds at concentrations lower than their human detection threshold, there are only a few in which two or more families of analytes have been determined with the same approach. Thus, the challenge for analytical chemists is to focus on developing reliable methods that can thoroughly cover the palette of cork-taint compounds present in defective wines, achieving simultaneous determination through new green sample-preparation approaches, and, at best, using an automated technique.

Acknowledgements

This work was supported by *Consejo Nacional de Investigaciones Científicas y Técnicas* (CONICET).

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