

Review

SIFT-MS: Quantifying the Volatiles You Smell ... and the Toxics You Don't

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Abstract: The human olfactory system is highly attuned to detection of a wide range of volatile organic compounds (VOCs), but the sensitivity varies considerably based on chemical functionality. Whereas most humans can appreciate the sensory properties of certain foods, beverages, and fragrances, and at times be alerted to volatile chemical hazards, many VOCs are hazardous below the human odor detection threshold. Since its introduction in the mid-1990s, selected ion flow tube mass spectrometry (SIFT-MS) has been widely applied to quantitative analysis of a broad range of VOCs in applications from food products to workplace safety to environmental monitoring, and most recently to pharmaceutical testing. This review surveys the applications of SIFT-MS in odor analysis and in workplace, environmental and consumer protection, with a particular focus on the complementarity of this real-time mass spectrometry analyzer to sensor technology and conventional laboratory techniques—in particular, gas chromatography–mass spectrometry (GC/MS).

Keywords: SIFT-MS; direct-injection mass spectrometry; DIMS; volatile organic compounds; VOCs; trace analysis; air analysis



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1. Introduction

Time-resolved volatile organic compound (VOC) analysis provides insight into processes of fundamental and industrial relevance that are extremely difficult to probe using conventional gold-standard chromatographic techniques (gas chromatography (GC) and liquid chromatography (LC) [1,2]). Chromatographic methods separate components in time before detecting them, making both response and sample analysis times long—typically tens of minutes to an hour. Direct-injection mass spectrometry (DIMS) analytical techniques for analysis of VOCs in air and breath were developed in the late 1980s and 1990s to address this shortcoming [3].

Three DIMS techniques dominate direct air analysis: atmospheric pressure chemical ionization-mass spectrometry (APCI-MS), proton transfer reaction-mass spectrometry (PTR-MS), and selected ion flow tube-mass spectrometry (SIFT-MS) [3,4]. SIFT-MS stands apart from APCI-MS and PTR-MS in that—despite being the last of these techniques to be commercialized—it has proportionally been adopted to a greater extent by industry than academia. For example, SIFT-MS has been adopted in frontline workplace safety and in semiconductor cleanroom applications (see Section 4.1) and has a very good fit in routine and automated VOC analysis [5]. Since chemosensors find broad industrial application, and to ensure manageable scope, this review focuses on the SIFT-MS technique. It should, however, be noted that the other DIMS techniques could be similarly considered for their complementarity to chemosensors in many of the applications discussed.

Since SIFT-MS is based on mass spectrometry (MS), it is significantly more complex than most chemosensors—as reflected in price differentials up to three orders of magnitude (in the case of the lowest cost chemosensors). All MS techniques require that analytes be ionized. In the case of SIFT-MS, very soft chemical ionization (CI) is utilized. As with other MS techniques, once ionized, the gas-phase ion products are subsequently separated by their mass-to-charge ratio (m/z) and then counted—the ion abundance being proportional

to analyte concentration. The spectral “fingerprint” generated by the MS instrument is determined by the elemental composition of the analyte and the ionization energetics. (An unusual feature of SIFT-MS is that for certain reaction mechanisms (especially association, Section 2.2) the chemical ionization agent (so the so-called “reagent ion”) may be incorporated into the detected product ion [6,7].) As will be described in the next section, this confers on SIFT-MS the ability to achieve multicomponent VOC analysis with high specificity, sensitivity, and direct quantitation with low calibration demand. In contrast, the output of chemosensors is typically an electrical signal generated in response to a VOC or class of VOCs [8], without identificatory mass information. Hence, sensory arrays are commonly used, combining sensors with varying responses to different VOCs that interact with their surface [8]. Sophisticated multivariate statistical analysis (pattern recognition) is utilized on a training set to build a model that can be used to identify and quantify patterns of analytes [8]. It should be noted, however, that greater certainty in identification can be achieved when chemosensors are used as detectors for chromatography systems (e.g., Alpha MOS, www.alpha-mos.com, accessed on 25 January 2023).

Given the very different technologies underlying SIFT-MS and chemosensors, and the distinctive analytical data that they generate, while both generally provide rapid speed of analysis, this review aims to demonstrate the complementarity of the approaches. Conventionally chemosensor performance has been benchmarked against chromatographic methods, with slow response time and time-to-result. SIFT-MS provides an alternative, generating analytical data in real time with high specificity and sensitivity. Therefore, this article is structured as follows. First, the SIFT-MS technique is introduced, focusing on the fundamental aspects that complement chemosensor analysis. Since comprehensive reviews of the SIFT-MS literature exist [6,9,10], this article focusses on two broad application areas in which SIFT-MS and chemosensors both find application (aroma/odor and toxics analysis), highlighting particularly new developments. Finally, recent applications of SIFT-MS that are more “chemosensor-like” are reviewed briefly. At all points the focus is on presenting the SIFT-MS literature in a manner that makes it accessible to experts in chemosensors, avoiding review of literature with which these experts are already familiar.

2. The SIFT-MS Technique—An Overview

This section introduces the SIFT-MS technique, providing an overview of the generic layout of instrumentation before it describes key analytical features pertinent to this article: breadth of analysis, specificity, and quantitation. More technical details can be found in Refs. [6,9].

2.1. Instrument Overview

All SIFT-MS instruments have three zones, as shown in Figure 1. In the first region, reagent ions are generated continuously in a plasma created at low pressure using a microwave discharge. For the positively charged reagent ions, H_3O^+ , NO^+ , and $\text{O}_2^+\bullet$, the ion source is operated at approximately 54 kPa (400 torr), while for the negatively charged reagent ions ($\text{O}^-\bullet$, $\text{O}_2^-\bullet$, OH^- , NO_2^- , and NO_3^-) it is operated at approximately twice this pressure to facilitate electron attachment. Multiple reagent ions provide two significant benefits that are elaborated below: (1) their different ionization properties enable a wide range of compounds to be detected, and (2) they are foundational to achieving specific analysis. The plasma containing a mixture of potential reagent ions is then passed into a quadrupole mass filter (QMF) that, using software control, selects the appropriate, single-reagent ion type (by its m/z ; e.g., H_3O^+ with $m/z = 19$) for introduction as a pure stream of reagent ion into the second region, the reaction chamber (or flow tube).

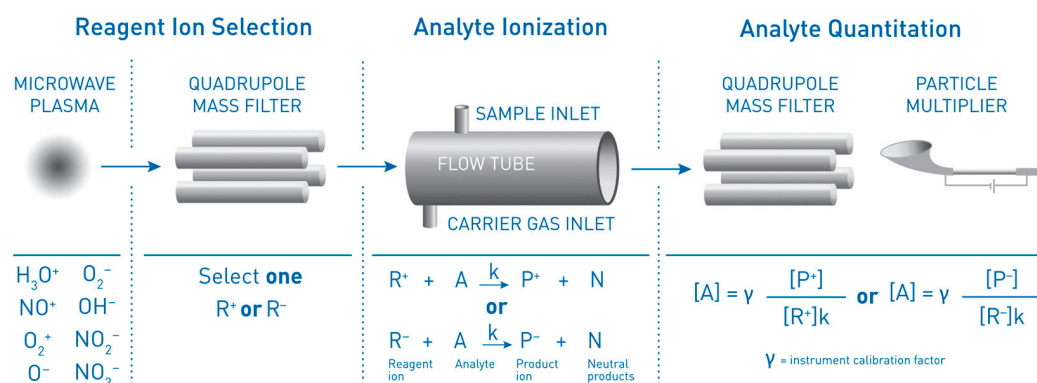


Figure 1. A schematic illustration of the SIFT-MS technique, showing the three zones in this continuous-analysis approach. Used with permission of Syft Technologies.

In the flow tube, reagent ions first encounter carrier gas molecules (either helium or nitrogen, depending on instrument application). Through collisions with the carrier gas, the energies of the reagent ions are reduced to approximately the temperature of the carrier gas itself (i.e., the reagent ions are “thermalized”) [7]. The sample is introduced after reagent ions have been in the flow tube for approximately 1 ms, then has a residence time of about 3 to 8 ms (configuration-dependent) for reaction with reagent ions. At the end of the flow tube, ions are sampled into the third region (detection), while the bulk of carrier and sample mixture is pumped away to exhaust. Note that the carrier gas and the bulk matrix must have ionization properties that render them essentially non-reactive with the reagent ions. Conveniently, this is the case for air, with which the reagent ions listed above either do not react or react only very slowly (nitrogen, oxygen, argon, carbon dioxide, and water).

The detection region comprises, firstly, an ion guide that improves transmission of heavier product ions, second a QMF that transmits just the ions with a given m/z , and finally a particle multiplier detector that counts ions at each m/z . Typically operation in the linear range means that less than 10% of the reagent ion signal is consumed [6] and concentration is proportional to the ratio of product ion count divided by reagent ion count (Section 2.4). This is essentially an auto-normalization feature, correcting for any drift of ion signal, should it occur, and supports stable long-term operation.

SIFT-MS instruments are completely computer controlled and can operate autonomously or via remote control. The stability of ionization means that—when required—re-calibration is an infrequent task (annual for many compounds due to drift less than 10%), and software supports the generation of laboratory-grade analytical results for non-technical operators for properly developed analytical methods.

2.2. Breadth of Analysis

Although, as noted in the previous subsection, the SIFT-MS technique is ‘blind’ to the bulk components of air due to the low ionization energies of its reagent ions, it has remarkable breadth of analysis for VOCs and trace inorganic gases. This is due to the multiple reagent ions that ionize compounds via a wide range of ion–molecule reaction mechanisms (Table 1). These mechanisms have been reviewed in detail elsewhere [6,7]. Essentially, if the ionization properties of the target compound are a match for SIFT-MS, then it will be ionized and detected. Note, however, that unlike the electron ionization (EI) method used commonly with GC or photoionization detectors (PIDs), the different mechanisms yield a wider range of product ions, potentially increasing specificity for isobaric compounds.

Table 1. The most common ion–molecule reaction mechanisms of the SIFT-MS reagent ions and the resulting product ion m/z , either relative to the molecular weight or a standard product ion.

Mechanism Name	Reagent Ion(s)	General Equation	Shift Relative to Parent Ion
Proton transfer (PT)	H_3O^+	$AH^+ + B \rightarrow BH^+ + A$	+1 (simple PT) −17 (loss of OH moiety)
Electron transfer (ET)	$NO^+, O_2^{+\bullet}, O_2^{-\bullet}$	$A^{+/-} + B \rightarrow B^{+/-} + A$	0
Dissociative ET	$NO^+, O_2^{+\bullet}$	$A^+ + B \rightarrow C^+ + \text{Products}$	Varies
Hydride abstraction	$NO^+, O_2^{+\bullet}$	$A^+ + B-H \rightarrow B^+ + HA$	−1
Association	$NO^+, O^{-\bullet}, O_2^{-\bullet}, OH^-$	$A^{+/-} + B + M \rightarrow \{B.A\}^{+/-} + M$	+Reagent m/z (e.g., +30 for NO^+)
Proton abstraction	$O^{-\bullet}, O_2^{-\bullet}, OH^-, NO_2^-, NO_3^-$	$A^- + BH \rightarrow B^- + AH$	−1
Mechanism Name	Reagent Ion(s)	General Equation	Standard Product* m/z
Hydrogen atom transfer	$O^{-\bullet}$	$A^- + BH \rightarrow AH^- + B^-$	Reagent ion $m/z - 1$ **
Displacement	$O^{-\bullet}, OH^-$	$A^- + RB \rightarrow RA + B^-$ (R = alkyl)	−35 and −37 for B = Cl −79 and −81 for B = Br
Elimination	$O^{-\bullet}, OH^-$	$A^- + RB \rightarrow R' + R''A + B^-$ (R' = alkene; R'' = alkyl)	−35 and −37 for B = Cl −79 and −81 for B = Br
Associative detachment	$O^{-\bullet}, O_2^{-\bullet}, OH^-$	$A^- + B \rightarrow AB + e^-$ (e^- = electron)	No product detected (e^-)

* The reactions in the lower section of the table yield a standard product ion. For displacement and elimination mechanisms, Cl^- and Br^- product ions have been most commonly encountered to date, so they are used for illustrative purposes. ** The reagent ion m/z is defined as a negative value here. Hence for $O^{-\bullet}$ ($m/z = -16$) the product ion following hydrogen atom transfer is OH^- ($m/z = -17$).

Table 2 illustrates the breadth of SIFT-MS analysis by giving examples of selected compounds that are practicably detectable in air using the indicated reagent ions. Assuming that specificity is achievable using SIFT-MS (see the next subsection), virtually any combination of compounds can be detected in a single analysis. This is possible with SIFT-MS due to the diversity of the ion chemistry and the broad-spectrum ion detection provided by mass spectrometry, coupled with removal of complications imposed by the use of chromatographic columns in conventional laboratory techniques. The subsequent sections describe applications where this multicomponent analysis of gas-phase compounds with diverse ionization properties is very beneficial.

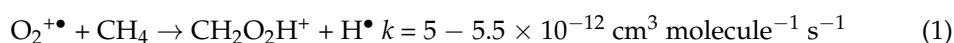
Table 2. Examples of compounds and the SIFT-MS reagent ions by which they are practicably analyzed (i.e., sufficient sensitivity and selectivity).

Compound	Reference(s)	H_3O^+	NO^+	$O_2^{+\bullet}$	$O^{-\bullet}$	$O_2^{-\bullet}$	OH^-	NO_2^-	NO_3^-
Ammonia	[11,12]	✓		✓	✓				
Benzene	[13]	✓	✓	✓					
Formaldehyde	[14]	✓					✓		
Hydrogen sulfide	[15–17]	✓			✓	✓	✓		
Ethanol	[18]	✓	✓	✓			✓		
Pyridine	[11,19]	✓	✓	✓	✓		✓		
Methyl bromide	[20,21]			✓	✓	✓	✓		
Carbon dioxide	[22–25]				✓	✓	✓		
Hydrogen chloride	[25]				✓	✓		✓	✓
Sulfur dioxide	[23,25,26]					✓	✓	✓	✓

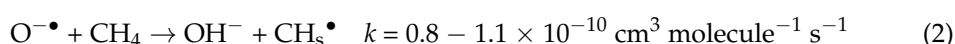
Since a substantial breadth of literature describes volatile compounds that are detectable using SIFT-MS (see, for example, very convenient review articles [6,9,10]), several examples of important compounds that are not analyzable, or have significant constraints, are discussed here.

First, consider methane which is of significant concern for climate due to its high global warming potential [27]. In positive ion mode, the $O_2^{+\bullet}$ reagent ion reacts with methane, as shown in Equation (1), whereas H_3O^+ and NO^+ are too inefficient to be useful [28,29].

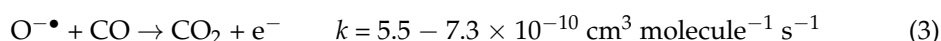
However, the sensitivity of SIFT-MS is lower than for most volatiles due to the slow reaction rate coefficient (k)—over 200-fold lower than typical k for VOCs. Nevertheless, methane analysis has been demonstrated for breath [29] and results for landfill and biogas analysis were reported to commercial customers by the present author over a 14-year period. Due to the low sensitivity, great care needs to be taken to ensure that the methane product ion does not suffer from interference.



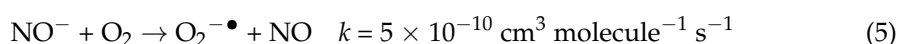
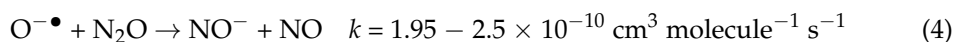
Interestingly, $\text{O}^{-\bullet}$ reacts with methane somewhat more rapidly (Equation (2)) [30] via the hydrogen atom transfer mechanism (Table 1). However, the product ion is also formed from reaction of $\text{O}^{-\bullet}$ with water [30] and other low-molecular-weight hydrocarbons [30], so it is not of practical use for specific detection of methane.



Second, carbon monoxide is toxic [31] and exposure is of significant concern in confined spaces and in the urban environment. Unfortunately, of the standard SIFT-MS reagent ions only $\text{O}^{-\bullet}$ reacts with CO [30] and this solely via the associative detachment mechanism (Table 1). As shown in Equation (3), no useful ion is obtained since free electrons (e^-) are not detectable in SIFT-MS instruments.



Finally, nitrous oxide (N_2O)—another important greenhouse gas [27]—reacts with $\text{O}^{-\bullet}$ as shown in Equation (4) [30]. In principle, this reaction rate coefficient provides adequate sensitivity for trace gas analysis. However, in air the NO^- product ion reacts with O_2 to form $\text{O}_2^{-\bullet}$ (Equation (5)) [30], which cannot be distinguished from $\text{O}_2^{-\bullet}$ formed at trace levels from other sources. N_2O is hence detectable, but it is only practicable to do so in oxygen-free matrices (e.g., in specialty gas applications).



Despite these limitations, SIFT-MS has found broad applications [6,9,10]. Later sections will review applications that are more closely aligned with chemosensor technologies.

2.3. Specificity of Analysis

Achieving specific analysis in moderately complex matrixes can be challenging for low-cost chemosensors. Eminent flavor chemist, Gary Reineccius wrote of the application of electronic noses (sensor arrays) in food flavor analysis that “one has no clear idea of what the instrument is responding to in making a judgement” [32].

In contrast, SIFT-MS achieves specific analysis in real-time by the combination of highly controlled, ultra-soft CI and MS, producing signals that are attributable to specific analytes. Table 1 illustrates the variety of common reaction mechanisms that occur for the standard SIFT-MS reagent ions and indicates the relative shifts from parent product ion m/z , or standard product ion m/z , for these mechanisms. Combining this behavior with the observation that different functional groups typically react in different ways [6,7], at least one unique ion for a given analyte is usually realized.

It is important to reemphasize that when using the phrase “real-time specificity” in the context of SIFT-MS, a user is not limited to a single reagent ion in each analysis. By means of the first QMF (Figure 1), combined with software control, reagent ions generated in a given ion source setting (e.g., positive ions with H_3O^+ , NO^+ , and $\text{O}_2^{+\bullet}$) are switchable in tens of milliseconds. This means that target compounds can be analyzed specifically across different reagent ions, if necessary. This contrasts with the other DIMS techniques [3]. Note

that where an ion source setting change is required—e.g., from positive ions to either of the negative ion settings—this is still near real time at approximately 10 s. Figure 2 summarizes the elements that contribute to specific analysis in SIFT-MS. Addition of a time-of-flight (TOF) mass spectrometer to SIFT-MS instruments (as has been done successfully for PTR-MS [3]) could further improve specificity, but at additional cost. However, regardless of the way that mass filtering is accomplished in SIFT-MS or PTR-MS, it is not reasonable to expect that the specificity of DIMS techniques will approach that of GC/MS with its temporal separation of analytes. GC/MS techniques—especially those utilizing high-resolution mass spectrometry—will remain the technique of choice for compound identification and analysis of very complex matrices.

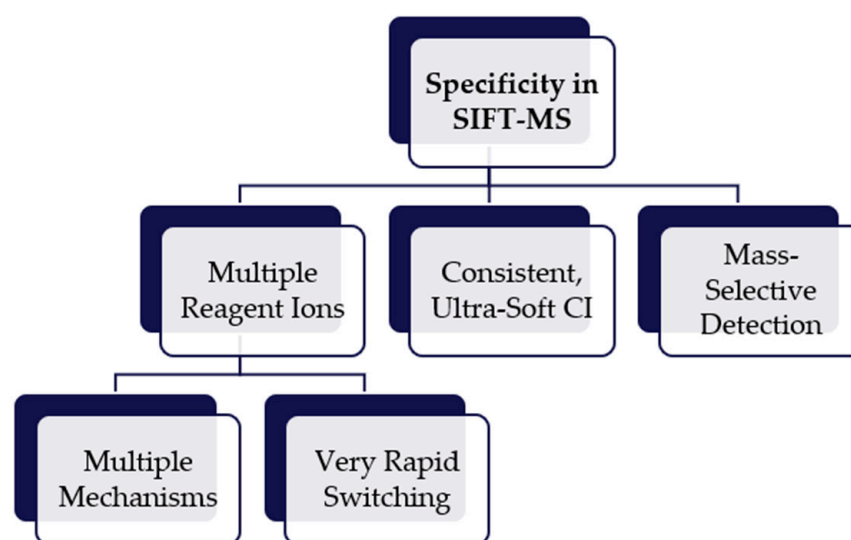


Figure 2. Specificity in SIFT-MS analysis is achieved through a unique combination of attributes.

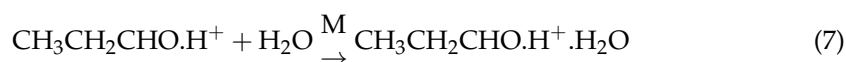
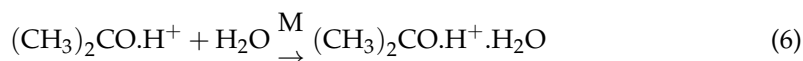
Since detailed examples of SIFT-MS specificity are given in Refs. [33–36], one simple example suffices here. Consider two structural isomers of molecular formula C_2H_6O and molar mass $58.0791\text{ g mol}^{-1}$: acetone (propan-2-one, $(CH_3)_2CO$) and propanal (propionaldehyde, CH_3CH_2CHO). Table 3 shows the primary product ions formed when acetone and propanal react with the three positively charged SIFT-MS reagent ions [14]. Use of the NO^+ reagent ion provides the most convenient resolution of these isomers. The H_3O^+ reagent ion cannot resolve the compounds, and matrix effects are encountered frequently for the unique $O_2^{+\bullet}$ product ions.

Table 3. Primary product ions formed from reaction of acetone and propanal with H_3O^+ , NO^+ , and $O_2^{+\bullet}$ [14]. The NO^+ reagent ion is most frequently utilized to achieve selective analysis.

Reagent Ion	Acetone			Propanal		
	Formula	<i>m/z</i>	br (%)	Formula	<i>m/z</i>	br (%)
H_3O^+	$(CH_3)_2CO.H^+$	59	100	$CH_3CH_2CHO.H^+$	59	100
NO^+	$(CH_3)_2CO.NO^+$	88	100	$CH_3CH_2CO^+$	57	100
$O_2^{+\bullet}$	$(CH_3)_2CO^{+\bullet}$	58	60	$CH_3CH_2CHO^{+\bullet}$	58	50
	$CH_3CO^{+\bullet}$	43	40	$CH_3CH_2CO^+$	57	50

Table 3 ignores the so-called secondary chemistry of acetone and propanal—only the primary ions formed because of reagent ion reaction with the analytes are shown. These primary product ions can react with matrix species—most commonly water, though carbon dioxide is common for negative ions—to form secondary product ions [6,7]. Secondary reactions are commonly association reactions (Table 1), requiring that a third molecule

(a so-called “third body”) is present in the reactive collision because it carries away sufficient kinetic energy for adduct formation to occur. The association mechanism is hence sensitive to the temperature and pressure in the SIFT-MS instrument flow tube [6,7]. The secondary reactions pertinent to these analytes occur for the H_3O^+ product (the most common situation):



In these equations, M represents the necessary third body and the secondary product ions are located +18 units higher than the primary product ion (i.e., at m/z 77). When they occur, it is necessary to measure the signals of secondary product ions for correct quantitation (see the next subsection). Method development should also ensure that they are not interfering with other analytes nor interfered with by other analytes.

2.4. Quantitation in SIFT-MS

The preceding subsections have described how SIFT-MS can analyze a wide range of compounds and generally do so with high specificity. It remains, then, to outline how quantitative results are obtained in SIFT-MS. Since the details of the gas-phase kinetic theory have been described elsewhere [6,37], and the detailed calculation of concentration presented [38], only a brief sketch will be given here. A future article will describe the calculation, as currently adapted in commercial SIFT-MS instruments, in more detail. In this article, the use of non-SI pressure units (torr) follows that of the SIFT-MS literature [38].

The master equation used in commercial instruments to determine the concentration of analyte A in air ($[A]_i$ in units of parts-per-billion by volume, ppbV) for each primary product ion (i) of A utilized in the analytical method is:

$$[A]_i = 1.035 \times 10^{-10} \frac{T_{FT}}{P_{FT}} \left(\frac{\varphi_{carr}}{\varphi_{samp}} + 1 \right) \frac{P_i^+ \cdot TF_{Prod}(i) + \sum_{all\ ki} P_{ki}^+ \cdot TF_{Prod}(ki)}{t_r \cdot br_i \sum_{all\ j} k_j R_j^+ \cdot TF_{Reag}(j)} \quad (8)$$

Here:

- T_{FT} is the temperature in the flow tube in Kelvin (K)
- P_{FT} is the pressure in the flow tube in torr
- k_j is the rate coefficient for reaction of reagent ion R_j^+ with the analyte (in $\text{cm}^3 \text{ molecule}^{-1} \text{ s}^{-1}$)
- t_r is the reaction time (in seconds)
- φ_{carr} is the carrier gas flow in torr L s^{-1}
- φ_{samp} is the sample flow in torr L s^{-1}
- P_i^+ is the primary product ion signal (in counts per second, cps) for primary product ion i counted by the particle multiplier detector
- $TF_{Prod}(i)$ is the transmission factor for the primary product ion P_i^+ (dimensionless)
- P_{ki}^+ is the secondary product ion signal (in cps) for secondary product ion k derived from primary product ion i
- $TF_{Prod}(ki)$ is the transmission factor for the secondary product ion P_{ki}^+ (dimensionless)
- R_j^+ is the reagent ion signal (in cps) for the injected reagent ion ($j = 0$) and its water cluster ions (if appropriate; $j = 1, 2, 3$)
- $TF_{Reag}(j)$ is the transmission factor for the reagent ion R_j^+ (dimensionless)
- br_i is the branching ratio for primary product ion i ($0 < i \leq 1$ for calculation purposes, but ordinarily tabulated as a percentage; see, e.g., Table 3).

The coefficient (1.035×10^{-10}) in Equation (8) is derived from several physical constants and unit conversions and has units of $\text{Torr cm}^3 \text{ molecule}^{-1} \text{ K}^{-1}$. Note that the

concentration $[A]_i$ is directly proportional to the ratio of measured product ion signal to measured reagent ion signal, which overcomes any ion source drift, should that occur, and confers measurement stability compared to MS detection coupled with chromatographic techniques. Clearly for correct calculation of $[A]_i$ the appropriate secondary ions need to be included in the analytical method (e.g., Equations (6) and (7)), otherwise the concentration will underreport.

The parameters in Equation (8) are obtained from various sources:

- Instrument operating parameters: T_{FT} , P_{FT} , φ_{carr} , and φ_{samp}
- The instrument's automated performance check on a certified gas standard: t_r , $TF_{Prod}(i)$, $TF_{Prod}(ki)$, and $TF_{Reag}(j)$
- Software library: k_j and br_i (clearly, together with the m/z at which the relevant reagent and product ions will be located)
- Measurement of sample: P_i^+ , P_{ki}^+ , and R_j^+ .

When more than one concentration determination is made for analyte A (i.e., several primary product ions are used in the method), then instrument software supports automated interference rejection through comparison of the $[A]_i$ values (within a user-chosen tolerance; by default, 20%) [39]. The most common failure mode for this approach is when secondary chemistry is omitted from the analytical method.

Several brief comments must be made to conclude the brief overview of SIFT-MS. First, SIFT-MS is quantifying compounds based on unique reagent ion-product ion pairs, not on pattern recognition from a sensor array—the analyst knows which compound is being detected using SIFT-MS, in contrast to sensors [32]. This confidence is evident in the extensive SIFT-MS literature reviewed elsewhere [7,9,10]. Second, several publications have compared SIFT-MS with gold-standard chromatography-based techniques and have reported favorable results, for example, Refs. [40–42]. Third, SIFT-MS analysis can be validated according to industry standard procedures (e.g., [43,44]), with only minor adaptations required despite the significant change in analytical approach from chromatographic separation to DIMS. Finally, the CI approach underpinning the SIFT-MS technique provides a wide linear range [6,45]. Ensuring that the instrument remains in the linear range is important for reliable concentration determination [6], although calibration and related approaches can circumvent this restriction when used with care [5]. Generally, however, SIFT-MS measurements do not drift with changes in matrix as chemosensors may. Hence SIFT-MS might provide an alternative to chromatographic methods for benchmarking chemosensors since it provides high-quality analysis in real-time.

3. Quantification of the Volatiles You Smell

Chemosensors—and, particularly, arrays of sensors—have been applied widely in odor assessment, as comprehensively reviewed by Guthrie [8]. Machine olfaction, however, does not currently provide an adequate representation of human olfactory response [8]. Braithwaite [46], however, has posited that SIFT-MS in combination with gas chromatography-olfactometry and the odor profile method may provide an effective complete odor solution—at least for environmental monitoring. Although correlation of SIFT-MS measurements with human sensory measurements is currently in its infancy, the technique has been valuably applied to quantitation of chemical odorants from shortly after it was introduced [6]. Hence the scope of this section is wider than sensory-related studies, encompassing chemical analysis of odorous compounds even when odor was not the main concern. It demonstrates the breadth of odorant analysis achievable with SIFT-MS. Where material has been reviewed in depth previously, that article is cited, and its conclusions summarized. Table 4 provides a convenient summary of the SIFT-MS applications below and lists the complementary chemosensor usage for each.

Table 4. The complementary nature of SIFT-MS and chemosensor detection of odorous compounds in the application areas discussed in Section 3.

Application	SIFT-MS	Chemosensors	Comment(s)
Breath analysis	Breath research Validation of sensor technologies Medical laboratory testing (centralized)	Routine clinic use (distributed)	Breath research is usually conducted in parallel with GC/MS (biomarker discovery) Chemosensor instrumentation is likely more affordable for clinics
Food, flavor, and fragrance	High-throughput sensory screening Product R&D/new product formulation	High-throughput sensory screening	Both technologies use pattern recognition for sensory analysis; SIFT-MS often adds ability to identify odorants
Materials and packaging	High-throughput sensory screening	High-throughput sensory screening	See comment above
Environment (outdoor)	Odor emissions and mitigation research Speciated odorant monitoring Sensory analysis Mobile laboratory	Distributed monitoring systems Sensory analysis Highly portable odor assessment	

3.1. Breath Analysis

Abnormal odors in exhaled breath have long been associated with potential ill health [47]. This prompted Linus Pauling and co-workers to pioneer analysis of breath VOCs using gas chromatography in the early 1970s [48]. The SIFT method was applied to breath analysis in one of the earliest articles describing its realization as an analytical technique [49,50], and since that time has found wide application in breath research as described in several reviews [6,9,10,51,52]. Detailed protocols for SIFT-MS analysis of breath are given in various articles [53–56].

Cross-over between direct-injection mass spectroscopy techniques and SIFT-MS is perhaps greatest for breath malodor, where SIFT-MS is used as the gold-standard technique for validation of lower-cost sensor technologies that are not only more affordable but can also be used as a point-of-care tools for rapid and early-stage diagnosis of disease in clinical practice [57]. SIFT-MS is used to understand the microbial generation of volatile organic compounds and volatile sulfur compounds resulting from microbial metabolism of oral biofilms [58] in parallel with sensory analysis for the development of improved oral care formulations that combat oral malodor [59]. Simple, direct, real-time, and quantitative analysis of malodorous ammonia, hydrogen sulfide, methyl mercaptan, amines, volatile fatty acids, and indoles on breath using SIFT-MS are important contributors to its success [60,61]. It has enabled evidence-based claims to be produced for different malodor products and to provide credibility and validity for all sensor technologies tested to date accelerating the route to market in the field of healthcare [57].

3.2. Food: Flavor and Fragrance

A comprehensive review in 2019 described food flavor applications of SIFT-MS amongst food safety and packaging applications [33], with newer literature summarized in recent articles [10,62,63]. The most relevant area for comparison with chemosensor arrays is human sensory analysis. A substantial subsection of the earlier review was devoted to these applications across a wide range of food products [33]. Although no studies to date have made direct comparison of SIFT-MS and chemosensors, the SIFT-MS studies have consistently demonstrated high correlation with human sensory panels. Recently, automated-SIFT-MS analysis has been adopted by industry for high-throughput screening of commercial dairy products, reducing the workload of a sensory panel [64].

3.3. Materials and Packaging

SIFT-MS is being applied increasingly to the analysis of materials, including packaging (see Sections 4.3 and 5), but largely remains unexplored from a SIFT-MS perspective, despite the potential indicated by food flavor research [33]. The sole exception is provided by a recent comprehensive study of recycled paperboard packaging, in which automated headspace-SIFT-MS analysis and human sensory analysis were compared [65]. The study concluded that SIFT-MS has potential for sensory classification of paper samples, both for odor intensity ratings and identification of sensory odor notes. Hence SIFT-MS may be able to address the expensive human sensory testing (due to the use of multiple highly trained panelists and low daily sample throughput) by predicting odor intensity rating and odor note.

3.4. Environment

Odors in the environmental context can arise from natural and industrial sources—and in the case of natural sources, these can be amplified through anthropogenic interventions, such as intense farming operations. Odors are usually complex and although chemosensors have been applied with some success [46], they do not qualify as equivalents to the human nose [66] and understanding odor composition at a chemical level is not possible [32]. This is where SIFT-MS can complement sensor data, since it is able to uniquely detect and quantify most odorants, including volatile sulfur compounds [15,16], ammonia and the amines [11,12], aldehydes and ketones [14,67,68], and volatile fatty acids [69,70]. Most compounds in these classes can be quantified by SIFT-MS to below human odor detection thresholds [71]. However, it should be noted that geosmin and 2-methylisoborneol, the well-known “earthy” compounds in drinking water, currently present a challenge for SIFT-MS in complex matrices such as wastewater headspace [72].

SIFT-MS has been applied to various environmental odor applications by van Langenhove and associates at Ghent University. Their early work profiled odors from facilities that intensively farmed laying hens, broiler chickens, and pigs [73–75]. The focus of their SIFT-MS research then turned to optimization of odor mitigation technologies, first establishing the scope [76], before determining fundamental parameters [77–79]. They then demonstrated that real-time analysis using SIFT-MS is very valuable to engineering of more advanced biofiltration technologies [80–85].

Odors emitted from intensively farmed poultry in southeast Queensland, Australia have also been probed—both on-site and in flux chambers—using real-time SIFT-MS [86]. The University of New England, Australia, also utilized SIFT-MS to better understand—and potentially mitigate—chicken litter odors through modified diet [87] and *in vitro* studies to better understand the microbial origins of increased litter odor during *Clostridium perfringens* infection [88].

Researchers in South Korea demonstrated the feasibility of odorant monitoring within a broader subset of VOCs in their ambient monitoring study (Section 4.2) [89].

In New Zealand, two industrial-scale odor studies have been performed. The first investigated odor at a gelatin factory, profiling odor sources (i.e., identifying specific odorants) and then assessing the effectiveness of ultraviolet odor neutralization controls on several odor sources [90]. In the second, a substantial study of odor sources was conducted at a large wastewater treatment plant (WWTP) [72]. Identification and quantitation of a wide variety of odorants (aldehydes, amines, organosulfur compounds, volatile fatty acids, etc.) was demonstrated and the results of SIFT-MS analysis were evaluated versus gold-standard olfactometry by a trained sensory panel. From this study, SIFT-MS may have potential as an improved tool for instrument-based sensory analysis compared to chemosensors, though further research and wider application is required. Of particular significance is the ability of SIFT-MS to easily distinguish hydrogen sulfide and methyl mercaptan which have very different odor characters and relative abundances as shown by the lack of correlation between these species in Figure 3.

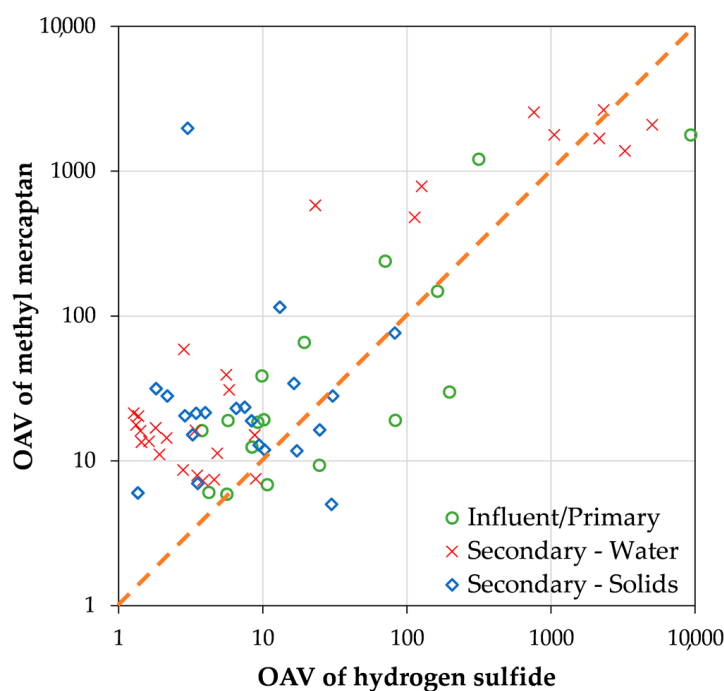


Figure 3. The relationship between the dominant sulfur odorants (hydrogen sulfide and methyl mercaptan) observed at a WWTP using SIFT-MS for the primary (green circles), secondary water (red crosses), and secondary solids (blue diamonds) odor sources. Note the use of odor activity values (OAVs) and logarithmic axes. From Ref. [72]; used with permission of the authors.

4. Protection from the Toxic Volatiles You Do Not Smell

A significant proportion of VOCs are toxic. For example, the United States Environmental Protection Agency's (US EPA) lists 197 hazardous air pollutants (HAPs), of which approximately half are VOCs [91]. In Chapter 467, the United States Pharmacopeia [92], following the International Council for Harmonisation [93], lists five residual solvents that are very toxic or hazardous to the environment (Class 1) and 29 solvents for which there are exposure concerns (Class 2). For such scenarios, if the matrix is consistent and only a handful of volatiles are present, relatively low-cost chemosensors may be appropriate for screening purposes. However, where the matrix is more complex and/or variable and quantitation of multiple components to low concentrations is required, then SIFT-MS likely provides a better fit. SIFT-MS applications of this type are reviewed in this section and summarized in Table 5 (together with the complementary chemosensor applications).

Table 5. The complementary nature of SIFT-MS and chemosensor detection of hazardous volatiles in the application areas discussed in Section 4.

Application	SIFT-MS	Chemosensors	Comment(s)
Occupational safety and health	On-site (fixed or mobile) or remote laboratory analysis of diverse toxic compounds Research	Devices for personal protection (limited capability per device)	Complex matrices, such as shipping container air, may reduce the usefulness of sensors due to false alarms
Indoor air quality	Protection of high-value, highly susceptible products (semiconductors) Research	Distributed monitoring systems Highly portable analysis	High sensitivity and selectivity are essential for semiconductor manufacturing, but this is a very specialized use-case

Table 5. Cont.

Application	SIFT-MS	Chemosensors	Comment(s)
Environment (outdoor)	Speciated 24/7 continuous monitoring of volatiles Mobile monitoring (including while driving) Validation of sensor technologies	Distributed monitoring systems Sensory analysis Highly portable odor assessment	Specificity of SIFT-MS provides validation of chemosensor performance
Pharmaceuticals	High-throughput quantitative product safety analysis (e.g., nitrosamines, ethylene oxide, residual solvents)	High-throughput product quality screening based on pattern recognition	Due to lower cost, chemosensors with appropriate performance may be a better fit for process monitoring
Personal care products	High-throughput quantitative product safety analysis (e.g., benzene, ethylene oxide) Product R&D/new product formulation	High-throughput product quality screening based on pattern recognition	See comment for Pharmaceuticals
Materials and packaging	High-throughput quantitative product safety analysis (e.g., benzene, styrene, formaldehyde)	High-throughput product quality screening based on pattern recognition	See comment for Pharmaceuticals

4.1. Occupational Safety and Health, and Indoor Air Quality

VOCs are important contributors to workplace exposure and indoor air quality (IAQ). Because people can be exposed to VOCs for long periods each day in these environments—and hence exposure can be chronic—these areas are treated together in this review.

Smith, Španěl, and coworkers pioneered quantitative analysis of toxic volatiles, and validation of the methodology, only a short time after the selected ion flow tube was adapted to gas analysis [94–96]. They focused on the potential of the emerging technique as a tool for evaluating chemical exposure. McEwan’s research group, with clinical co-workers explored several additional applications, including breath alcohol [97] and exposure to common industrial solvents [98,99].

Detection of fumigants and toxic industrial chemicals (TICs) in shipping containers [10] is a significantly more challenging application of SIFT-MS—in terms of both the gaseous chemicals that must be detected and the intended instrument users. The chemical diversity is illustrated in Figure 4 based on their polarity and ionization energy properties. This means that multiple GC analyses are required to report the full suite of volatiles, which is impractical for frontline, non-technical staff. Prior to adoption of SIFT-MS, colorimetric tubes have been utilized by some organization—with very high consumable costs and low user confidence—while handheld photoionization detectors (PIDs), metal oxide-based sensors, and portable infrared spectrometers had unacceptable false positive rates due to poor specificity. Since its adoption in 2006, SIFT-MS instrumentation has proved very effective in this application [100–103], addressing both the need for broad-spectrum analysis and ease-of-use in an industrial environment. By using both positive and negative ionization, while having a wide range of ionization mechanisms available (not just electron transfer; Table 1) even hydrogen cyanide, with its high polarity and ionization energy, is readily detected [104]. Samples are analyzed for all compounds within 2 min. by operational staff.

Other applications of SIFT-MS in workplace exposure assessment include speciating and quantifying airborne solvents in the collision repair industry [105] and identification and quantification of leakage from closed system drug-transfer devices [106]. SIFT-MS has also been used to monitor of a new dosing system for preparation of reference gases at the German Institute for Occupational Safety and Health (IFA) [42]. This study involved full validation versus GC and high-performance LC (HPLC) for routine VOCs and aldehydes, respectively.

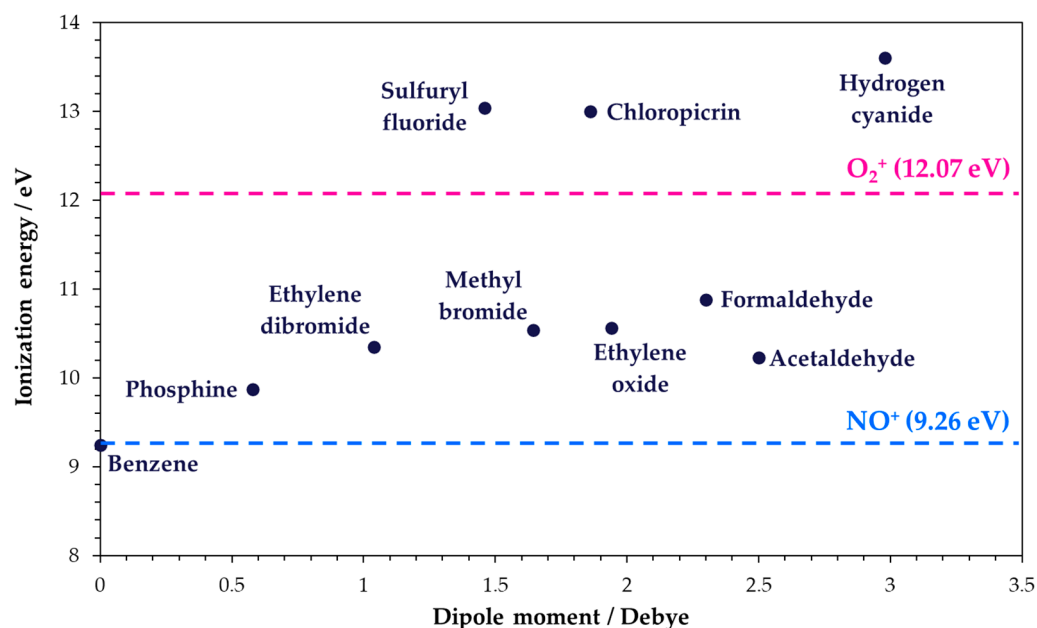


Figure 4. Illustration of the diversity of gaseous fumigants and several TICs based on their polarity (as indicated by the dipole moment) and ionization energy (in electron volts, eV). The ionization energies of NO and O₂, corresponding to the NO⁺ and O₂^{+•} reagent ions of SIFT-MS, are shown for reference.

Indoor air quality analysis is an expanding area for SIFT-MS, especially through adoption by the semiconductor industry, where it protects both employees and product [10]. SIFT-MS provides broad-spectrum detection of compounds of greatest concern, which cover VOCs [7], acidic gases (HF, HCl, SO₂ [25]), and ammonia [12]. With most compounds requiring sub-ppbV detection limits, this application is beyond the capabilities of most chemosensors, but within those of SIFT-MS [45,107].

SIFT-MS is emerging as a powerful tool for the quantification of volatile emissions from diverse materials into residential indoor air. Emissions from personal care products have been reported for aerosol-based hairsprays (in which benzene was detected) [108], non-aerosol products [109], and facial moisturizers [110]. Cleaning [111,112] and cooking [113–115] emissions are a very recent focus of research. SIFT-MS has also been applied to analysis of hazardous semi-volatile organophosphate esters used as flame retardants [116], and—by using negatively charged reagent ions—ozone [117]. Exposure to volatile emissions in automobile interiors has also been demonstrated [118], with simultaneous analysis of VOCs and aldehydes, rather than separate GC and HPLC analyses, respectively.

4.2. Environment

This subsection highlights the contributions that SIFT-MS is increasingly making to environmental protection, covering air quality monitoring, water analysis, and an emerging application: microplastics.

4.2.1. Air Quality Monitoring

In 2010, Prince et al. [45] demonstrated high-sensitivity continuous ambient monitoring for the first time, targeting benzene, 1,3-butadiene, ethanol, ethene, and toluene. This work demonstrated low part-per-trillion by volume (pptV) detection limits for the first time. Side-by-side comparison with gold-standard GC/MS [40] using a subset of the US EPA TO-15 method [119], which is based on canister sampling, gave excellent comparability for benzene, toluene, ethylbenzene, and the xylene isomers (BTEX) across diverse field samples. Field deployment of an instrument operating on the newly released nitrogen carrier gas was trialed in mid-2015 [120]. Combined, these studies provided a platform

for wider adoption in field monitoring. In Korea, Son et al. monitored 60 volatiles with a cycle time of 3.2 min [89], achieving good linearity over their calibration range (0.174 to 100 ppbV), good repeatability (10% relative standard deviation, %RSD), and sub-ppbV LODs across a wide range of chemical functionalities. This work was followed by a mobile monitoring campaign [121].

The Wolfson Atmospheric Chemistry Laboratory (WACL) at the University of York (UK) has extended the application of SIFT-MS into atmospheric research. In 2016 and 2017 they participated in a campaign in Beijing, China [122]. The campaign comprised two six-week deployment periods (winter and summer) and included automated calibration on a three-day cycle [123]. Air was sampled at a height of 102 m and delivered to the instrument located in a hut at ground level. Figure 5 shows comparative concentration data for SIFT-MS and dual-channel gas chromatography–flame ionization detector (DC-GC-FID) over a 10-day period in the winter campaign [123]. Agreement is excellent for at least one reagent-product ion pair in each case (despite the GC sampling from only 8 m), illustrating the benefit of rapidly switchable reagent ions in SIFT-MS for providing specific analysis and interference rejection in real time. Effective, real-time analysis of nitrous acid (HONO) was also demonstrated during the campaign [124].

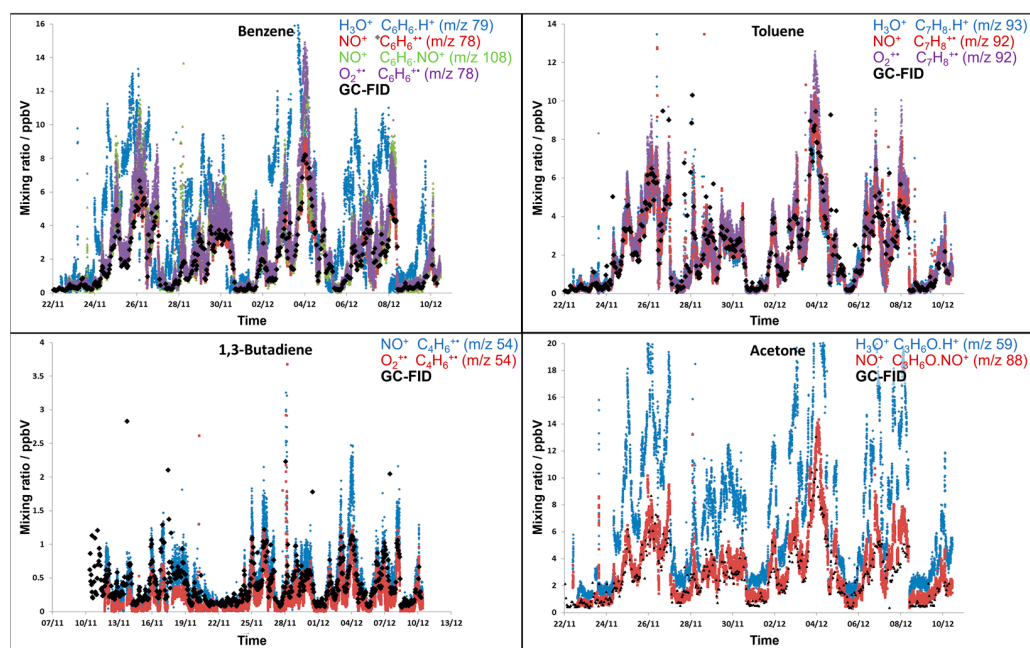


Figure 5. Mixing ratios (concentrations) for ambient air in Beijing during winter 2016, as measured using DC-GC-FID and SIFT-MS [123]. Legend text color matches relevant data series. Unpublished conference poster illustration reproduced with permission of the authors.

More recent campaigns have demonstrated the benefit of SIFT-MS analysis for (i) both organic and inorganic compounds in the field [125,126], (ii) accurate, high-sensitivity analysis of oxygenated VOCs [127], and (iii) monitoring in a moving laboratory [128] with sub-ppbV detection limits.

4.2.2. Water

Automated SIFT-MS may have benefits for water analysis as a screening tool because of its high-sensitivity direct analysis that is robustness to water content. Laboratory analysis of a range of VOCs in water has demonstrated ongoing improvements in quantitation limits [36,43,129]. The latest of these [36] has achieved a 100 ppt limit of quantitation for benzene in water, exceeding European Union and United States maximum contaminant levels by 10- and 50-fold, respectively. Lee et al. [130] demonstrated that SIFT-MS has

potential for online analysis of industrial wastewater, but their prototype automated system did not achieve the detection limits required for drinking water.

4.2.3. Soil

SIFT-MS has significant potential for soil analysis, but relatively little research has been conducted to date. Langford et al. [40] analyzed soil gas samples as part of their evaluation of SIFT-MS compared to GC/MS and found that BTEX compared very well. In complex soil-gas samples (e.g., those sampled near a gas station), low-molecular-weight chlorinated hydrocarbons were prone to interference from saturated hydrocarbon residues. Perkins [131] has demonstrated that methanolic extraction [132] can be utilized with SIFT-MS, although only the NO^+ reagent ion can be utilized. Good results were obtained for BTEX, with a sample throughput threefold higher than GC/MS.

4.2.4. Microplastics

Researchers at the University of Pisa, Italy, have demonstrated that SIFT-MS is well-suited to analysis of volatile residues in environmental microplastics—pollutants of increasing concern [133,134]. Rapid SIFT-MS analysis is presented as a valuable part of a protocol for comprehensive microplastics identification, since it can rapidly quantify toxic volatile degradation products [134].

4.3. Pharmaceuticals, Personal Care Products, and Packaging

Potential for providing rapid screening of pharmaceutical and personal care products, and their packaging, for toxic chemicals was only realized after automation was seamlessly integrated with SIFT-MS [135]. Automation enables the power of direct sample analysis to be applied repeatably in routine analysis [5], even for compounds that are chromatographically challenging and require special sample prep or instrument configurations [136]. This subsection highlights this emerging application.

4.3.1. Pharmaceutical Products (Including Active Pharmaceutical Ingredients (APIs) and Excipients)

Although few pharmaceutical products are volatile, VOCs can be used as reagents, as solvents in synthesis and/or purification, and may form as byproducts in synthesis or through degradation during storage. In the pharmaceutical industry, GC-based techniques are primarily utilized for these analyses.

The procedure detailed in chapter 467 of the United States Pharmacopeia (USP), “Residual Solvents” [92], is perhaps the most widely employed procedure for the analysis of residual solvents. As promulgated, it utilizes headspace-GC (with flame ionization detection, FID, or mass spectrometric detection), but alternative procedures can also be validated [137]. Recently, a feasibility study was conducted across Class 1 and 2 solvents for water-soluble drug products using headspace-SIFT-MS, with full validation of the Class 2A and 2B solvents according to USP 1467 [44]. The validation study met USP 1467’s acceptance criteria for all solvents except pyridine and hexane (recoveries failed in selected drug products). Work is ongoing because of the throughput benefit (up to 16-fold increase compared to GC), and potential for online monitoring.

SIFT-MS can also be applied to target volatile impurities. Since volatile, carcinogenic nitrosamines were discovered in sartan-class drug products in 2018, widespread nitrosamine testing has been implemented [138,139]. They have since been found in other drug products, but all sources of nitrosamines are yet to be identified [138–140]. Discussions about the extent of drug product testing required, and the high-sensitivity analytical methods to do so, are ongoing [140]. Nitrosamines are readily detected using SIFT-MS [141] and recent work has demonstrated a 2-ng g^{-1} quantitation limit for *N*-nitrosodimethylamine (NDMA) in 500 mg of pharmaceutical product [142,143], well below the acceptable intake of 96 ng day^{-1} [138,139].

Ethylene oxide—another toxic impurity in drug products—is also readily analyzed using SIFT-MS. It is a widely used feedstock in the chemical industry [144], including in the manufacture of polyethylene glycols (PEGs) used as surfactants and emulsifiers perfumes, cosmetics, and pharmaceuticals. The United States Pharmacopeia (USP) monograph *Polysorbate 80* [145] describes the conventional gas chromatography-flame ionization detection (GC-FID) method for ethylene oxide analysis. This approach is slow, both from the perspective of sample preparation [146] and sample analysis. The rate-limiting step in sample preparation is the 6-hr purification of the PEG matrix for matching to the sample. Furthermore, the GC-FID run time is 38 min. per sample (Figure 6). In contrast, the higher sensitivity of SIFT-MS removes the requirement for matrix matching through 40-fold higher dilution of the sample in water, enabling aqueous ethylene oxide standards to be utilized [147]. Through direct, chromatography-free analysis, SIFT-MS also provides much faster time to result and higher sample throughputs (Figure 6).

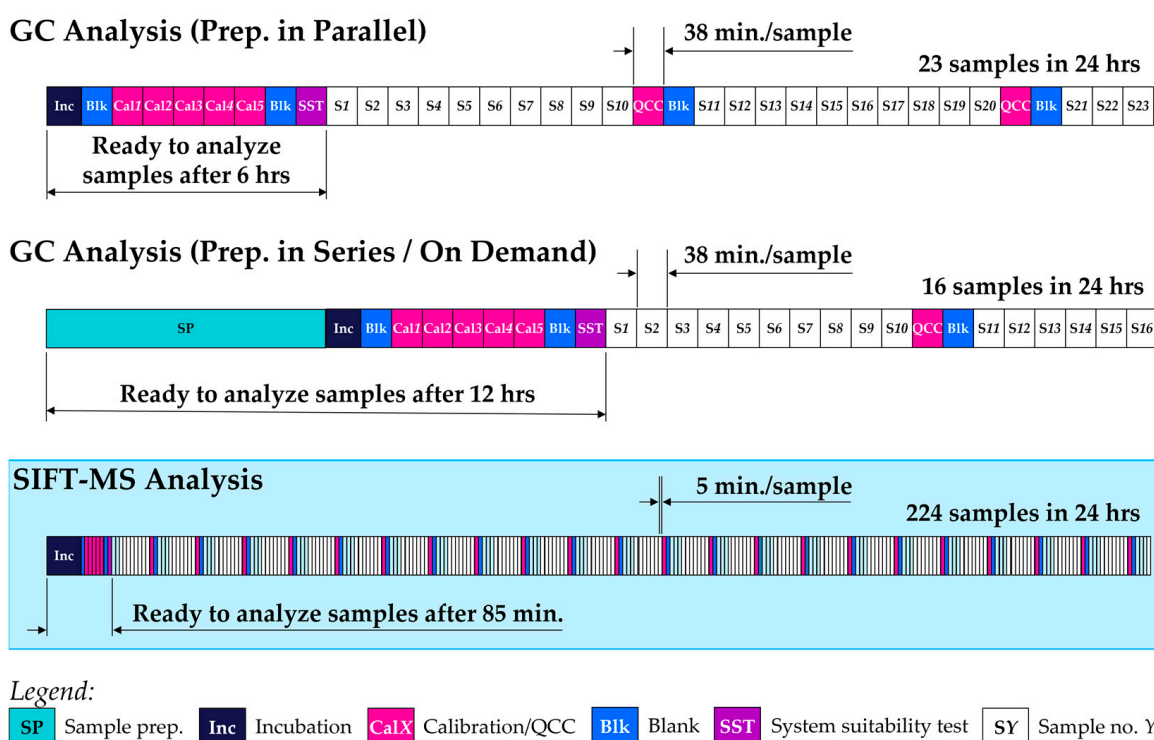


Figure 6. Headspace SIFT-MS enables analysis of ethylene oxide in Polysorbate 80 samples to be conducted at significantly higher throughput, while eliminating very slow sample preparation, due to enhanced sensitivity. Used with permission of Syft Technologies.

Formaldehyde is another compound of concern because it is a known human carcinogen [148,149]. It can arise in polyethylene glycol (PEG) ester surfactants, which are widely used as excipients [150], through autoxidation and thermal degradation. Formaldehyde is, however, challenging to analyze using conventional chromatographic techniques due to its high polarity and reactivity, so typically involves derivatization (and, for high-sensitivity analysis, sample preconcentration). SIFT-MS simplifies formaldehyde analysis via direct analysis from air and headspace at toxicologically relevant concentrations [14,151]. A recent multiple headspace extraction (MHE) study has described quantitation of formaldehyde at low $\mu\text{g g}^{-1}$ concentration in Gelucire 44/14, a PEG ester used as an excipient in drug products [152].

4.3.2. Personal Care Products

Benzene has recently been detected as a contaminant in diverse commercial personal care products (PCPs), including sunscreens, body sprays and dry shampoos [153]. Chronic exposure to benzene is linked to a significantly increased risk of certain cancers, including leukemia. As noted above, benzene has been quantified to sub-ppb levels in water using headspace-SIFT-MS [36]. Recently, by using the method of standard additions, benzene concentrations in the ppb range have been measured in various suntan lotion matrices using headspace-SIFT-MS analysis [154]. A recent citizen's petition to the United States Food and Drug Administration (FDA) utilized—in part—SIFT-MS real-time analysis of benzene from dry shampoo products as they are sprayed [108].

Mentioned previously in the context of IAQ, the work of Yeoman and co-workers [109,110] demonstrates that personal exposure to volatiles is significant during use of cosmetic products.

4.3.3. Packaging

Volatile compounds in packaging materials, adhesives, inks, etc., can transfer to pharmaceutical and consumer products—even passing through other packaging barriers—and present a health risk. Automated SIFT-MS has been successfully applied to detection of volatiles in polymeric packaging (e.g., polystyrene [155], high-density polyethylene (HDPE) [156], polyoxymethylene (POM) [157]) and paper/cardboard [65]. A preliminary investigation of detection of mineral oil saturated hydrocarbons and mineral oil aromatic hydrocarbons (so-called “MOSH and MOAH” [158]) on a variety of polymer and paper products holds promise for a rapid screening test using SIFT-MS [159]. Particularly significant, given the recent publicity on personal care product contamination [108,153], was the detection of benzene in most products (Figure 7).

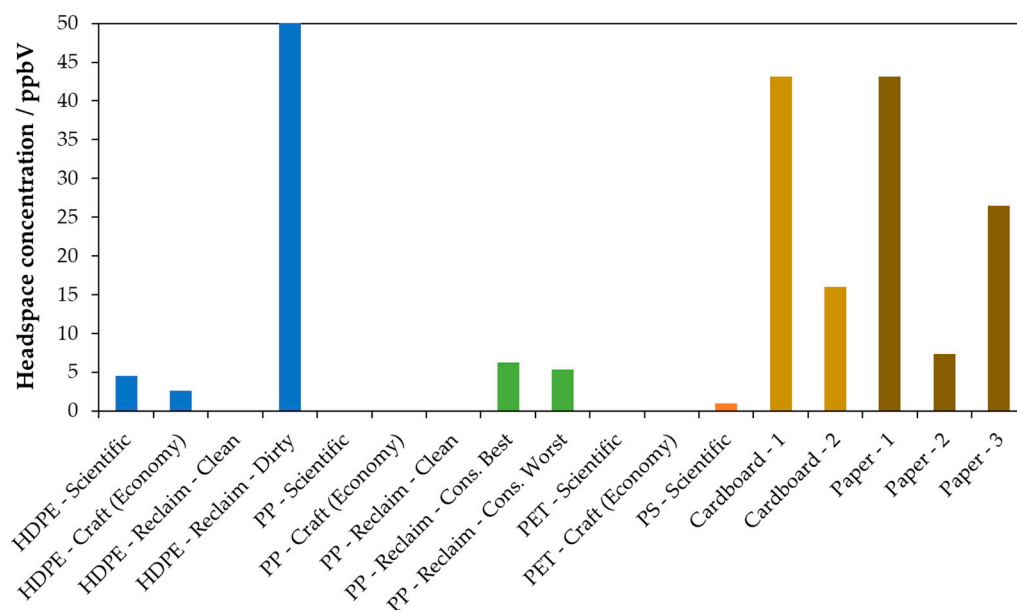


Figure 7. Benzene headspace concentrations (in ppbV) determined using automated SIFT-MS for various packaging materials. See Ref. [160] for full details. Used with permission of Syft Technologies.

To date the most thorough SIFT-MS study focused on packaging safety targeted formaldehyde in drug delivery devices [160]. The method was validated successfully and approved in a regulatory submission. Direct injection of whole-air samples into the SIFT-MS instrument greatly simplified and accelerated method development and product testing compared to the conventional approach involving derivatization with 2,4-dinitrophenylhydrazine (DNPH), solvent elution, and analysis using HPLC with ultraviolet detection (HPLC-UV).

5. Untargeted SIFT-MS Analysis: Parallels with Sensor Arrays

SIFT-MS instruments can be utilized in a manner analogous to the so-called electronic noses, or enoses (sensor arrays), by acquiring sample data in full-scan mode followed by post-processing using multivariate statistical analysis. The basic parallels are illustrated schematically in Figure 8. This approach has emerged in recent years, with applications including rapid origin authentication of Moroccan Argan [161] and Mediterranean olive [162] oils, detection of trace adulterants in Moroccan Argan oil [163], strawberry flavor mixes [164], classification of parmesan cheese [62], rapid discrimination of *Vitis vinifera* berries [165,166], determination of human diseased states via breath [167,168], and virgin and recycled HDPE [156]. The main advantage of this approach is that it is of broader scope than targeted analysis, detecting a wider range of compounds, including potentially important species that may lie outside the scope of a targeted analysis, including contaminants.

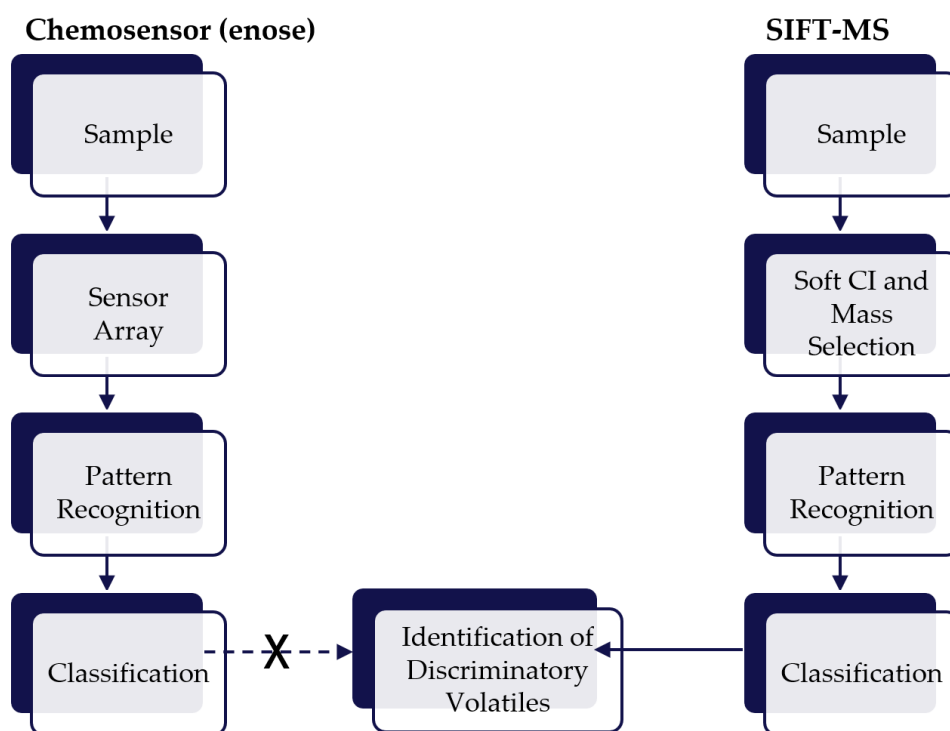


Figure 8. A simplified schematic representation of the parallels between chemosensors (enoses) and untargeted SIFT-MS sample classification approaches. SIFT-MS has an advantage in that compounds cause sample discrimination can often be identified.

Although the above studies utilize the SIFT-MS technique essentially as a “black box” there is always the ability to retrospectively interrogate the full-scan data to identify the compounds whose spectral features are responsible for classifying different types of samples (Figure 8). This approach has been utilized recently by Langford and coworkers for strawberry flavors [164] and HDPE [156], and by Geffroy and co-workers for wine grapes [165,166]. This capability is lacking for sensor arrays, as noted by Reineccius (Section 2.3 above) [32], but is possible where chemosensors are coupled to gas chromatographs. With SIFT-MS, however, it can be used to create optimized targeted methods through identification of the significant discriminatory variables.

It must be noted, however, that for untargeted SIFT-MS analysis extra care is required in method development and routine analysis, since the normalization of ion signals and robustness to humidity, are no longer handled automatically—in contrast with concentration calculation in targeted analysis [6,38]. Hence it is of particular importance that: (1) reagent ions and their ^{18}O isotopologues should not be included, (2) samples should

be well within the linear range (for matrix volatiles as well as target analytes) [6], and (3) humidity should be kept constant. Failure to do so can result in the statistical analysis generating spurious results through assigning importance to variables that are merely indicators of humidity changes and/or volatiles present at high concentrations undergoing secondary reactions [6,7]. These factors will be addressed in detail in a forthcoming article.

6. Conclusions

The SIFT-MS technique has found broad applications in the detection of odorous and hazardous volatile compounds during the nearly three decades since it was introduced. Its applications can generally be characterized as those that require specific analysis of multiple compounds with diverse chemical functionalities at high sensitivity in real-time (or with high sample throughput). For industrial applications, robustness and ease of use are also important attributes, enabling laboratory-grade analysis to be conducted by non-technical staff in less-controlled environments. Fumigant analysis furnishes a good example of an industrial application ideally matched to SIFT-MS. In terms of technical applications, SIFT-MS odor analysis shows promise for effective instrument-based sensory analysis because of the broad-spectrum detection of chemically diverse odorants (including hydrogen sulfide, ammonia, and low-molecular-weight aldehydes and volatile fatty acids) in a single run. In the pharmaceutical industry, the ability to rapidly switch between very different analytical methods—due to chromatography-free analysis—is highly valued (e.g., from nitrosamine analysis to ethylene oxide to residual solvents).

SIFT-MS better complements chemosensor technologies than do more conventional off-line, laboratory-based techniques such as GC and LC because it is real-time and field-portable, while results compare favorably with the “gold standard” GC and LC techniques. This means that SIFT-MS may be better suited to benchmarking chemosensor performance than GC and LC—especially for organizations manufacturing, standardizing, or utilizing sensors for diverse volatile compounds.

The broad applications of the SIFT-MS technique enable it to complement low-cost chemosensors. The very soft chemical ionization coupled with mass spectrometry enables one SIFT-MS instrument to be applied to a wide variety of matrices, providing specific, sensitive, and quantitative analysis of diverse volatile compounds. Because chemosensors usually exhibit higher susceptibility to interference they typically do not perform well in matrices that are complex or show significant variability. SIFT-MS applied in parallel may support faster development and tuning of chemosensors (for example, for oral malodor diagnosis). Chemosensors and SIFT-MS instruments have important and complementary roles to play in gas-phase volatiles analysis.

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Conflicts of Interest: The author is an employee of Syft Technologies Limited, a manufacturer of commercial SIFT-MS instruments.

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