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Proton transfer reaction mass spectrometry: A green alternative for food volatilome profiling

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ABSTRACT

Proton transfer reaction mass spectrometry (PTR-MS) has been developed for the direct, high sensitivity and high time resolution monitoring of volatile organic compounds (VOCs). Although PTR-MS development was not guided by greenness goals, most of its features perfectly fit within the green analytical chemistry (GAC) principles, making PTR-MS an intrinsically green analytical technique. Indeed, in its basic implementation, it does not require solvents or non-renewable carrier gases and, in principle, distilled water, used to feed the source where precursors ions are formed, is the only consumable.

Food science and technology and agroindustry are amongst the fields where PTR-MS has been successfully exploited. Here we review and discuss, with emphasis on the GAC requirements, the potential of PTR-MS as a tool for both fundamental research and industrial applications in different food-related themes: i) food consumption and sensory, ii) bioprocess monitoring, iii) traceability, iv) quality control, and v) high-throughput food volatilome phenotyping.

The outcome of all these related studies indicates PTR-MS both as a complementary tool to gas chromatographic methods and as a valuable technique when reduced analysis time, high sensitivity and/or on-line measurement are required.

1. Introduction

In recent decades, we have been witnessing a growing awareness of the environmental impact of human activities and the effort to reduce it. To introduce sustainable practices in chemical processes, in 1998, Atanas and Warner proposed the concept of Green Chemistry and elaborated a set of its 12 principles [1]. Not all these guidelines fit well within the scope of analytical chemistry, which concerns the application of measurement protocols and not the yield of chemical reactions. Therefore, Green Analytical Chemistry (GAC) emerged in the 2000s as an area of green chemistry whose ultimate aim is the reduction of the environmental impact of analytical methods and technologies. In 2013 Galuszka et al. [2] significantly contributed to the development of GAC by proposing a specific set of 12 principles (reported in Table 1) and four key goals underlying these principles: (1) reduction of chemicals, (2) minimisation of energy consumption, (3) management of analytical waste, and (4) increase in operator safety. These goals have been pursued through several approaches: i) developing evaluation frameworks [3] or exploiting the life cycle approach (LCA) [4] to assess and quantify the environmental impact of the analytical techniques; ii) increasing commitment from manufacturers to ameliorate the existing instruments [5]; iii) moving toward a green sample preparation, considered the most environmentally critical step of analytical workflows, through the development of novel strategies and the establishment of dedicated principles [6] and metrics [7]; iv) exploiting alternative analytical techniques with intrinsically lower environmental impact compared to the benchmark ones. Pallone et al. [8], for instance, reported the successful application of vibrational spectroscopy, associated with chemometrics, as a green alternative to conventional analytical methodologies for several food analyses.

Following the latter example, this review aims to demonstrate how proton transfer reaction mass spectrometry (PTR-MS) complies with the principles and objectives of GAC. Indeed, PTR-MS was developed in the 1990s as a tool for high-sensitivity real-time monitoring of volatile or-

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Table 1
List of the 12 GAC principles and the corresponding PTR-MS characteristics.

The 12 Principles of GAC [2]	PTR-MS green features
Direct analytical techniques should be applied to avoid sample treatment	Since PTR-MS is highly sensitive and based on direct injection, it is in most cases possible to avoid VOC extraction or preconcentration. This allows direct headspace sampling, non- invasive/destructive analysis (e.g. plants and fruits) and on-line process monitoring.
Minimal sample size and minimal number of samples are goals	PTR-MS requires low sample quantities, and it mostly depends on an experimental setup. Grinded material (0.5–1 g) or small size samples (a single coffee bean [21]) are used for large screenings with PTR-ToF-MS equipped with an autosampler. On-line monitoring experiments may require a higher amount of sample depending on an experimental scope (e.g. bread baking, food consumption).
In situ measurements should be performed	Food VOCs analyses are usually carried out off-line in dedicated laboratories; however, in situ measurements are feasible, for instance for industrial or environmental applications.
Integration of analytical processes and operations saves energy and reduces the use of reagents energy and reduces the use of reagents	The number of analytical steps depends on the application. It ranges from no analytical steps before the measurement, in case of non-destructive analysis, to a maximum of 3–4 steps for samples requiring freezing and grinding.
Automated and miniaturised methods should be selected	Depending on the sampling configuration, the automation can be achieved by: – Headspace sampling using an autosampler – Multiplexing the gas inlet using automated multiport sampling devices, such as multiplexing valves, to monitor different spots e.g. in a plant Miniaturisation is limited by the size of mass analysers and vacuum systems.
Derivatization should be avoided	No derivatization required
Generation of a large volume of analytical waste should be avoided and proper management of analytical waste should be provided	– No toxic analytical waste is produced. – Only vial septa are single-use consumables (vials and screw caps can be properly washed and reused). – Sample is usually not treated, and its disposal is managed according to the sample nature, which, in the case of food matrices, is usually not critical.
Multi-analyte or multi-parameter methods are preferred versus methods using one analyte at a time	PTR-MS is usually applied for multi-analyte characterisation, especially in the case of ToF analyser. As a rapid technique, it allows the processing of numerous samples per time unit.
The use of energy should be minimised	The energy consumption ranges between 0.7 kW and 1.2 kW depending on the mass analyser [22,23]. Screening of samples in vials requires 3–5 min/sample, corresponding to approximately 0.05 kWh/sample.
Reagents obtained from renewable source should be preferred	If H_3O^+ is the precursor ion, the only reagent required is distilled water to feed the source where precursor ions are generated. In the case of O_2^+ or NO^+ as precursor ions, oxygen cylinder and nitrogen generators can be used. Kr^+ and CH_4^+ as precursors must be provided in pressurised cylinders, however the use of these reagent ions is uncommon in food science and technology applications.
Toxic reagents should be eliminated or replaced	No toxic reagent is necessary.
The safety of the operator should be increased	The absence of toxic reagents ensures the safety of the operator.

ganic compounds (VOCs) and, despite its development not being guided by greenness goals, most of its features perfectly fit within the GAC principles.

The first section provides a brief description of PTR-MS fundamentals and a discussion of the features that make PTR-MS an intrinsically green analytical technique.

The second section of this paper refers to the application of PTR-MS in food science and technology (FST). This section includes a paragraph dedicated to meta-analysis of the available literature and five paragraphs addressing specific application areas where PTR-MS has been successfully applied (food consumption and sensory, bioprocess monitoring, traceability, quality control, and high-throughput food volatilome phenotyping).

1.1. PTR-MS fundamentals

Here we limit ourselves to briefly reporting some salient features of PTR-MS because exhaustive reviews on its fundamentals are available [9,10] and we encourage the reader to refer to them for details.

In short, PTR-MS technology is based on soft chemical ionisation by means of proton transfer reactions. The generation of protonated water takes place at an ion source (a hollow cathode) from pure water. Then the reactions occur in a drift tube operated at a low pressure (approximately 2 mbar) between H_3O^+ primary ion and VOCs fed directly and continuously in the drift tube from the gas sample.

The VOCs with proton affinity higher than water (691 kJ/mol) are protonated, while the major components of air (N_2, O_2 and CO_2) are not, because of their lower proton affinity, thus allowing the use of air as carrier gas.

To extend the application range of PTR-MS, other ionisation agents such as O_2^+, NO^+ [11,12] and Kr^+ [13] have been tested. The possibility to use different primary ions was implemented in commercial instruments with the development of the switchable reagent ion (SRI) technology, which enables a rapid change of the ionisation agent.

Ionised VOCs are then separated according to their mass-to-charge ratio (m/z) into a mass analyser. Quadrupole, ion trap [14] and time-of-flight (ToF) mass analysers have been coupled to PTR [15]. Commercially available instruments are equipped with quadrupole (PTR-Q-MS) or time-of-flight (PTR-ToF-MS) analysers.

PTR-ToF-MS has the advantage of providing a higher time resolution and enabling the separation of compounds with the same nominal mass (isobaric compounds) due to its higher mass resolution. With PTR-MS the analytes are characterised based on their m/z, which is not sufficient to provide a reliable identification of the VOCs and cannot differentiate the signal of isomers. To overcome this limitation, efforts have been made to introduce a fastGC separation step prior to the PTR-MS analysis to make possible the separation of isomers [16].

The performance of mass spectrometers and detectors is crucial for the sensitivity of PTR instruments. That is why some efforts were done to refocus the ion beam coming from the drift tube. In 2012, Barber et al. presented the drift tube capable of simultaneously functioning as an ion funnel which increased the sensitivity by more than two orders of magnitude for the majority of VOCs [17].

In 2014 Sulzer et al. introduced a PTR-ToF-MS instrument equipped with a quadrupole ion guide (PTR-Qi-ToF-MS) which was aimed to improve the transfer of ions from the drift tube into the ToF mass spectrometer [18]. The addition of a quadrupole ion guide helped to optimise maximum sensitivity or maximum mass resolution.

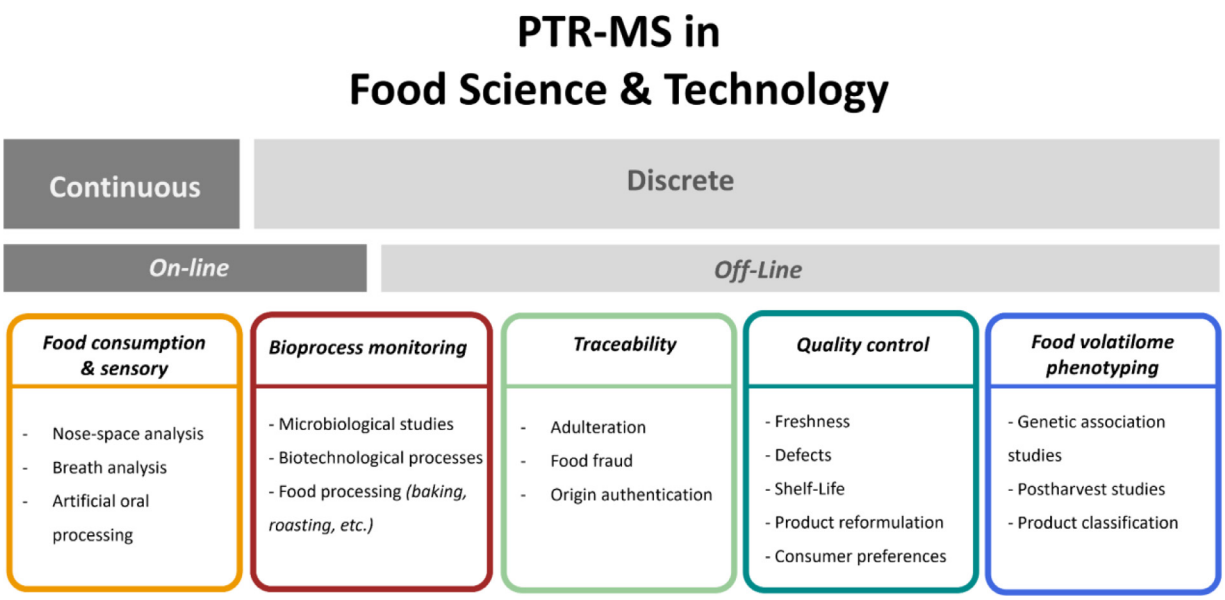

Fig. 1. Classification of different PTR-MS analytical approaches and their application in the FST field.

Further remarkable advantages of PTR-MS include the possibility to obtain quantitative data avoiding to perform an external calibration with analytical standards [19], the capability to achieve low detection limits and the broad dynamic range.

Using PTR-MS, the VOCs can be analysed without the need for a sample enrichment step, however, different headspace sampling strategies can be applied according to the application field and the aim of the measurements. It should be taken into consideration that PTR-MS analysis is suitable only for highly volatile and volatile compounds, which are present in the gas phase introduced into the instrument (e.g. from the headspace of a food).

Fig. 1 provides a classification of the different sampling and sample introduction approaches and examples of applications with a focus on the food science and technology (FST) field.

Direct injection allows continuous measurements, and thus on-line analysis of the volatile profile evolution over the time scale, making possible the real-time monitoring of processes and the combination with sensory methods.

Alternatively, the equipment of PTR-MS with a tri-axis multipurpose autosampler (hereafter AS) combines highly sensitive and time-resolved VOCs detection with automated and controlled sampling conditions, which expands the throughput of discrete measurements [20]. Small aliquots of the sample matrix (0.5–1 g) are placed into headspace glass vials (20 ml). The AS allows for precise control of flows and temperatures during the sampling phase but also the possibility to load and keep up to more than hundred samples in controlled temperature and time conditions throughout the entire analytical sequence. Moreover, different headspace sampling options such as static (SHS) and dynamic headspace (DHS) can be exploited.

Discrete measurements apply to all the applications entailing off-line analysis and large samplings. However, the AS-PTR-MS configuration can be used also for process monitoring by repeatedly analysing the headspace of the samples over time.

A limiting factor in the spread of PTR-MS technology in the agri-food sector is the cost of the instrumentation. However, there are situations where the investment in PTR-MS instruments or, more generally, in direct injection mass spectrometry (DIMS) is justified. In the case of nose-space analysis, for instance, only DIMS provide the required sensitivity and time resolution. Other examples are applications entailing a large number of samples, like in the case of phenotyping programs or the monitoring of key processes in large industrial plants.

1.2. Is PTR-MS a green analytical tool?

The 12 GAC principles are reported in Table 1; for each of them, the corresponding PTR-MS green features are described. Although this review focuses on PTR-MS, it should be considered that most green traits described for PTR-MS are shared by other DIMS techniques (e.g. SIFT-MS and APCI-MS).

As mentioned above, most of the PTR-MS features well-align with the GAC requirements. Possible weaknesses are related to the complexity and weight of the instruments, which make them difficult to be miniaturised and made handheld; and the use of disposable septa in the case of headspace vial measurements. This weakness is, however, common to most headspace analyses.

In regard to PTR-MS strengths, the possibility of using air or nitrogen as gases is favourable since they are both obtainable with generators. The use of compressed gases is not specifically evaluated in the available assessment metrics, however, the possibility to avoid the use of gas cylinders offers some advantages from a green perspective. It reduces both the hazards and the environmental impact associated with compressed gases handling and production (e.g. cleaning, filling and transportation of cylinders). Furthermore, Raccary and co-authors, in their LCA approach [4], highlighted the limitations of using helium as carrier gas for GC due to its non-renewable nature and depletion situation.

The aim of this review is to highlight the potentialities of PTR-MS as a green alternative technique for food volatilome analysis, therefore, we compared it with headspace solid phase microextraction (HS-SPME) coupled to GC–MS which is the reference analytical approach for food VOCs characterization. This has been carried out with the AGREE metric approach, an environmental impact assessment tool proposed by Pena-Pereira, Wojnowski and Tobiszewski in 2020 [24].

The calculation is based on the 12 GAC principles and provides the assessment of all aspects defining the environmental impact of the analytical procedure. The assessment is not general for the analytical technique, but specific for a selected application. Our case study is the characterization of Mascarpone cheese aroma by HS-SPME-GC–MS and DHS-PTR-ToF-MS [25], which is an example of the two techniques applied in complementarity to the same matrix. The evaluation is not biased by the contribution of other application-specific aspects impacting on the AGREE score. During the calculation, equal weights of the scores were selected attributing to all the 12 GAC principles equal importance.

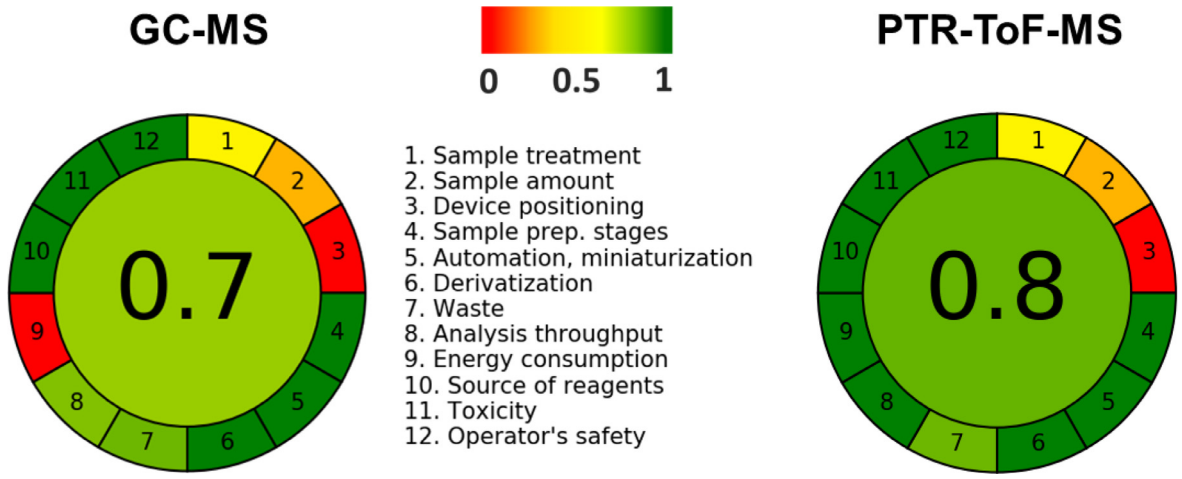

Fig. 2. AGREE software output for Mascarpone cheese aroma characterisation by GC–MS and PTR-ToF-MS.

The AS was not included in the assessment since its contribution to the total energy consumption can be considered equal for both the analytical techniques.

Fig. 2 reports the graphical output from the AGREE software (https://mostwiedzy.pl/wojciech-wojnowski,174235-1/AGREE) for the Mascarpone cheese case study. The final scores, 0.7 for GC–MS and 0.8 for PTR-ToF-MS on a scale from 0 to 1, are both significantly high values indicating a remarkable degree of greenness.

The 10% greener score obtained for PTR-ToF-MS is due to higher values related to principles 8 (analysis throughput) and 9 (energy consumption). These two values are closely related to each other: the high analysis throughput of PTR-ToF-MS (5 min/sample) remarkably lowers the energy consumption per sample.

The source of the consumed gases (helium for GC–MS, air or nitrogen for PTR-ToF-MS) is not captured within this assessment framework, however, as mentioned before, it contributes to lower the environmental impact of PTR-ToF-MS.

The complementarity approach used in this case study (and in many others e.g. [26,27]) is one of the possible ways to apply PTR-MS for food volatilome studies. It provides comprehensive results in terms of volatilome characterisation due to the combination of accurate VOC identification, performed with GC–MS on a few representative samples, and the high throughput of PTR-ToF-MS. This complementarity approach entails also an overall lower environmental impact as proposed by Majchrzak et al. [28].

2. Application of PTR-MS in FST

VOCs are constantly released by food products and they are key drivers of food perceived quality both before (odour), during (flavour and aroma) and after (aftertaste, after-flavour) food consumption. Moreover, they are produced and released in most stages of the food-production chain “from farm to fork” making them a crucial subject when dealing with traceability along the supply chain. VOCs also have a huge impact on the consumer sensory experience and they can be detected in a non-invasive way [29]. Finally, measuring VOCs released during consumption in the nose is the most direct way to investigate the mechanisms underlying flavour perception [30].

The first papers about PTR-MS technology and its applications were published in 1995. Since that time, according to Scopus [31], 1444 manuscripts have been published (research keywords: “PTR-MS or PTR-ToF-MS or SRI-ToF-MS” within Article title, Abstract, and Keyword on 14/04/2022). Based on article title, abstract and keywords, 362 manuscripts were assigned into the topic “FST” (25% of all manuscripts and 25% of the mean value of manuscripts per year). These articles were further subdivided into six areas: “Biological monitoring”, “Quality control”, “Traceability”, “Food consumption and sensory”, “Food volatilome phenotyping” and “Other”. All paper references are reported in the **supplementary Table 1**.

In Fig. 3, the bar plot shows the total number of manuscripts by year related to the general PTR-MS topic in grey and to food science and technology in specific in black. The doughnut plot shows the number of publications for each area. The bar related to 2022 is marked with “*” since the research was performed in April of 2022.

Fig. 1 aggregates the type of measurements performed in FST by PTR-MS and the main examples of application fields for each area. PTR-MS can be used for continuous measurements when rapid and continuous sampling is needed, e.g. nose-space analysis, breath analysis, artificial oral processing and other studies of food consumption and sensory. The discrete analysis is used in applications where measurements could be single or repeated with different frequencies according to the needs of the experiments. PTR-MS technology gives, therefore, the opportunity to perform on-line and off-line measurements. For the experiments of food consumption and sensory and studies of bioprocess monitoring, especially in food processing (baking, roasting, etc.) the measurements should be performed by on-line sampling directly from a place where the process takes place. Other fields like traceability, food quality, food volatilome phenotyping, and, in part, bioprocess monitoring need to measure each sample once and characterise them in a fast way. Sometimes the repetition of the measurements is needed for the experimental design as in postharvest studies.

A Sankey diagram (Fig. 4) shows the connection of FST fields and food matrices. This type of graph is used for the visualisation of flows between nodes. The thickness of the connections between nodes depends on the flow values between them. In our case, the nodes on the left side are areas of FST, and the ones on the right side are the different food matrices which were studied with PTR-MS. The flow is related to the number of papers published in a certain area and food matrix. For better visualisation, only food matrices with at least three papers are present in the diagram. Some works were merged into two common matrices: “general” and “food science”. The papers classified as “general food matrix” are mainly describing cross-area topics, which is why it is widely connected to the area “Other”. The term “food science” was used when some model food (gel, capsules, etc.) or chemical reactions and processes (oxidation, Maillard reactions, etc.) were studied. This explains the connections of “food science” to the areas of online measurements such as “bioprocess monitoring” and “food consumption and sensory”.

The application areas reported in the following paragraphs (i. Food consumption and sensory; ii. Bioprocess monitoring; iii. Traceability; iv. Quality control; v. High-throughput food volatilome phenotyping) are characterised by different degrees of greenness. For some of these

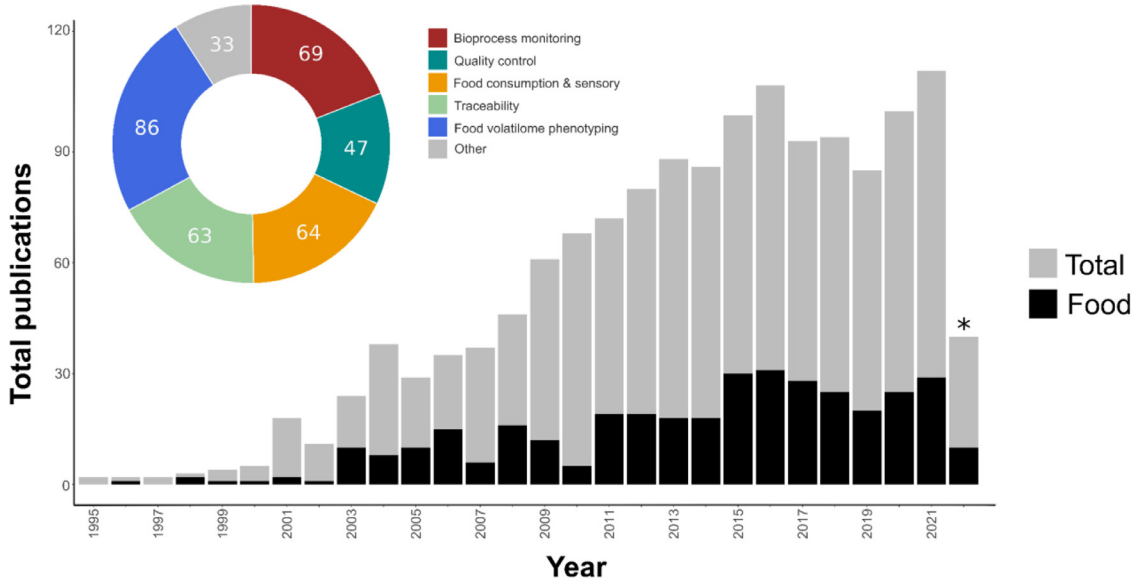

Fig. 3. Total number of manuscripts (grey bars) and manuscripts related to FST topic (black bars). The bar of 2022 is marked with "*" since the Scopus search was performed during 2022. On the left top side, the doughnut plot shows the number of papers published in each of six areas of FST topic.

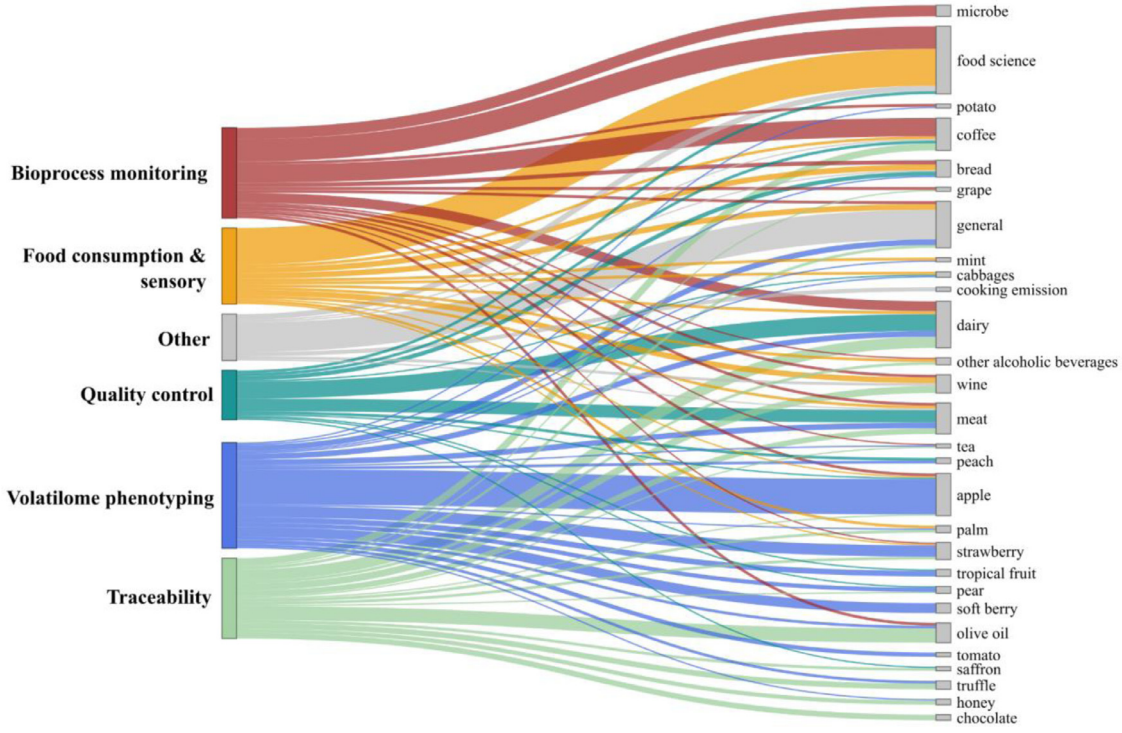

Fig. 4. Sankey diagram of the connection between the fields of FST and the food matrices studied with PTR-MS.

examples, the environmental impact is complex to quantify because of the peculiarity of the measurement methods. This is the case with food consumption studies and on-line process monitoring. However, together with non-destructive headspace analysis, these are the applications where the intrinsically green potential of PTR-MS is more evident since they are based on-line and non-invasive measurements.

Off-line analyses, instead, usually require a few steps of sample processing before the headspace sampling (e.g. nitrogen freezing, grinding, aliquoting) and the green benefits of using PTR-MS are based on the analysis throughput, the low energy consumption per sample and the renewability of gases used.

2.1. Food consumption and sensory evaluation

The study of the fundamental principles involved in aroma release during consumption and perception of foods is of major relevance, as the release of flavour components has proven to be key factor for determining how pleasant and how long-lasting a flavour will be perceived [32], which ultimately will affect the acceptability of the food [33,34]. However, relating flavour compounds to perception is not straightforward because it is not completely understood how cross-modal sensory interactions, such as aroma-taste, flavour-texture and trigeminal sensations with aroma and taste, affect perception [35].

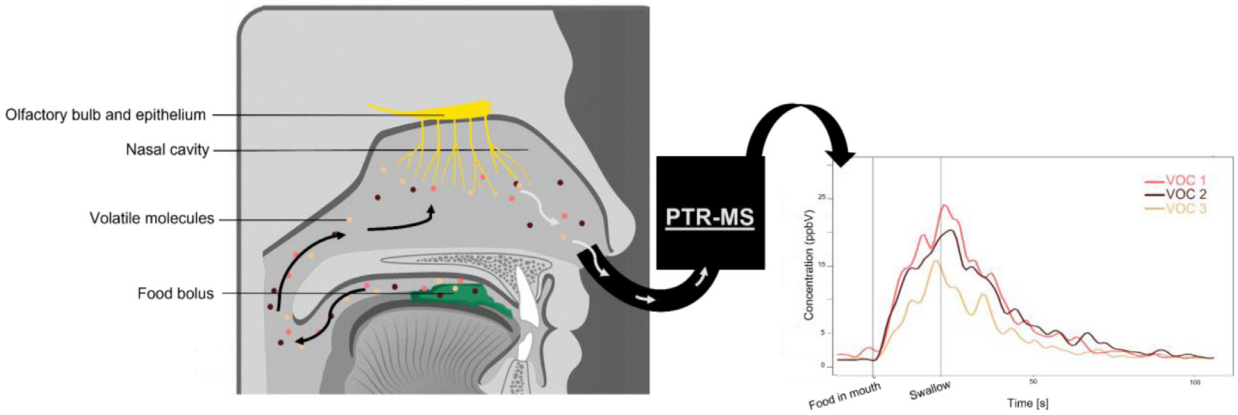

Fig. 5. From left to right, display of retronasal olfaction during food consumption and real-time quantification of volatiles coming from the nose via PTR-MS.

Perception of flavour is a dynamic process [36]. During food consumption, the concentration of the aromatic molecules that are delivered into the nasal cavity via the nasopharynx, and interact with the olfactory receptors (retronasal pathway) [37], varies with time as flavour components are being released progressively from the food. The release kinetics depends on the food matrix itself but also on in-mouth physiological mechanisms such as salivation and mastication behaviour that lead to bolus formation, mechanisms for which inter-individual variations are important [38,39].

The combination of valid and relevant instrumental tools with dynamic sensory methods has allowed for a more comprehensive analysis of human perception. However, using human subjects to evaluate sensory properties of the food, having a non-invasive green analytical tool that has the desirable features in terms of operating speed, ease-of-use, and minimal or no sample preparation, is of extreme importance.

Because of its high resolution, real-time monitoring, and minimum sample pre-treatment, PTR-MS, in particular when equipped with a ToF mass analyser (PTR-ToF-MS), has been used for monitoring VOCs in nasal breath air during the in vivo mastication [29], and in the food headspace during in vitro mastication [40–44], which has allowed a more realistic measurement of dynamic VOCs release during food consumption (Fig. 5).

Numerous research articles during the past two decades not only have demonstrated the many novel applications and robustness of this innovative technology but also have highlighted the need for multidisciplinary approaches to have a high ecological validity of the food on the release, evolution, and fading of aroma compounds that are being perceived during and after mastication.

In the early 2000′s, the focus of diverse studies was set on model foods such as custards, gels or egg foams [45–48], as they proved to be a useful tool to study aroma release and therefore were a key step in understanding, for example, the role of the product (e.g. composition and structure). There was also interest in examining phenomena taking place in the nasal cavity. In a novel study, the PTR-MS sampling inlet tube was placed inside the nose under endoscopic direction and positioned to sample at one of four positions: the nostril, the middle turbinate, the olfactory cleft, and the nasopharynx. Flavoured custards of different viscosity were then administered orally and, the concentrations and latency of response of selected aroma compounds were explored in relation to the sampling location in the nose [49]. This study yielded several interesting findings, namely that the duration and degree of in vivo release of aromas varied between the compounds and that their distributions in the nasal cavity exhibited different latencies and maxima according to the nasal anatomy, as well as other insights in relation to flavour delivery and food matrix consistency.

Over the last years, several studies have investigated the relationship between in vivo flavour compounds release and sensory perception during food consumption by coupling in vivo nose-space analysis by PTR-MS with temporal sensory methods (e.g. Time-Intensity, Temporal dominance of sensations, and more recently, Temporal Check-All-That-Apply) for numerous foods such as candies [50,51], coffee [52], cereal bars [53], wine [54–56], white bread [57], and dark chocolates [58]. Furthermore, the effect of interindividual differences like salivary composition, [35], oral processing parameters [59], inter-individual retronasal aroma release [60,61], ethnicity, gender and physiological parameters [62–64], as well as aroma persistence in the nasal and oral cavities [65] have been studied.

Although it is undeniable the great progress done regarding aroma release and perception, most studies involve single or model foods that do not necessarily represent the real eating context. It is only in the last few years that the focus has slowly shifted in studying food matrices made up of different components and contrasting textures, which adds a degree of complexity [62,63], as the characteristic of one component will influence the flavour release and perception of the other components [66,67].

Furthermore, during oral processing of food, VOCs are released from the matrix and then transported to mouth and nose receptors. This release of VOCs varies according to different oral parameters, which are highly dependant on individual oral physiologies and may influence human aroma perception during food consumption. To overcome this high degree of variability, chewing devices have been designed to simulate in vitro the oral processing of food [43]. The main advantage of these models, connected in-line with PTR-MS, is the ability to isolate a single parameter (such as the frequency and force of biting, or the salivary flow rate) and study its influence on food breakdown and VOC release [40–42,44]. In vitro and in vivo analysis via PTR-MS have proven to be a green analytical technology that has yet much to contribute to food science. Foremost, its full potential to explore sensory perception in relation to flavour release during consumption has yet to be reached. This will help in the design of food products that meet the preferences of consumers while at the same time taking into account physiological characteristics of individuals (e.g. young or older people, or people with clinical pathologies such as dysphasia) [68].

2.2. *Bioprocess monitoring*

In the context of food technologies, when a biological component drives a transformation, the phenomenon falls under the umbrella of bioprocesses. The biological agent responsible for the desired modulations can be a microorganism (fermentation/bioconversion) or an enzyme (enzymatic treatment). Bioprocesses represent a cornerstone for developing sustainable food systems [69]. A leading example, in this sense, is fermentation, which is the transformation of food that exploit the metabolism of eukaryotic (yeast and filamentous fungi) and prokaryotic (bacteria) microbes to modify the global quality of the final products radically [69]. ‘Fermentation’ summarises a heterogeneous family

of bioprocesses exploited for millennia, improving food shelf life, sensory, nutritional and functional quality, as well as food safety standards, through low energy inputs [69]. Yeasts and lactic bacteria are the principal microbes of pro-technological interest in the food industry. They are responsible, respectively, for alcoholic and lactic fermentation in a wide diversity of traditional and innovative fermented products.

As introduced in the previous sections, PTR-MS provides a green analytical solution of particular interest for high-sensitivity, rapid and non-invasive monitoring in the dynamic and low-impact field of bio-based innovations tailored for the food sector [20]. Indeed, with its versatile potential in the study of VOCs, PTR-MS allows on-line monitoring and massive screening of microbial volatilome with a special focus on a class of aroma-active molecules. Thus PTR-MS was applied in various studies of microorganisms, matrices and their interconnections [20,70]. PTR-based VOCs monitoring has been used to study both eukaryotic (*Saccharomyces cerevisiae, Metschnikowia pulcherrima, Torulaspora delbrueckii*, [71–73]) and prokaryotic (e.g. *Lactiplantibacillus plantarum* [74]; *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus*, [75]; *Oenococcus oeni*, [76]) resources but also complex consortia (e.g. kefir grains, composed of both yeasts and bacteria, [74]; spontaneous cocoa fermentation, [77]). Considering the diversity of matrices, fermentations are distinguished according to the raw material subjected to fermentation, mainly encompassing animal (fermented milk products; fermented and preserved meat products; fermented, dried and smoked fish products) and plant-based (fermented cereals, fermented vegetables and bamboo shoots, fermented legumes, fermented roots/tubers, miscellaneous fermented products, and alcoholic beverages) categories [69]. From this point of view, PTR-MS found application in studying dairy (e.g. kefir [74]; yoghurt [75]; cheese [70]), bakery (e.g. bread [78]; gluten-free breads [79,80]), cereal-based beverages (e.g. kefir-like products [74]), miscellaneous fermented products (e.g. cocoa bean [77]), and alcoholic beverages (e.g. beer [72]; wine [73,76]). A selected number of recent publications can well exemplify the versatility of PTR-MS in the field of bioprocess monitoring, targeting microbial-based applications.

Khomenko et al. [71] proved the potential of AS-PTR-ToF-MS and tailored data analysis for the on-line discrete analysis of yeast volatilome for fundamental and applied in vitro studies. The authors monitored the growth of six *S. cerevisiae* strains on a cultural medium for 11 days (DHS sampling every 4 h). 70 out of more than 300 mass peaks were selected for further analysis, tentatively identified and subjected to univariate and multivariate statistical analysis. The findings highlighted the volatilome evolution and strain-dependant patterns, paving the way for high-throughput microbial phenotyping (if possible with the complementary identification by GC–MS) to select potential biomarkers for process control and confirm existing metabolic pathways and discover new ones.

Richter *et al.* [72] used AS-PTR-ToF-MS for monitoring of VOCs associated with three diverse hop cultivars during the alcoholic fermentation of beer inoculated with two different commercial *S. cerevisiae* strains. The findings demonstrated the successful discrimination amongst hops and yeast biotypes, underlying the evolution of VOCs (e.g. branched-chain esters) characterising the different specific hop-yeast combinations, and depicted three behaviours that described the release patterns of VOCs during experimental brewings [72].

Berbegal et al. [73] delve into studying the impact of different combinations of pro-technological microbes co-inoculated as starter cultures to drive food fermentations. Commercial grape juice and fresh grape must were used as tested matrices for the inoculation of pure cultures from four different yeast strains (two *S. cerevisiae* and two non-*Saccharomyces* strains). All possible binary and ternary combinations were tested, including the simultaneous inoculation of all four yeasts [73]. The principal component analysis in Fig. 6 provided a visual representation of the distribution of variances of the PTR-ToF-MS results for the tested experimental modes. The results demonstrated the presence of distinguishable trends based on different substrates, single strains and their binary and ternary combination as starter cultures for alcoholic fermentation in wines [73].

PTR-ToF-MS has also been proposed for the high-throughput volatilome analysis of filamentous fungi [81], leading the way to new studies connected to emerging biotechnological applications of food interest and to the possible rapid detection of spoilage moulds in edible samples. Intriguingly, the focus on spoilage phenomena allows us to reflect on the connection between shelf life and bioprocesses of food interest. The deterioration of perishable foods during storage is intimately connected with the growth of undesired microbes, a field of investigation that found valuable applications for PTR-based analytical strategies (e.g. [82]).

2.3. Traceability

The Codex Alimentarius Commission described the concept of 'traceability' as "the ability to follow the movement of a food through specified stage(s) of production, processing and distribution". Product tracing is a strategic asset in modern food systems given that the ability to 'trace' along the food chains represents one of the keystones to furnishing attested product information, warranting correct risk management, and assuring product authenticity. Because of its crucial role, the Food and Agriculture Organization (FAO) recognizes that traceability responds to a plethora of business needs, embracing: "product recalls/market withdrawals, regulatory compliance, market access, public health trace-backs, food safety and quality assurance, and process and order management".

Adequate analytical tools, such as PTR-MS, are required both for ensuring quality foods and for tracing products with peculiar qualitative specifications. The volatile fraction associated with an edible matrix is closely related to relevant and intimately connected aspects such as food quality, traceability and authenticity [83]. The qualitative and quantitative variability of the food volatilome is influenced by various factors, such as the variety, the geographical origin, the treatments to which it is subjected, transportation and storage [83,84]). The main advantage of volatilomics for traceability/authenticity application is linked to the amount of data generated. However, the reliability of these "big data" highly depends on all aspects of the analytical protocol, such as the sample preparation (including any extraction process), instrumentation and analytical conditions, and, not least, data elaboration/management [83,84].

From this point of view, PTR-MS offers an environmentally friendly monitoring tool for authenticity/traceability aims, considering its non-destructive character, the slight sample preparation, and the low environmental impact of the technique/ method [20]. PTR-MS finds application in the food sector for several purposes dealing with traceability (Table 2): i) to define the origin of the raw material (e.g. [76,77,85,86]), ii) to demonstrate the presence/absence of a given treatment/processing (e.g. [25,87]), iii) to discriminate amongst different production systems/seasonal products (e.g. [88,89]), and iv) for 'farm to fork' tracing approaches for a given ingredient (e.g. [90]).

Foods related to the Columbian exchange, such as coffee and cocoa, are useful case studies to deepen the potential of PTR-MS. Yener *et al.* 2015 [85] exploited the AS-PTR-ToF-MS for the rapid and automated analysis of brew and powder coffee samples of seven different geographical origins (Brazil, Colombia, Costa Rica, Ethiopia, Guatemala, and India). This approach allowed the evaluation of one sample every 5 min and application of SRI with H_3O^+, NO^+ and O_2^+ primary ions. Classification models built on a dataset of each precursor ion separately and their data fusion showed the great effect of geographical origin on the volatile profile of coffee. In the case of cocoa [90], experimental evidence demonstrated the potential of PTR-MS in tracing from raw material to finished product. In this scientific work three different techniques (i) PTR-MS, (ii) inductively coupled plasma-MS, ICP-MS, (iii) isotope ratio-MS, IR-MS) were compared for the capability to distinguish the persistent chemical signatures of geographical origin from cocoa to

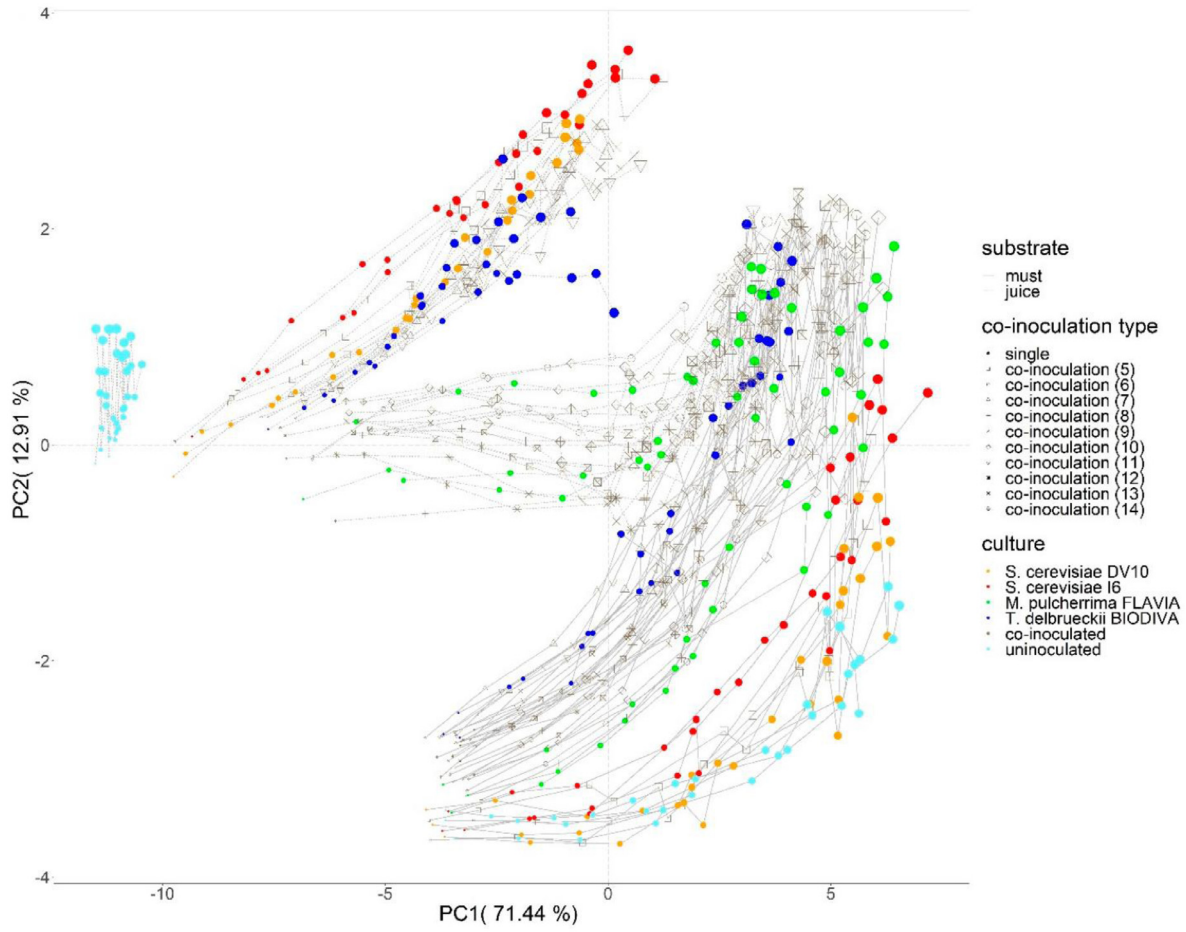

Fig. 6. Data logarithmically transformed and centred on the score plot of the principal component analysis for VOCs time-dependant changes during the three days of alcoholic fermentation (AF). The bioprocess was promoted in both commercial grape juice and fresh grape must inoculated with different single yeast cultures and diverse combinations of the four tested yeast strains. The colours indicated the different yeast inoculations and uninoculated samples. The point size grew with the evolution of AF. Figure reproduced with permission from Berbegal *et al.* [73]. Copyright 2019 MDPI.

chocolate. PTR-MS has been proved to be the most suitable analytical solution to maintain the chemical information capable of tracing the product along the supply chain (from this point of view, deserved particular attention the VOCs acetic acid; benzene; pyridine; 2-phenylethanol; maltol). VOCs appear to be establishing the most robust link between cocoa beans and corresponding chocolates. Inversely, the elemental and isotopic characterisations have been found connected to the amount of cocoa and other ingredients in the finished product (quality control) of [90]. New works published in 2022 testify to the constant interest in the applications of the PTR-MS in this field of agri-food research. In fact, PTR-ToF-MS has recently found application to distinguish extra virgin olive oils (EVOO) from non-EVOO [91], white tea leaves with diverse marked ages [92], and to discern lemon from lime juice [93], helping to strengthen GAC strategies to assure traceability and for fraud prevention.

2.4. Quality control

Food quality is a key determinant of consumer choices and food intake. Establishing and maintaining food products' sensory quality during the product's shelf life is a critical task since it is the basis for gaining consumer confidence and ensuring future market success [94]. Sensory techniques have become an essential part of industrial quality control (QC) programs to guarantee competitiveness by assessing the factors contributing to perceived quality. However, new technological approaches are needed to support sensory methods in agroindustry due to their intrinsic limitations. The ideal situation would be to establish correlations between sensory response and instrumental measures since instrumental tests have a variety of advantages such as precision, accuracy, reproducibility and the possibility to perform continued operation without restrictions on number of samples [94]. In this way, instrumental measures could support sensory testing, especially when a rapid turnaround is needed or for products which are fatiguing to the senses, repetitive or involve health risks evaluations [95]. PTR-MS VOCs analysis through rapid direct injection with limited sample preparation and usage of solvent, seems a promising green tool for monitoring industrial processes and supporting sensory QC in agroindustry.

In Fig. 7 we suggest a two-phases conceptual framework for implementing this technique in industrial quality control. In phase I, a predictive model based on PTR-MS VOCs fingerprints is built and trained to predict sensory classification. By training the model with a sufficient number of samples to cover industrial quality variability, it is reasonable to expect a robust model with a significant predictive power. Once the model is validated (Fig. 7, Phase II), PTR-MS volatilome analysis can be used to test a higher number of samples than on a classic QC approach, thanks to the analysis rapidity which could be considered as more sustainable. Only samples discarded by this fully automated procedure will be tested through industrial sensory evaluation and/or other instrumental methods to confirm the defected quality.

PTR-MS headspace analysis has been increasingly used for quality control purposes in agroindustry. Two of the main technique applications in the quality control domain are: (i) to monitor products' fresh-

Table 2
A list of recent studies (2015–2020) that applied PTR-MS for VOCs monitoring to determine attributes of interest for product traceability.

Traceability goal/purpose	Food matrix	Attribute that PTR-MS contributes to discriminate	Instrumental configuration	Ref.
Origin of raw materials	Coffee	Discrimination of coffee from different origins by direct injection headspace associated with coffee brew and powder	PTR-ToF-MS	[85]
	Wine	Discrimination of wines from different geographical origins analysing VOCs in the wine headspaces	PTR-ToF-MS	[76]
	Meat	Discrimination of regionally unique South African lamb exploring the VOCs composition of the meat	PTR-Q-MS	[86]
	Cocoa beans	Studying the diverse quali-quantitative VOCs abundance associated with fermented cocoa beans from different origins	PTR-QiToF-MS	[77]
Presence/absence of a given treatment/processing	Cheese	Robust detection methodology to distinguish cheeses made from raw milk and from heat-treated milk	PTR-Q-MS	[87]
	Cheese	Preliminary information on the differentiation of the aroma of different brands and product types (e.g. without lactose and with different shelf-life)	PTR-ToF-MS	[25]
Production system/seasonal products	Milk	Tracing the impact of different production systems (organic, conventional, pasture) and seasonal products (winter, summer) on the VOCs composition of milk	PTR-Q-MS PTR-ToF-MS	[88]
	Cheese	VOCs profiling for the authentication and characterisation of different dairy systems (traditional, modern) in ripened cheese production	PTR-ToF-MS	[89]
Tracing of an ingredient "Farm to fork" strategy	Cocoa beans	Defining the potential of VOCs in tracing cocoa beans from farm to chocolates	PTR-Q-MS	[90]

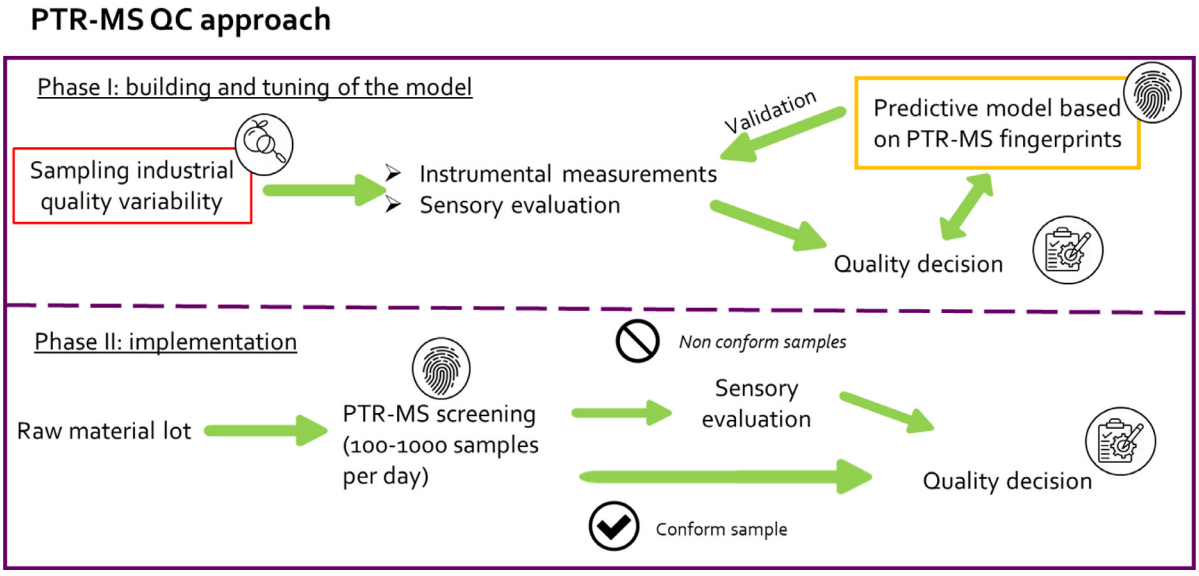

Fig. 7. Two-phase conceptual framework for PTR-MS applications to industrial quality control.

ness and quality changes during shelf life and (ii) to perform and predict quality classification estimated by sensory tests or other instrumental methods.

In relation to volatilome changes during product's shelf life, in the last years, different researches focused on meat products. Wojnowski and co-workers investigated chicken and turkey meat samples freshness by comparing classic microbial analysis with rapid PTR-MS fingerprinting during cold storage (4 °C over a period of 5 days) [82]. The authors indicated that this non-invasive assessment, coupled with supervised pattern recognition techniques, may be used to supplement the traditional meat freshness evaluation methods in facilities where meat is produced and distributed. In a similar study, PTR-MS and SPME-GC–MS were used for rapid volatile profiling of vacuum packaged chilled beef during cold storage (−1 °C) for about 140 days [96]. Together with VOCs, total lactic acid bacteria, pH, colour, non-volatiles (LC-MS) and sensorial changes were monitored for both raw and grilled steaks. The study indicates that some VOCs detected by PTR-MS (e.g. ethanol, acetaldehyde and acetone) can be used as non-microbiological biomarkers for quality control.

Monitoring changes of samples volatilome at different shelf-life conditions have also been applied for dairy products. A recent study investigated the effect of shelf life and packaging on anhydrous milk fat

(AMF) volatilome by applying PTR-ToF-MS headspace analysis [97]. AMF is an important industrial raw material containing at least 99.8% dairy fat. Three production batches were stored at 4 °C for 9 months in two different types of packaging: cardboard and bag-in-box. Significant differences for some key butter aroma compounds, including 2-pentanone, 2-heptanone, 2/3-methylbutanal, acetoin, and butanoic acid indicated that the bag in box packaging had a better performance than cardboard packaging by offering a better protection to lipid oxidation. PTR-MS analysis has also been used to determine the relationship between changes in VOCs composition, sensory evaluation and total microbial number of pasteurised milk during refrigerated storage (4.5 °C for up to 26 days) [98,99]. Changes in both VOC profile and sensory characteristics were observed during the shelf life tests. These changes are related not only to the number of microorganisms but also to the spoilage potential of specific microorganisms during the post-pasteurization contamination. Similar research was performed also for lactose free milk due to the growing demand for food products for lactose intolerant people. Bottiroli and co-workers [100] used PTR-ToF-MS to explore changes in volatile profile occurring during storage for 150 days at 20 °C of ultra-high-temperature lactose-free milk produced with different lactases preparations. While no significant differences were found between the commercial lactases in terms of aroma compounds (with the exception of benzaldehyde), significant changes in methyl ketones like 2-pentanone and 2-heptanone were observed during shelf life.

Along with applications during shelf life, PTR-MS has been used to predict the quality class of different foods, including spices [101], chocolate [102], milk [103], and AMF [104]. In all the cases, PTR-MS volatile fingerprints were used to predict the quality classes obtained from sensory and standard quality measurements. The technique showed promising results in raw hazelnuts by identifying different classes of visual defects assigned by visual inspection from an industrial panel [105]. Noncompliant hazelnuts showed higher concentrations for the majority of the detected VOCs, including some hazelnut key odorants such as 5-methyl-4-heptanone, 5-propyldihydro-2(3H)-furanone, octanal, 2,4-nonadienal and hexanal. The technique was also able to discriminate samples containing 20% of grounded hazelnuts with unacceptable quality from samples made with only good quality grounded hazelnuts. Unsupervised clustering provided a classification rate higher than 90% for all the VOCs data obtained with the SRI system from 44 hazelnuts samples classified according to industrial evaluation. In this case the SRI system was applied to check if $NO^+$and $O_2{}^+$ionisation can lead to a better classification prediction.

All together, the results demonstrated the viability of PTR-MS as a rapid and highly sensitive tool for monitoring aroma changes during shelf life and predicting quality of different food products.

2.5. *High-throughput food volatilome phenotyping*

Several VOCs have been demonstrated to influence consumers' overall liking [106], suggesting that these metabolites are key targets to improve the flavor perception of fruit and vegetables. The end of the "flavour life", mainly due to changes in aroma compound concentration and off-flavours development, often precedes the end of shelf life as determined by visual and textural modifications. Thus, VOCs should be considered as a central trait to determine the "from farm to fork" strategies (Fig. 8). However, the so-called "phenotyping bottleneck", caused by the absence of high-throughput and non-invasive methodologies, impedes an effective evaluation and prediction of fruit and vegetables VOCs [107]. The analytical limitations of VOC analysis by conventional GC techniques, mainly time-consuming sample preparation and consequently the limitations of running exhaustive and complex experimental designs with a lot of samples, limits the practical research of this field. PTR-MS application has recently been demonstrated as a powerful phenotyping tool for destructive and non-destructive assessment of food volatilome in both genetic and quality-related studies. PTR-MS was successfully applied to discriminate the aroma variability in several horticultural crops such as tomato [41], apple [108], blueberry [109], raspberry [46], strawberry [110], almond [111], pepper [112], melon [113], and peach [114].

Although VOC profiles of many fruit and vegetables species have been characterised, less is known about the genetic basis underlying their variation amongst genotypes, which hinders their modification in breeding programs. Thus, high priority should be given to replace poor flavour cultivars with favourable ones, exploiting the variability already available in nature. VOC phenotyping is currently a limiting step in breeding programs, due to high costs, complex and time-consuming analytical techniques. Another limitation also raised by the elevated and difficult to be controlled interaction between fruit genetics and environmental effects. While there is substantial flavour variation within fruit species, most plant breeding programs have historically neglected it, given its intrinsic complexity and costs to phenotype [106]. As a consequence, the drop-off in flavour quality has become one of the major causes of consumer dissatisfaction. To correct this inconsistency and incorporate flavour into breeding program routines, it is necessary to identify the sources of flavour variability, understand its genetic architecture, and define cost-effective selection methods such as the application of molecular and/or biochemical markers.

The study of the link between fruit and vegetables genotypes and aroma profile assessed by PTR-MS has therefore attracted increasing attention, especially for genetic association studies aimed to identify QTLs (quantitative trait loci) related to the biosynthetic pathways of VOCs [108,111,115,116]. Genetic association studies require a detailed characterisation of the aroma profile of a wide number of accessions; thus, fast techniques such as PTR-MS are particularly suited for this application. Combining these research approaches, applied on a large germplasm collection and on segregating populations, allow a deeper investigation and step forward in the comprehension of the genetic and physiological aspects controlling flavours and off-flavours production. Recently, the PTR-ToF-MS volatilome phenotyping was also successfully applied for genome-wide association studies (GWAS) of dairy products [117].

The comprehensive understanding of food VOC composition may become more efficient by applying specific and synergic analytical approaches, based on PTR-MS technology, suitable to address the aroma complexity in different circumstances: i) high-throughput destructive headspace analysis; ii) non-destructive headspace analysis (Fig. 8).

The high biological variability between samples is one of the major risks that should be considered during the design of an experiment focused on VOC assessment. Therefore, a high number of biological replicates is fundamental for a statistically correct experimental design. The possibility of coupling a PTR-ToF-MS instrument with an AS allowed for the analysis of more than 300 samples per day with high reproducibility and reduced laboratory labour. However, the limiting factor of this methodology is the restricted volume of the vials compatible with the AS (usually 20 mL), that does not allow the headspace analysis of voluminous samples (i.e. most part of fruit and vegetables). This restriction is exceeded by using powdered frozen tissue of the fruit mixed with an antioxidant solution (e.g. a mixture of ascorbic acid, citric acid and sodium chloride) [109].

The non-destructive headspace VOC assessment by PTR-MS provides a potential non-invasive tool appliable in physiological studies related with fruit ripening and host-parasite interactions and for discriminating fruit and vegetables, not only based on genetic differences, but also on origin and maturity stages [118,119]. A great task in postharvest management is the monitoring and prediction of biotic and abiotic disorders that may reduce product marketability. The non-destructive application of PTR-ToF-MS allows to detect putative VOC markers, produced before any visible disorder symptoms at very low concentrations (ppb_v). For instance, these VOCs can be related with the product ripening stage (e.g. ethylene [26,120]), the senescence level (e.g. ethanol, methanol, acetaldehyde or acetone [109,121]), or with some specific abiotic and

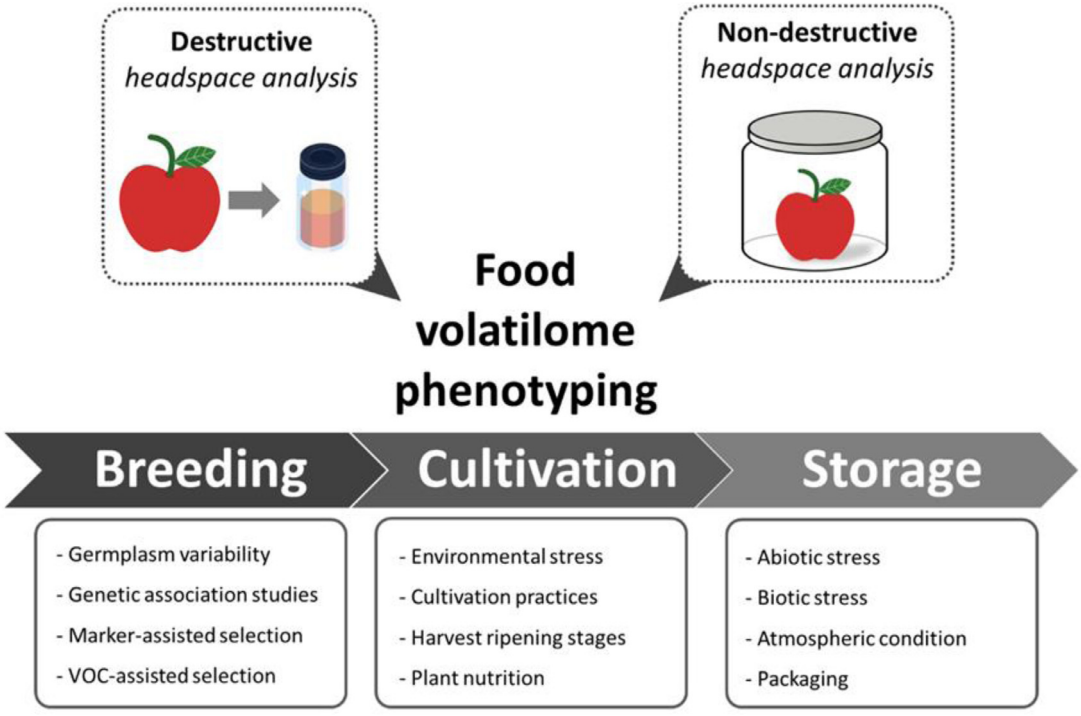

Fig. 8. Possible applications of PTR-MS technology for the food volatilome phenotyping to determine the "from farm to fork" strategies.

	Breeding	Cultivation	Storage	Transformation	Consumer
Destructive analysis	- Fruit chemiodiversity (1) - Germplasm (1) - GWAS (1) - Segregating population (1)	- Fruit ripening (1) - Cultivation practices (1)	- Abiotic stress (5)	- Fresh juice (1)	- Sensory analysis (1)
Non-Destructive analysis	- Segregating population (5) - Fruit chemiodiversity (1) - Clones identification (2)	- Fruit ripening (1) - Effect of altitude (1) - Effect of crop load (1)	- Abiotic stress (1) - Biotic stress (1) - Ethylene control (2) - Controlled atmosphere (1) - Fruit conservation (1)		
Nose-space analysis	- Fruit chemiodiversity (2)				
Artificial oral processing	- GWAS (1)		- Fruit conservation (1)		

Fig. 9. Published studies that support the PTR-MS applications to evaluate apple fruit volatilome changes during all steps of the production chain: from breeding activity support to consumer acceptability. The total count of articles for each PTR-MS application is reported in brackets.

biotic stress triggered during storage (e.g. 6-methyl-5-hepten-2-one or α-farnesene [122]).

Another non-destructive application is the discovery and quantification of VOC off-flavours that are commonly perceived by consumers before the fruit consumption, even at low concentrations, such as several volatile sulphur compounds (e.g. methanethiol, dimethyl sulfide, dimethyl trisulfide, or methyl thioacetate) or butyric acid and related butyric esters [123]. amongst all horticultural crops, apple (*Malus* x *domestica*) is the plant species that has been mostly studied with PTR-MS technique (30 articles; Fig. 4) using both destructive and non-destructive approaches. Based on that, apple fruit can be considered as a suitable study case to confirm all possible PTR-MS applications as a support tool to evaluate volatilome changes during the whole production chain: from breeding activity to consumers (Fig. 9). Most of the studies related with breeding activity and cultivation and storage management were equally conducted using both destructive and non-destructive headspace analysis applying the "off-line" PTR-MS setting. Nevertheless, PTR-MS was also applied, in four studies, in the "on-line" setting for continuous measurement of the apple volatilome by using nose-space and artificial oral processing methodologies. These "on-line" results helped to better understand the link between fruit texture properties and VOC kinetic release during fruit consumption.

Conclusions

The increased awareness of environmental issues is leading to many efforts to make analytical chemistry a greener discipline. This review describes the PTR-MS fundamentals and features from the GAC perspective and provides an overview of the areas of the food science and technology field where PTR-MS has been successfully applied.

Suggesting PTR-MS as an analytical technique with intrinsically low environmental impact, we introduce the concept of considering PTR-MS as both a rapid and high-performance platform and a green alternative for applications targeting food volatilomics.

PTR-MS was originally developed without green goals, but this review proved it to be well aligned with the GAC guidelines. Galuszka *et al.* [2] reported the need for compromise between analytical performance and GAC requirements as a possible drawback of greener practices adoption. However, due to the intrinsically green nature of PTR-MS, the low environmental impact is not the result of trade-offs.

PTR-MS technology provides several advantages in VOC analysis, finding its application not only in scientific research but also in industrial activities where high stability, reproducibility, automation, and throughputness are required. Its key feature is the possibility to detect and quantify VOCs at very low concentrations (ppt_V) in a direct, continuous, and real-time way, with both high mass and time resolution. On the one hand, the high time resolution allows on-line monitoring of fast processes such as the evolution of VOCs during thermal processes or food fermentations or their release during food consumption. On the other hand, the high throughput meets the requirements of applications entailing large sampling screening such as traceability, quality control, and phenotyping.

Overall, it has to be noted that the aforementioned instrumental characteristics suggest PTR-MS both as a complementary tool to gas chromatographic methods for the study of volatile compounds and as a valuable technique when speed, sensitivity and on-line measurements are required.

In regard to future perspectives, over the last years, we are observing a trend toward miniaturisation of conventional analytical platforms (e.g. miniGC instruments) and their components (e.g. chip GC columns), reducing the required bench space and increasing the portability. This is currently a limit for PTR-MS, and for MS in general, because of the dimension of the mass analysers and the need of vacuum pumps. Despite these evident technological challenges, advancements in that perspective would improve PTR-MS portability and would further increase the alignment of this analytical technique with GAC principles.

Declaration of Competing Interest

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

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.greeac.2022.100041.

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