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Review on chromatographic and specific detection methodologies for unravelling the complexity of MOAH in foods

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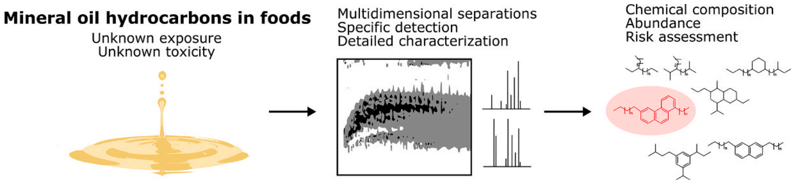
HIGHLIGHTS

- There is a need for detailed characterization of mineral oil aromatic hydrocarbons in foods.
- Advances in chromatographic separations and detection methods are discussed.
- GC × GC-MS with LC pre-fractionation is the most promising approach for maximizing separation.

GRAPHICAL ABSTRACT



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ABSTRACT

Contamination of foods with mineral oil hydrocarbons, particularly mineral oil aromatic hydrocarbons (MOAH), can potentially pose a health hazard to consumers. However, identifying toxic substances among the many thousands of compounds comprising mineral oils in food samples is a difficult analytical challenge. According to the European Food Safety Authority, there is a lack of concentration and structural data about mineral oil hydrocarbons in foods, and therefore it is not clear to what extent consumers in Europe might be exposed to toxic levels of MOAH. The current gold standard method for determination of mineral oil hydrocarbons is online high-performance liquid chromatography (LC)-gas chromatography (GC) with flame ionization detection, which quantifies total saturated/aromatic content, but gives no qualitative information. The objective of this review is to explore the future prospects in mineral oil hydrocarbon determination and MOAH characterization in foods. To that end, peer reviewed literature was explored, particularly from the viewpoint of a methodology for detailed characterization of the MOAH fraction that can aid toxicological assessment. The literature clearly shows that there is much to be gained from the orthogonality power of multidimensional chromatographic separations and mass spectrometric (MS) detection. Comprehensive two-dimensional GC coupled to MS, preceded by pre-fractionations of MOAH by LC is suggested to be the most promising approach for further research. In addition, the strengths and weaknesses of a number of other, alternative approaches, both for qualitative and quantitative analysis, are discussed.

Abbreviations: MOAH, mineral oil aromatic hydrocarbons; MOSH, mineral oil saturated hydrocarbons; PAH, polyaromatic hydrocarbons.

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1. Introduction

In the last two decades, contamination of foods with mineral oil hydrocarbons has gained attention as a potential health hazard [1,2]. Mineral oils are widely used in food harvesting, production, storage, transportation, and even as food additives [1]. They are very complex mixtures of hydrocarbons with an astounding number of components. Because of their immense complexity, mineral oils are usually characterized in terms of bulk properties, e.g., viscosity and average molecular weight, rather than their chemical composition [3,4]. Mineral oil hydrocarbons are usually divided into two categories: mineral oil saturated hydrocarbons (MOSH) and mineral oil aromatic hydrocarbons (MOAH). The main concern with regards to mineral oil hydrocarbons exposure through foods is that some compounds in the MOAH fraction can be genotoxic and/or carcinogenic [3,5], especially those with three or more aromatic rings [6]. Although MOSH may also have some toxic effects by accumulating in various tissues [4,6,7], MOAH remain the main focus of this work. MOSH will not be addressed in this review, but only included where appropriate for supporting the discussions. With regards to toxic MOAH species, it can be expected that exposure to food grade mineral oils (highly refined, low viscosity, low aromatic content) is not particularly harmful. Indeed, toxicity studies suggest that food grade high viscosity mineral oils have no carcinogenic or genotoxic effects [4,7]. However, technical grade mineral oils (less refined, medium to low viscosity, higher aromatic content) that may contaminate foods have an aromatic content in the range of 10–40% [8,9]. Exposure to foods contaminated with technical grade mineral oils containing potentially hazardous MOAH compounds is therefore of much greater concern. The toxicity of non-alkylated aromatics is well-known and has been extensively studied. For naked and lightly alkylated (e.g. methylated) aromatics, there is a consensus that mainly compounds with 3–7 rings are toxic [7]. Heavy alkylation can counteract these toxic effects, but how these effects depend on size, location, and branching of the alkyl chain is not known [7]. Hence, the toxicity of MOAH mixtures, which may include hundreds of aromatics with varying degree of alkylation, is poorly understood and there is no dose-response data available [6,10,11]. As a result, there are no well-defined acceptable daily intake values either. For high- and low-viscosity mineral oils (in bulk, not considering any specific compound groups), the Joint FAO/WHO Expert Committee on Food Additives has defined ADIs of 20 and 10 mg/kg body weight, respectively [12]. It had also defined a temporary ADI for MOSH in 2002 (0.01 mg/kg body weight [12]) but this has been withdrawn due to lack of supporting data [13]. Possibly, only a limited number of (alkylated) MOAH are genotoxic or carcinogenic, but key information is missing as to the number and the position of the alkyl groups on the aromatic compounds that cause the potential toxic effects. To fill this knowledge gap, we need analytical approaches that provide this molecular structure information and enable identification of MOAH sub-classes and individual compounds. This, in turn, should be combined with quantitative analysis and toxicity studies in individual compounds to make a proper risk assessment. This requires reliable methods for quantitative analysis of MOAH in food samples, as well as confirmatory methods that provide molecular information for identification of potentially toxic MOAH species.

The current gold standard method for determination of mineral oil hydrocarbons in foods is online high-performance liquid-gas chromatography with flame ionization detection (HPLC-GC-FID), which was first described by Biedermann et al. in 2009 [14] and reviewed and updated in later publications [15–17]. In 2017, it became the basis for the European standard method EN 16995:2017 [18]. This method is very suitable for the routine quantitative analysis of MOSH and MOAH in food samples and is applied in many research and commercial laboratories. Plenty of examples of HPLC-GC-FID analysis of mineral oil contaminations in various foodstuffs can be found in the literature (see for example surveys of the Belgian [19] and German food markets [20,21]).

However, there are also several disadvantages to this method. The main issue is that individual components of the MOSH and MOAH fractions are very poorly separated, each fraction elutes as broad humps of co-eluting compounds. Interferences co-extracted from the food sample matrix are also poorly separated, and can deteriorate the accuracy of the results if not properly taken account for. Moreover, FID detection is neither sensitive nor selective. Consequently, HPLC-GC-FID is only suitable for quantifying the total MOSH/MOAH content, since it provides no structural information that can help distinguish different compounds.

According to the European Food Safety Authority (EFSA), data about the occurrence of mineral oil hydrocarbons and their composition (e.g., number of rings in the case of MOAH) in foods is lacking. EFSA states that exposure to MOAH through foods is of potential concern [10], but on a case-by-case basis (different food products, different mineral oil composition, different amounts of consumption) it is not clear if consumers are exposed to potentially toxic levels of MOAH. Addressing the knowledge gap about the chemical composition and toxicity of mineral oil hydrocarbons in foods requires standardized, validated analytical methods with good inter-laboratory reproducibility as well as confirmatory methods for more detailed characterization [2].

The objective of this review is to explore and critically examine which analytical methods, specifically based on orthogonal multidimensional separations and various detection methods, could achieve in-depth characterization of mineral oil hydrocarbons. Weber et al. [22] have previously reviewed applications of chromatographic methods for determination of MOSH/MOAH (mostly LC-GC and GC for determination of saturated/aromatic fractions) in food and cosmetic samples. Their review covers a range of two-dimensional chromatographic methods, either heart-cut but also a few comprehensive,[2] that have been applied for determination of MOSH/MOAH in food and cosmetic samples. The review by Sdrigotti et al. [11] discusses the evolution of multidimensional separation methods in the context of mineral oil hydrocarbon determination. This review provides a more complete overview of multidimensional mainly comprehensive separations as well as detection methods that either have been used for mineral oil hydrocarbon determination, or for analysis of similar hydrocarbon mixtures. Special focus is given to techniques that enable the identification of potentially toxic MOAH compounds, as sub-groups of similar compounds (e.g., 3-, 4-, 5-ring aromatics) or even selected individual compounds. The discussion covers the strengths and weaknesses of various comprehensive two-dimensional separations, combinations with heart-cut fractionations, and detection methods that can resolve the complexity of MOAH mixtures. Some aspects of sample preparation and quantification are discussed as well, but not in full detail. In this way, we aim to aid scientists and food control laboratories in implementing the most promising analytical approaches that will support better risk assessments and food safety.

2. Chromatographic separation of MOSH/MOAH

2.1. Online HPLC-GC

As already mentioned, the current gold-standard for MOSH/MOAH determination is online HPLC-GC-FID, developed by Biedermann et al. [14–17]. The basic principle of this method is that MOSH and MOAH fractions are separated by normal-phase liquid chromatography (NPLC) and transferred to GC-FID for quantification. Both the MOSH and MOAH fractions are eluted as broad humps that are integrated to give an

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[2] Heart-cut methods (indicated with a hyphen, e.g. LC-GC, LC-LC-GC) refer to those where one or selected fractions from the first dimension are transferred to the second dimension. Comprehensive methods (indicated with a cross, e.g. GC × GC, LC × GC) in contrast transfer the complete eluting sample from the first dimension to the second dimension in small fractions.

estimate of the total MOSH/MOAH content. The NPLC pre-separation serves an additional purpose of removing non-volatile components that may be present in the sample, such as triglycerides and wax esters. The pre-separation can also be performed with argentation chromatography (AgLC) [23], which is more selective towards the aromaticity of MOAH [23]. AgLC is more commonly employed in offline LC and SPE, where separation of the MOSH/MOAH fractions is often incomplete [15]. With the higher separation efficiency of HPLC, however, the additional selectivity of a silver-impregnated column does not give much additional benefit compared to standard NPLC columns [15]. The development of online HPLC-GC-FID has offered several advantages to offline methods, including higher separation efficiency, high sample throughput, reduced solvent consumption, and reduced risk of sample contamination [24]. Another advantage of this approach is that it is a well-established quantitative method, applied in many laboratories.

However, the chromatographic overlap between mineral oil hydrocarbons and interferences with the absence of qualitative information from FID remains an issue. The analyst needs to be able to recognize characteristic chromatographic patterns of MOSH/MOAH and distinguish them from potential interferences without any qualitative information from the detector. It can also happen that the MOSH tail into the MOAH fraction, causing an overestimation of the MOAH content. Incorrect interpretation of chromatograms is a common source of uncertainty in quantification of MOSH/MOAH [15,16]. The uncertainty of the obtained result due to integration and interpretation (i.e., variation in setting the baseline, trimming interference peaks, etc.) of the chromatogram can be as high as ~20% [25]. Readers interested in a detailed description of chromatogram integration and interpretation are referred to Biedermann et al. [16].

In addition, food samples often require laborious sample preparation to remove interfering compounds and to pre-concentrate the sample. Making a decision about the optimal sample preparation adds another challenge for the analyst to tackle. The Joint Research Center's guidance [24] features a decision tree that shows the complexity of the decision making process but can also serve as a useful guide for analysts dealing with challenging samples. A typical sample preparation involves extraction, removal of triglycerides, if needed removal of interferences (removal of long-chain alkanes and/or epoxidation of olefins) and enrichment. MOSH/MOAH are extracted from food matrices using non-polar solvents, such as *n*-hexane or dichloromethane [18], which also co-extracts interferences. Fatty samples may require additional removal of triglycerides prior to NPLC fractionation, because the column's capacity to retain triglycerides is limited (typical limit ~20 mg) which in turn limits the method sensitivity in case large amounts of triglycerides are present [15]. The accuracy of the quantification of MOAH can be deteriorated by interfering olefins and other unsaturated compounds. These can be removed through epoxidation, although this should be used with care to avoid loss of MOAH (which can also be epoxidized) from the sample. Because of the low amounts of MOSH/MOAH in food samples, enrichment may be required to reach the desired LOD and LOQ. Another interesting study, recently published by Carrillo et al. [26], reported on selective extraction of MOAH from mineral oil products by DMSO, making use of π-interactions between the aromatics and the solvent. Whether or not this extraction is applicable to foods, remains to be investigated. Sample preparation is not discussed in further detail in this review, but the reader is referred to existing literature [14,18,24,27–31].

Obviously, one of the requirements for achieving detailed characterization of the chemical composition is more comprehensive separations. Biedermann and Grob pointed out that in order to detect all substances, including anything that might be unexpected, the analysis method needs to be as comprehensive as possible [32]. Sdrigotti et al. [11] argues that additional hyphenations, including comprehensive techniques, is probably the best approach to achieve an in-depth characterization of MOSH/MOAH and identification of toxic compounds of interest that can later then be addressed by targeted analysis for quantitative analysis. The following sections discuss the potential of different comprehensive multidimensional separations for MOAH characterization.

2.2. Comprehensive GC × GC

Comprehensive two-dimensional gas chromatography (GC × GC) is gaining popularity as a confirmatory method to complement HPLC-GC-FID analysis of MOSH/MOAH, and in food analysis in general, especially combined with mass spectrometry (MS) [11,33]. According to Biedermann et al. [17], GC × GC is the most effective method of verifying results obtained from HPLC-GC-FID. GC × GC has already contributed to new insights about potentially toxic fractions of mineral oil hydrocarbons and to the improvement of the HPLC-GC-FID methodology [11]. The strengths of GC × GC include its great separation power, that it is a mature well-established technique [34] and that it is easily combined with MS. A separation in two dimensions resolves the sub-classes of MOAH (with respect to aromaticity and alkylation) and facilitates their identification by MS. However, there is still no standardized and interlaboratory-validated GC × GC-MS method for MOAH determination [2] and method for determining the position of alkyl group(s).

GC × GC alone does not fully separate MOSH and MOAH [8,17]. Cyclic MOSH such as steranes and hopanes co-elute with MOAH (Fig. 1). Furthermore, the less abundant MOAH may become invisible in 2D plots dominated by much more abundant MOSH [8]. GC × GC analysis therefore requires a pre-separation of the MOSH/MOAH fractions with (HP)LC or SPE (Fig. 2). The pre-separation by LC prior to GC × GC is usually performed offline. An online HPLC-GC × GC setup could offer a more automated, faster analysis with less risk of sample contamination. Zoccali et al. [35] have demonstrated that an online HPLC-GC × GC-MS setup can be used for the analysis of complex samples such as coal tar. Purcaro et al. have presented their development of a completely hyphenated HPLC-GC × GC platform used specifically for MOSH/MOAH determination at several conferences [36–41] and the platform has been implemented in a publication by Bauwens et al. [25].

However, even in GC × GC there is not always a perfectly clear group-type separation – MOAH are still eluted as a broad hump in the 2D plot. This is especially true if the mineral oil is partially hydrogenated, in which case hydrogenated species elute in between the non-hydrogenated species.

Note that the MOSH/MOAH fractions in the example shown here (Fig. 2) are separated using the same temperature programs and the same columns. It may be possible to optimize each of the two separations. For example, Adam et al. [42] used a twin-GC × GC system (two different GC × GC column sets placed in the same oven) to achieve optimal separation of saturated and unsaturated hydrocarbons. If the goal is to perform a detailed characterization of MOAH, the GC × GC separation of the MOAH fraction should be optimized to use as much of the separation space as possible, rather than implementing a method designed for both MOSH and MOAH. GC × GC is usually performed with a nonpolar first-dimension column which separates compounds based on their volatility and a polar second-dimension column which separates based on polarity (for example Fig. 2). For MOAH, this means that the retention time in the first dimension increases with increasing degree of alkylation, and separation according to ring number takes place in the second dimension. For MOSH/MOAH analysis, however, the reverse configuration (polar first-dimension column, non-polar second-dimension column) is often used (Fig. 1). The choice of configuration depends on which compounds are most important to analyze – the reverse configuration is better for resolving MOSH from polyolefin oligomeric saturated hydrocarbons but not as good at resolving MOAH [11].

Note also that the examples presented so far (Figs. 1 and 2) have shown chromatograms of mineral oil products, not mineral oil contaminations extracted from foods, and therefore do not show the effect of matrix interferences. Even in GC × GC, interferences such as squalene,

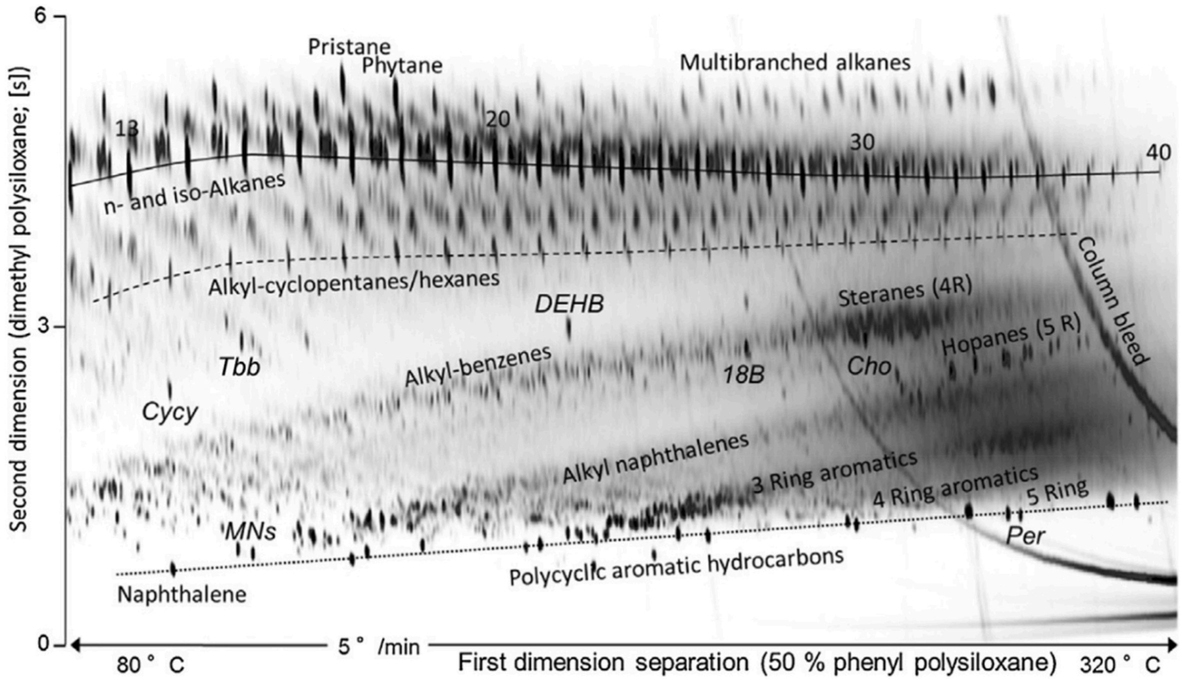

Fig. 1. GC × GC analysis of a mineral oil mixture. Note that poly-cyclic MOSH like steranes and hopanes co-elute with MOAH species. Text in italics marks internal standard added to the sample; cyclohexyl cyclohexane (Cycy), cholestane (Cho), 1- and 2-methyl naphthalene (MNs), tri-tert-butylbenzene (Tbb), perylene (Per), di (2-ethylhexyl)benzene (DEHB), *n*-octadecylbenzene (18B). Figure obtained from Biedermann et al. [12] with permission. First dimension separation is polar and second dimension separation is nonpolar (reverse configuration).

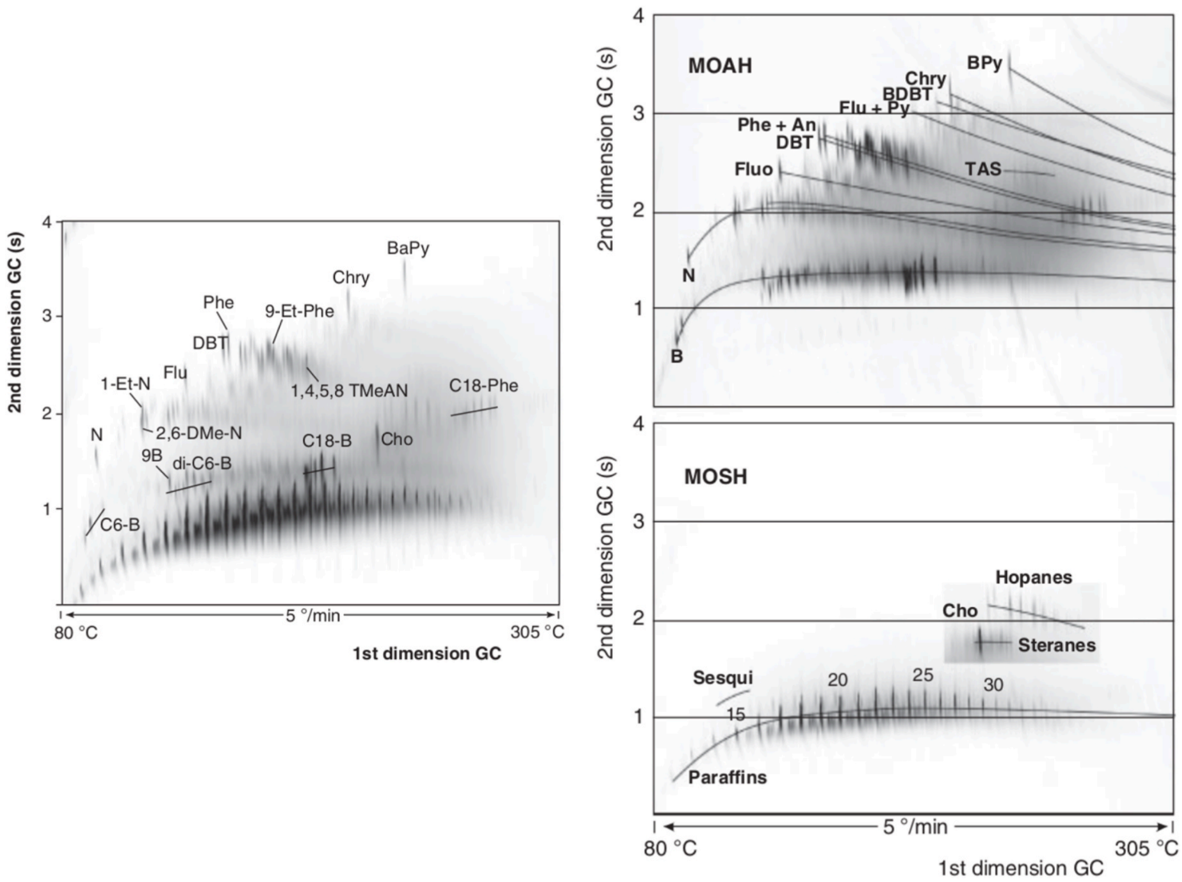

Fig. 2. Comparison of GC × GC chromatograms obtained from a mineral oil mixture analyzed directly (left panel) or after pre-separation of MOSH/MOAH fractions (right panel). This clearly shows that without pre-separation, hopanes and steranes would overlap with the aromatic compounds. Figure obtained from Biedermann et al. [7] with permission. First dimension separation is nonpolar and second dimension separation is polar.

sterenes, and carotenoids are still co-eluted with the MOAH hump. Just as HPLC-GC-FID, the sample might require extensive preparation to get rid of interferences.

2.3. Comprehensive LC × GC

GC × GC clearly demonstrates the benefit of a comprehensive analysis for MOAH characterization. However, GC × GC does not always give a clear separation between different groups of MOAH compounds. To identify toxic compounds, a separation based on number of aromatic rings is most useful, but the selectivity towards aromaticity in GC × GC is limited. The polar separation dimension separates based on polarity, which is partly related to aromaticity but is also affected by the alkyl side-chains. LC has the benefit of more control over selectivity using a variety of stationary and mobile phases. Therefore, comprehensive LC × GC could be an interesting alternative to GC × GC for MOAH determination.

A first attempt at LC × GC analysis of MOAH in foods was made by Grob et al. in 1991 [43]. The aromatics were separated by ring number on a LC amino column and 500 μL fractions were directly transferred to GC with an online setup. Hyphenated comprehensive LC × GC can be achieved with a stop-flow method in which narrow LC fractions are transferred to the GC and the flow is stopped for the duration of the GC run [44]. Because mineral oil components have a wide range of boiling points, their separation in GC requires a temperature-programmed run, which takes too much time to allow the LC separation to be run with a continuous flow [44]. Alternatively, LC × GC can also be performed with offline transfer of the LC fractions to the GC [45]. There are two more recent prominent examples demonstrating the use of LC × GC for analysis of hydrocarbon mixtures: de Koning et al. used NPLC × GC with an amino column to characterize diesel oil [44] and García-Cicourel et al. used AgLC × GC to characterize mineral oils [45].

LC × GC gives a separation of a few groups (Fig. 3). The AgLC × GC analysis of García-Cicourel et al. [45], for example, only separates mono- from poly-aromatics, and provides no resolution within these groups (unlike e.g., GC × GC). With regards to toxicity, a group-type separation between mono-/di-aromatics and tri-/poly-aromatics would therefore have been more useful. Even better, a separation between multiple groups with one, two, three, etc. rings would have been ideal for a group-type analysis of MOAH.

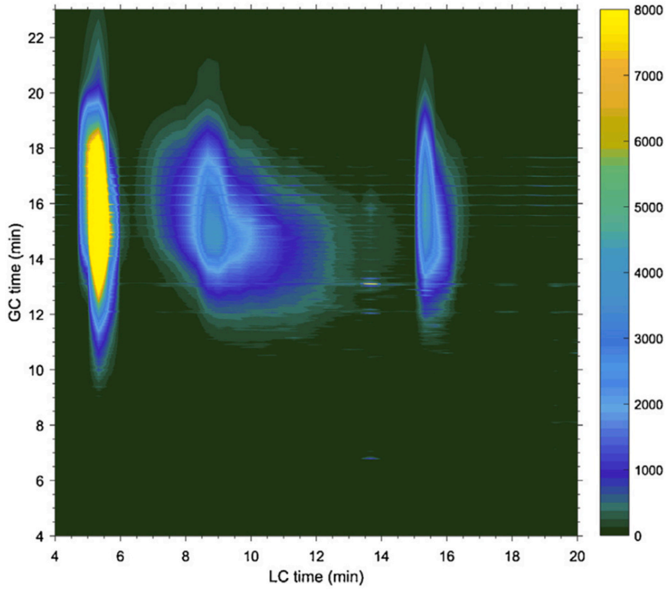

Fig. 3. AgLC× GC-FID analysis of mineral oil. The mineral oil hydrocarbons are separated into three groups: MOSH (4.7–6.5 min), mono-aromatics (6.6–14.6 min) and poly-aromatics (15–16.6 min). Since the first dimension has a high selectivity towards aromaticity, a clear separation between the MOAH subgroups is obtained. Figure obtained from García-Cicourel et al. [43] with permission.

Note that LC × GC has so far only been applied to samples of crude or purified mineral oil, but not mineral oil contaminations extracted from foods. It is therefore not clear how well it would separate interferences from MOAH. In the case with AgLC × GC, unsaturated olefins would also be retained on the silver-impregnated column and have similar boiling points in GC, consequently overlapping with MOAH. In other words, LC × GC would probably suffer from the same interference problem as HPLC-GC and GC × GC. Now, even if LC × GC would be dismissed as unfeasible MOAH characterization, there are other ways in which adding LC dimensions could be useful.

2.4. Multidimensional LC

There are several examples of LC-LC-GC approaches to MOSH/MOAH determination, but most of them are developed for the purpose of removing olefins rather than increasing the separation of MOAH. For example, Lommatzsch et al. [46] developed an extension of the online HPLC-GC-FID method to also include an additional AgLC step to separate unsaturated species from MOSH. Zoccali et al. [47] used a similar approach to remove olefins from the MOAH fraction. Another example is the method proposed by Fiorini et al. [48] using two consecutive silica columns, one for retaining triglycerides and one for separating olefins from mineral oil hydrocarbons. These methods do indeed efficiently remove interferences, yielding a more accurate quantification of the total MOAH fraction without the use of epoxidation. The question now is whether multidimensional LC also can be used for detailed characterization.

No examples of comprehensive LC × LC for mineral oil hydrocarbon characterization have been found in the literature. Although LC × LC could very well be successful at separating MOAH into multiple groups, it would be a challenge to extract relevant information from the chromatogram. LC is not well compatible with FID and no other LC-compatible detector can give the same robust response that allows quantification of a mixture of hydrocarbons without any reference standards. As for identification, mineral oil hydrocarbons would be difficult to ionize with the most commonly used ionization techniques in LC-MS. For MOAH, however, it could be possible to perform LC-MS with atmospheric pressure photoionization (APPI). APPI is especially suitable for compounds that cannot be ionized with electrospray or atmospheric pressure chemical ionization, including polyaromatic hydrocarbons [49]. In principle, an ultraviolet (UV) detector could give some information about the number of rings, but it would not provide additional information that cannot be obtained by MS.

LC-LC-GC and LC-LC-GC × GC, however, has the potential to enable isolation and detailed characterization of specific groups of aromatic compounds. Koch et al. [50] proposed a two-step separation with AgLC followed by donor-acceptor chromatography to further separate the MOAH into fractions of compounds with one or two aromatic rings and three or more rings. The entire MOAH fraction, as well as the mono-/di-aromatic and tri-/poly-aromatic fractions were analyzed both with HPLC-GC-FID and GC × GC-MS (Figs. 4 and 5).

This approach shows potential for in-depth characterization of tri-/poly-aromatic compounds. By separating them from mono-/di-aromatics, the GC × GC separation can be optimized to better separate individual components. The analysis by Koch et al. [50] performed on mineral oil products shows a good separation in the tri-/poly-aromatic fraction, which perhaps could be improved even further to use more of the available separation space.

Dividing the tri-/poly-aromatics further into even smaller fractions could perhaps enable an even more detailed analysis of smaller groups of compounds. If the fractions are small enough, the analysis could be considered comprehensive LC × GC × GC, similar to the offline LC × GC described by García-Cicourel et al. [45]. As pointed out by de Koning

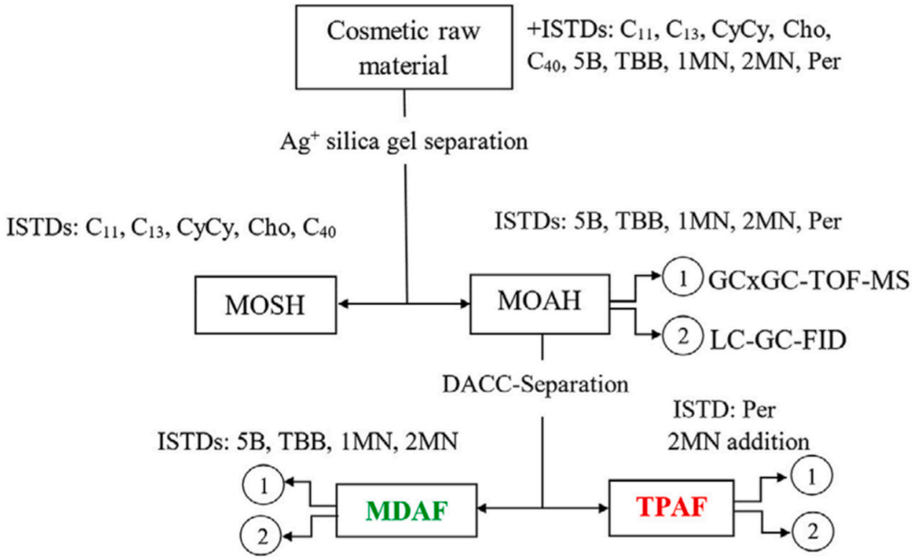

Fig. 4. Overview of separation procedure described by Koch et al. for detailed analysis of MOSH and MOAH. MOAH are separated further into mono-/di-aromatics (MDAF) and tri-/poly-aromatics (TPAF). Figure obtained from Koch et al. [48] with permission.

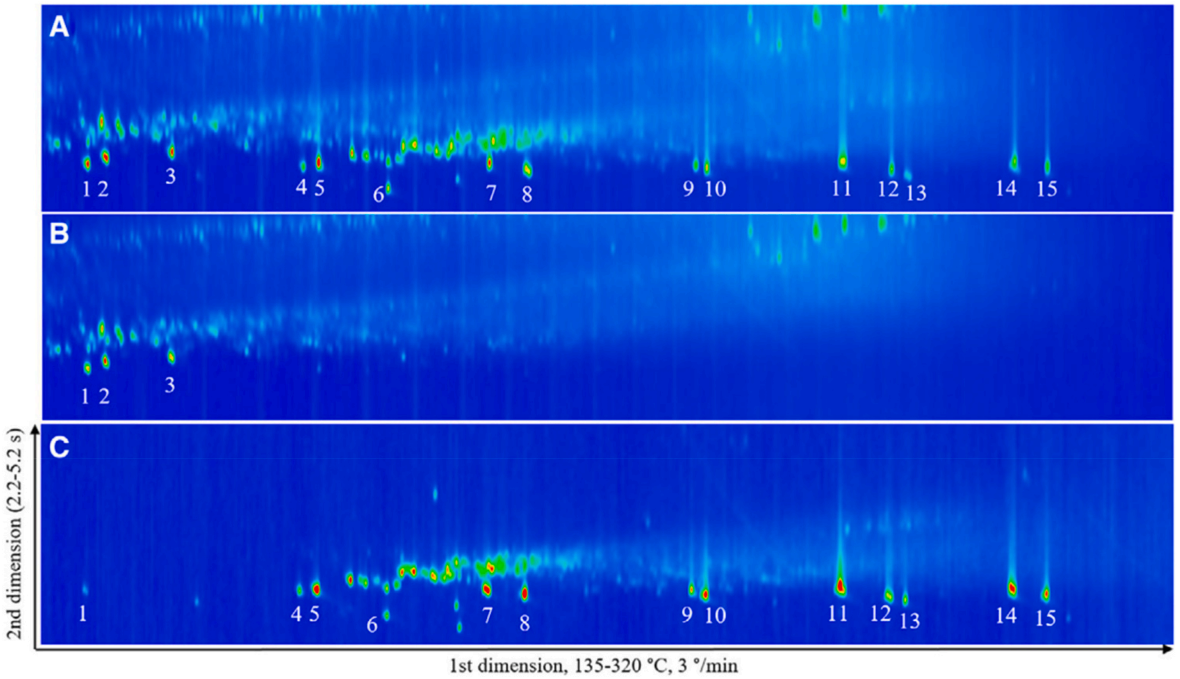

Fig. 5. GC × GC-TOF-MS analysis of A) MOAH fraction, B) mono-/di-aromatic fraction, C) tri-/poly-aromatic fraction of a mineral oil sample. The numbered peaks indicate PAH standards added to the sample. Figure obtained from Koch et al. [48] with permission. First dimension separation is polar and second dimension separation is nonpolar (reverse configuration).

et al. [44], LC × GC × GC could potentially give additional analytical benefits compared to LC × GC. In addition, the multiple pre-separations could help remove interferences and allow for a simpler sample preparation, although this remains to be tested in practice.

On the other hand, multiple offline transfers can lead to sample losses and each LC separation dilutes the sample. Koch et al. [50] addressed this issue by including a concentration step (vacuum evaporation) between the two separations. Evaporation between LC separations can also be done online, as shown by Moret et al. [51]. With several LC separation steps and GC, it is difficult to perform the entire analysis in an online setup to minimize losses. Since it is already difficult to reach target LOQs for MOAH in food samples, working with even smaller isolated MOAH sub-fractions could become a challenge.

In short, the addition of multidimensional LC separations could overcome the limitations of GC × GC that prevent a detailed characterization of specific groups of aromatic compounds. On the other hand, performing multiple LC separations and several GC × GC analyses for quantification and identification results in a complex method that will require analytical expertise and will be difficult to implement in routine applications. From a research point-of-view, however, this kind of complex approach is necessary to unravel the composition of MOAH mixtures.

2.5. Supercritical fluid chromatography

Supercritical fluid chromatography (SFC) is often described as a technique that can combine the separation power and detector compatibility of GC with the selectivity of LC. SFC is widely used in the petroleum industry for analysis of high molecular weight compounds [52]. In multidimensional separations, SFC is also commonly used as the second-dimension separation in combination with LC, but it is also possible to apply SFC as the first-dimension separation followed by GC. The hyphenation of SFC-GC is less instrumentally complicated than HPLC-GC. The supercritical CO_2 can be easily removed by decompression without losing volatile sample components [52,53]. As compared to solvent evaporation in HPLC-GC hyphenation, this requires less instrument modifications [52]. Trapping of analytes at the head of the GC column can be achieved by cryogenic focusing [52]. For MOAH determination, SFC could provide both the selectivity of LC towards aromaticity and the possibility using FID [54], as well as easy hyphenation to GC or GC × GC.

García-Cicourel et al. [54] have developed an SFC-FID/UV method that allows quantification of total MOSH/MOAH fractions from pure mineral oil samples with a simple one-dimensional separation. The MOSH/MOAH fractions were not baseline-separated, but with the use of dual detection with UV their peaks could be deconvoluted [54]. The resolution between the MOSH/MOAH fractions can be different depending on the mixture's composition and viscosity and it was determined that the SFC method was not suitable for samples with high viscosity [54]. However, this should not be a concern for food extracts which only contain small amounts of MOSH/MOAH dissolved in a less viscous solvent. What might be problematic is that triglycerides, olefins, and other interferences co-extracted from food samples might behave unexpectedly in a SFC separation and could be co-eluted with MOSH/MOAH. Although the retention in SFC can be expected to be similar to NPLC, there could be other retention mechanisms at play, resulting in unexpected retention behavior that is difficult to predict.

SFC can be used instead of LC for pre-fractionation prior to GC × GC analysis and there are several examples of SFC-GC × GC being used to characterize hydrocarbon mixtures. Adam et al. [42] described a characterization of diesel using SFC-GC × GC. Potgieter et al. [53] made a comparison between online SFC-GC × GC and offline HPLC-GC × GC with light oil samples, concluding that the SFC separation was just as effective as HPLC. This might not hold true for heavier mineral oils [54] but, as discussed above, should not be a concern for food extracts. Provided that SFC also separates non-volatile compounds (e.g., triglycerides) from the MOSH/MOAH fractions as effectively as NPLC before GC injection, SFC-GC and SFC-GC × GC could become a useful alternative approach for MOSH/MOAH quantification.

As for multidimensional separations, SFC × SFC could be a powerful alternative for achieving a better group-type selectivity compared to GC × GC and greater separation power compared to LC × GC. Guibal et al. [55] demonstrated how an SFC × SFC with a nonpolar C18 first-dimension column and a bare silica second-dimension column could achieve a group-type separation of a test mixture of aromatic hydrocarbons by ring number (Fig. 6). Analysis of a coal tar vacuum distillate (Fig. 7) also showed some separation of groups. In a later publication, Petkovic et al. [53] improved upon this system by introducing active modulation to achieve a peak compression effect and reach a peak capacity closer to GC × GC (Fig. 7). Rather than passive transfer of the first-dimension effluent to the second-dimension separation, their transfer module allowed pressure and flow rate in the first dimension, transfer region, and second dimension to be modified independently. Different modulation strategies for hyphenation of SFC to both LC and GC have been described by Schiewek et al. [56].

For MOAH determination, this kind of separation would be ideal to get an overview of which groups (with respect to ring number and their alkylation range) are pre-dominant. If also active modulation can enable higher peak capacities, SFC × SFC could perhaps compete with GC × GC for in-depth MOAH characterization. Data presented by Guibal et al. [55] also suggests that aromatics are separated not only from alkanes, but also from alkenes. In other words, a similar SFC × SFC approach might also to some extent separate MOAH and interfering olefins. However, the alkenes in this case were not bigger than 20 carbons, and it is not certain if larger olefins from food matrices (for example squalene with 30 carbons) would be separated from aromatics just as well. The main weakness of SFC × SFC compared to GC × GC is that it is a less mature technique that is still in development. More recent papers describing further developments of SFC × SFC for analysis of complex

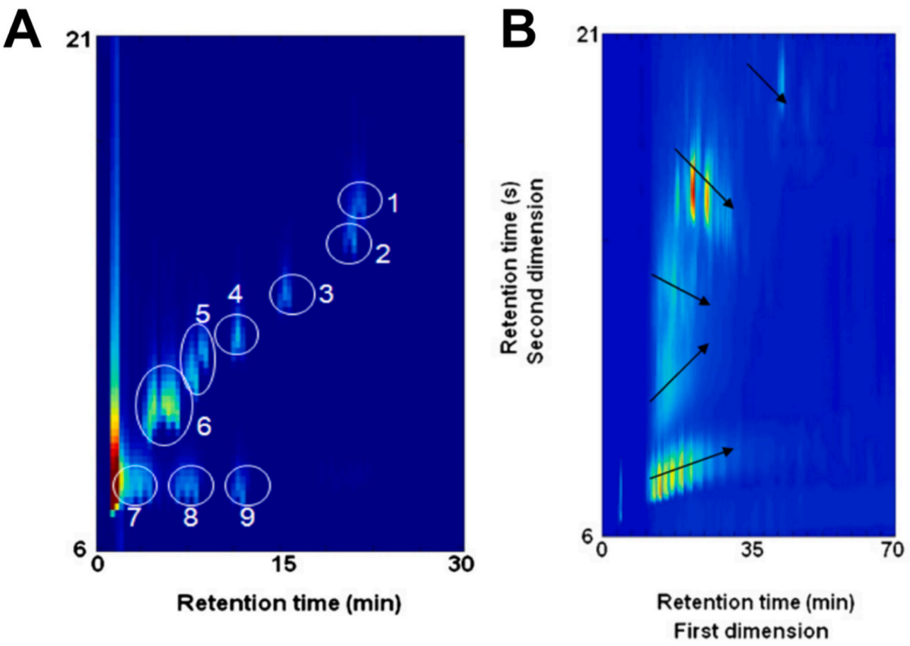

Fig. 6. A) SFC × SFC-FID analysis of a test mixture of hydrocarbons. Group-type separation between (1) triphenylene, (2) benzanthracene, (3) fluoranthene, (4) anthracene, (5) 3-ring PAH, (6) naphthalene and alkyl naphthalenes, (7) C11 and C12 alkanes, (8) C15 and C16 alkanes, and (9) C20 alkane is observed. B) SFC × SFC analysis of a coal tar vacuum distillate. Figures obtained (layout modified) from Guibal et al. [52] with permission.

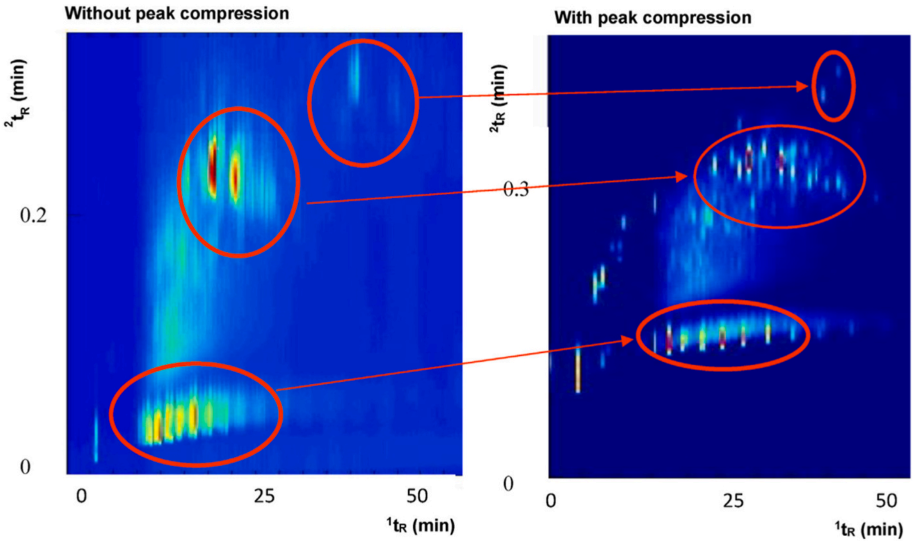

Fig. 7. SFC × SFC-FID analysis of coal tar distillate with and without a peak compression effect. The peak compression effect (achieved using active modulation) improves the resolution in the first dimension. Figure obtained from Petkovic et al. [53] with permission.

hydrocarbon mixtures have not been found. The lack of commercial SFC × SFC instruments [57] makes GC × GC a far more useful alternative in most laboratories. It is noteworthy to point out that both Guibal et al. [55] and Petkovic et al. [58] evaluated their SFC × SFC separation using only FID detection. Without qualitative information about each peak, the separation might still be poorly understood, especially for real samples such as the coal tar distillate. In-depth MOAH characterization will in any case require a detector that provides information about the molecular structure.

3. Detection and quantification

3.1. Flame ionization detection

FID is the ideal detector for reliable quantification of total MOSH/MOAH content with only a few standards. As the response factors in FID are based on carbon atoms rather than molecular geometry, the calibration is particularly robust compared to many other detectors. However, FID is neither sensitive nor selective, and therefore not ideally suited for detailed characterization of compounds with low abundance in the sample. The same kind of group-type calibration with other detectors, especially MS, can be very challenging. When the sample contains a mixture of many unknown samples and pure chemical reference standards are lacking, performing a calibration is very difficult. However, MS is the detection method of choice for specific detection and identification, and will be discussed first, followed by spectroscopic alternatives. Considerations for quantification and dual detection modes will then be discussed in a separate section.

3.2. Mass spectrometry

The Joint Research Center's guidance on MOSH/MOAH determination [24] states that MS should be used for confirmatory purposes but does not give any further advice on how the analysis is best performed. According to Sdrigotti et al. [11] there is still some resistance towards acceptance of GC × GC-MS as a confirmatory method. MS analysis of MOSH/MOAH mixtures is not straightforward even after GC × GC separation. Due to significant overlap between individual components and the sheer number of compounds in mineral oil mixtures, identifying specific structures is very difficult. There have been claims that GC-MS can be used for reliable quantification and determination of the contamination source using specific markers [59], but these claims were later criticized by Biedermann et al. [60]. The fragments generated by electron ionization (EI) in GC-MS are generally not very specific, and many fragments originating from MOAH can also be generated by for example squalene isomers, carotenoids, sterenes [60]. For complex hydrocarbon mixtures, GC-MS can only give information about broad chemical classes, for example as demonstrated by Isaacman-VanWertz et al. [61].

In GC × GC-MS, specific MOAH compounds can be extracted by the mass of their molecular ion. Their ring number and degree of alkylation (mass of the alkyl chain) can be deduced from their retention behavior (Fig. 8) [8,35]. As already mentioned in the *Introduction*, it is known that the number of aromatic rings can give an indication about potential toxicity, but it is not clear to what extent the alkylation plays a role. Simply determining the degree of alkylation (number of carbon atoms) might not be enough and it may be important to identify specific isomers with the alkyl chain at different locations or with different branching.

GC-MS and GC × GC-MS is usually performed with EI – a hard ionization technique that gives extensive fragmentation. Matching EI spectra to library reference spectra usually works for identification of compounds with very characteristic fragmentation patterns, but it is not always the case that the generated fragment ions are highly specific [62, 63]. For similar isomers it can be difficult to make unambiguous assignments. This is especially challenging if the molecular ion has a very low abundance or is completely absent due to extensive fragmentation. For complex hydrocarbon mixtures, the NIST database may not be enough to assign all peaks [64]. If the peaks are co-eluted, it can become a major challenge to distinguish and deconvolute isomers with similar spectra. The work of de Koning et al. [44] demonstrates how selection of characteristic mass fragments can be used to deconvolute hydrocarbons co-eluted in a multidimensional separation (in their case LC × GC) followed by library searching for identification. However, the authors did not comment on exactly how many compounds could be identified. The results only reported how MOAH were unraveled into general compound classes (alkylbenzenes, indanes and tetralines, indenes, etc.) and the data was not shown.

For MOAH characterization, it could be more useful to use a softer ionization technique and preserve the molecular ion. For nonpolar compounds like MOAH, feasible soft ionization techniques include chemical ionization (CI), atmospheric pressure chemical ionization (APCI), atmospheric pressure photoionization (APPI), atmospheric pressure laser ionization (APLI). APPI especially favors ionization of unsaturated and aromatic compounds [65]. For analysis of MOAH, APLI

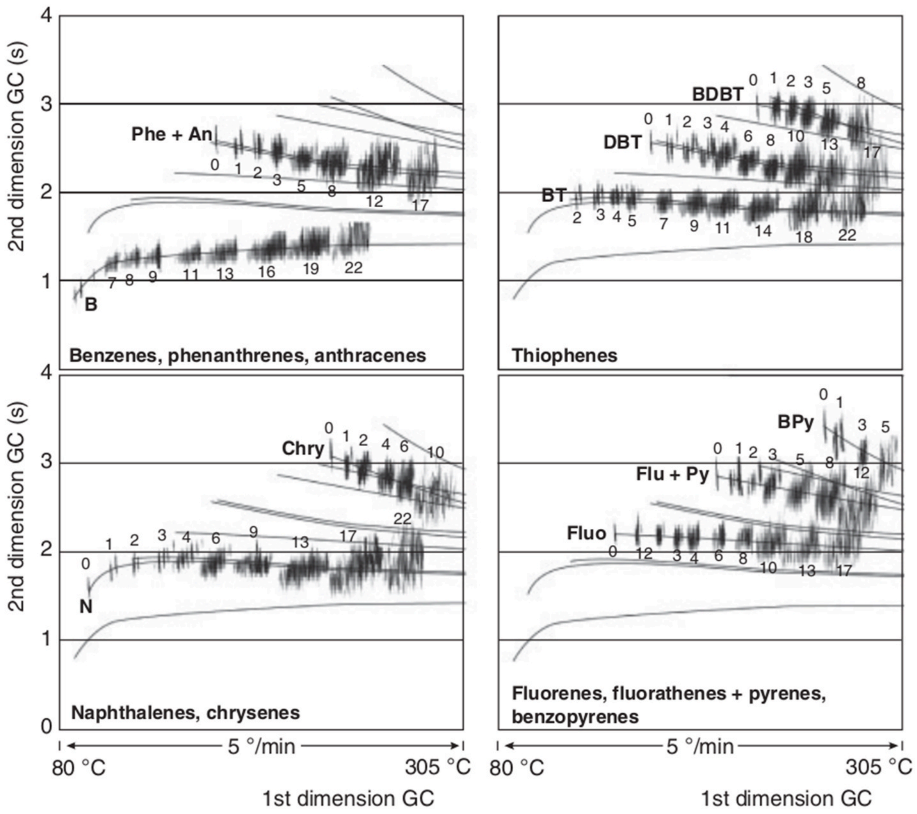

Fig. 8. GC × GC-MS plots of extracted ions from the MOAH fraction extracted from sunflower oil. The number of aromatic rings and mass of the alkylation chain (indicated with numbers in the plots) were determined based on the mass of the molecular ion and the retention behavior. Non-MOAH compounds with identical masses as the selected ions eluting in different locations have been removed. Figure obtained from Biedermann et al. [7] with permission. First dimension separation is nonpolar and second dimension separation is polar.

can offer very sensitive and selective ionization of aromatic compounds [56]. In fact, APLI can reduce the signal from non-aromatic background interferences [66]. With an abundant molecular ion, specific compounds can be detected with both higher sensitivity and selectivity as compared to EI fragment spectra. In addition, soft ionization facilitates specific selection of the molecular ion as a precursor in a tandem MS experiment with high sensitivity [62,63].

Tandem MS could potentially provide additional molecular information for more reliable identification. According to Giri et al. [67], fragmentation spectra of the molecular ion obtained from APPI tandem MS can show similarities with library spectra obtained from simple MS with EI and could therefore be used to identify unknown compounds by matching these spectra. In fact, spectral matching of EI spectra sometimes fails due to low abundance of the molecular ion. APPI tandem MS, which would provide both a diagnostic molecular ion as well as a fragmentation spectrum, could very well be more reliable [67].

Collision-induced dissociation, which is most commonly used in tandem MS experiments, is known to dealkylate aromatic compounds, generating fragments related to the aromatic core structure and alkyl group(s) [68]. This fragmentation alone will not provide much additional information compared to GC × GC-MS analysis of the molecular mass and retention behavior, but it may be informative to distinguish different aromatic core structures (not only ring number) and alkyl chains (length, branching). Sørensen et al. [69] used tandem MS (in their case with EI) with multiple reaction monitoring to analyze lightly alkylated PAH of biotic origin, showing that there are predictable trends in fragmentation patterns and optimal collision energy depending on molecular size, geometry, and alkylation. However, this analysis was only concerned with 69 compounds that were lightly alkylated (the largest substituents were butyl groups and none of them were branched). For MOAH, a far more extensive analysis of fragmentation patterns of heavier alkyl chains would be required. In short, distinguishing between very similar isomers will probably remain difficult even with tandem MS.

In terms of instrumentation, GC-MS is commonly performed with quadrupole MS instruments [61]. Zoccali et al. [35] have demonstrated that a triple-quadrupole MS can be used for analysis of complex hydrocarbon mixtures (in their case coal tar) with a GC × GC setup. GC × GC, however, requires rapid acquisition rates in the range 10–100 Hz, in which case a time-of-flight (TOF) MS is more suitable [70]. The higher data density of TOF-MS spectra (compared to quadrupole MS) also makes them more suitable for spectral deconvolution algorithms. However, a reliable deconvolution requires some degree of chromatographic separation and difference in the MS spectra [34]. If two very similar compounds are co-eluted with a significant amount of overlap, deconvolution becomes increasingly difficult even with TOF data. In this case it would again be beneficial to use a soft ionization technique to preserve the molecular ions and separate them based on *m/z* [34,60].

3.3. Spectroscopic detection

MS is not the only detection technique that can provide qualitative information about MOAH. Although not widely used, GC can also be coupled to spectroscopic detectors, such as vacuum ultraviolet (VUV) detection. VUV is based on measuring the absorption of light with wavelengths 100–200 nm. VUV can distinguish between saturated, unsaturated, and aromatic compounds (Fig. 9) [71,72].

García-Cicourel et al. [45] demonstrated that GC-VUV can be used for direct analysis of MOSH/MOAH without a pre-separation of the saturated and aromatic fractions, by deconvolution of the overlapping humps. The estimates of MOSH/MOAH content obtained using GC-VUV were similar to those from HPLC-GC-FID and SPE-GC-FID, but with improved repeatability. However, in this case the analysis had been performed on pure mineral oils. For analysis of food extracts, a pre-separation would still be required to remove non-volatile triglycerides before GC injection. Distinguishing MOAH and co-eluting olefins with VUV could also be troublesome because some species may have similar absorbance maxima.

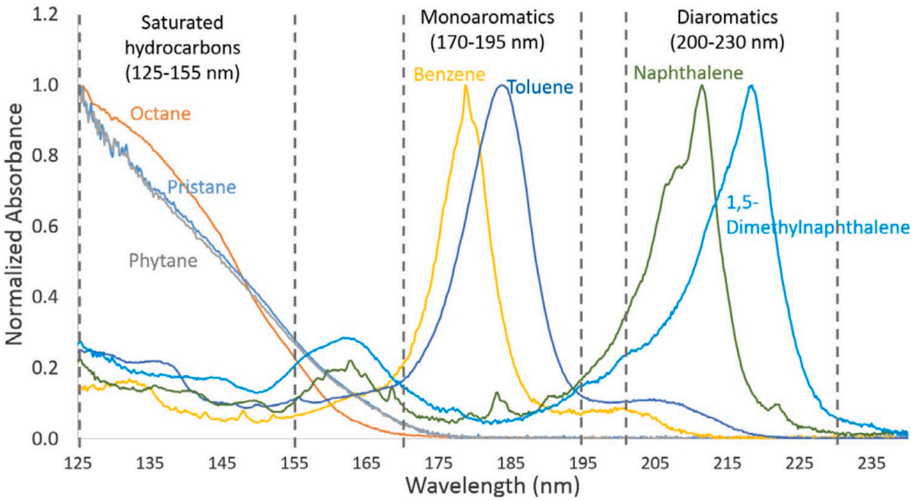

Fig. 9. VUV spectra of saturated and aromatic hydrocarbons. Although not shown in this figure, VUV should also be able to distinguish three-, four-, and five-ring aromatics, as the absorbance bands shift to higher wavelengths with increasing number of fused rings. Figure obtained from Bai et al. [69] with permission.

What is more interesting, is that VUV can also distinguish compounds with different aromaticity (Fig. 9) [45,71]. The main absorption bands shift to higher wavelengths with increasing number of fused aromatic rings. Polyaromatic systems absorb above 200 nm outside the range that is typically referred to as VUV, but VUV detectors with an expanded wavelength range 120–430 nm are commercially available [73]. Therefore, VUV could give an indication of whether a MOAH mixture contains large amount of potentially toxic poly-aromatic species (three or more aromatic rings) or if it is a relatively non-toxic mixture of mono- and di-aromatic compounds. VUV spectra are also dependent on the alkylation, but the differences are much smaller as compared to compounds with different aromatic cores.

GC-VUV can sometimes be used to deconvolute spectra of similar co-eluting isomers [71], provided that their reference spectra are known and not too similar [74]. In principle, this could potentially be useful for isomers that are difficult to distinguish by MS [74]. However, for mixtures as complex as MOAH with many components with unknown spectra, VUV can only provide compound class information.

3.4. *Considerations for quantification*

In order to understand what toxicity effects MOAH present in foods might have on consumers, potentially toxic compounds do not only need to be identified but also quantified. As already mentioned, FID is the detector of choice for robust quantification of complex mixtures with only a few standards. However, FID is not particularly sensitive. As estimated by Biedermann et al. [15], a detectable hump in FID requires ~50 ng of MOSH/MOAH, which in turn requires injection of about ~100 mg food material to reach a target LOQ of 0.5 mg/kg (target LOQ for fat/oil samples).

The much greater sensitivity of MS, in combination with the sensitivity enhancement of GC × GC as compared to one-dimensional separations, would be of great benefit for trace analysis of MOAH. It could facilitate quantification not only of the MOAH fraction, but also less abundant sub-groups with different aromaticity. Reduced requirements on sample preparation and sample amount would also simplify the overall analysis procedure. However, in contrast to FID, quantitative MS requires an appropriate reference standard for every compound to make a calibration. Consequently, for a complex MOAH mixture making a robust calibration with MS very challenging.

There are examples of targeted quantitative MS analysis of polyaromatic hydrocarbon mixtures [75,76] with many compounds, but still nowhere close to the thousands of unknown compounds that can be present in MOAH mixtures. Jennerwein et al. [78] has described a GC × GC-MS approach for group-type quantification of petroleum middle distillates. According to the authors, it is possible to derive response functions that can be interpolated to obtain the response factor of compounds for which there is no standard available. In comparison to a standard HPLC method with refractive index detection (EN 12916), this approach gave similar results and a good precision. Based on this information, however, it is not clear whether a similar approach would achieve group-type quantification of MOAH as reliable as with HPLC-GC-FID. An additional problem is that isolated MOAH compounds that can be used as standards are unavailable. There are mineral oil certified reference materials, but these are also mixtures with a poorly characterized chemical composition. As pointed out by Lachenmeier et al. [77] (in the context of cosmetics rather than foods samples) MOAH analysis should be untargeted, as potentially toxic compounds from an unexpected contamination should not be overlooked. However, a much more feasible approach is to perform targeted quantification based on a combination of MOAH characterization and toxicological studies.

Another point of consideration is that MOAH quantification is likely to be complicated by peak overlap, even with multidimensional separations. In this case, one might consider using chemometric methods to resolve overlapping peaks. Now, the question is whether this is feasible for a very complex hydrocarbon mixture. Quantification of hydrocarbons in complex mixtures with the use of chemometric deconvolution has been demonstrated, for example Parastar et al. [76] have shown how polyaromatic hydrocarbons in a heavy fuel oil can be quantified with the help of multivariate curve resolution. However, this was a targeted analysis of only 10 compounds. A similar analysis of MOAH would also have to restrict itself to a few selected compounds, but as already discussed the selection of toxicologically relevant compounds is not trivial.

Aside from FID and MS, VUV could also be useful for compound class quantification. A group-type quantification can be done based on relative response factors for groups of compounds [72,79]. With this approach, VUV could perhaps be used to quantify MOAH sub-fractions of mono-, di-, and poly-aromatic species. It should be noted, however, that the relative response factor is an average for a large number of molecules that has to be determined from a reference with similar bulk properties as the analyzed sample. With this approach, the accuracy of a VUV-based group-type quantification will therefore depend on the similarity between the reference, from which relative response factors are determined, and the sample. Alternatively, Lelevic et al. [80] has described a methodology for determining relative response factors in complex mixtures. The methodology is said to be suitable for complex samples, although the test mixture with which this was demonstrated was much less complex than a mineral oil sample.

Quantitative data for MOSH/MOAH from comprehensive two-dimensional separations is rarely reported [25]. While interfering peaks or humps can be manually subtracted from one-dimensional chromatograms, data processing of 2D plots is more complicated. In Biedermann's analysis of sunflower oil [8], the integration was performed using a grid of second-dimension chromatograms with an interval of 5 min. The sharp peaks from interferences fell between the grid lines (and were therefore omitted), but this gave limited accuracy in the integration of the hump. With modern software it is possible to select a polygonal area for integration and easily subtract single peaks arising from interferences [28]. Using this approach, Purcaro et al. [28] obtained similar results for MOSH/MOAH content from Ag-SPE-GC × GC-FID and HPLC-GC-FID analysis. However, the commonly used algorithms have several flaws. Sdrigotti et al. [11] pointed out that they can be improved further to be more robust even with varying peak intensities arising from the interferences. Furthermore, 2D software often includes the area of the underlying hump when removing a peak [11, 25]. Ideally, peaks from interferences riding on the MOAH hump should be "trimmed" in the same way as in 1D GC-FID chromatograms. Bauwens et al. [25] developed an algorithm that performs this kind of trimming of interference peaks above the mineral oil hydrocarbon hump in a 2D plot. The algorithm also allows the analyst to evaluate the smoothing using extracted 1D chromatograms (Fig. 10) and can therefore rely in their expertise of interpreting 1D GC-FID chromatograms to also analyze 2D data. In short, this shows promise for accurate quantification from 2D GC × GC data. If combined with MS, this could be useful for both identification and quantification of specific groups of MOAH compounds, for example poly-aromatics, rather than the entire MOAH fraction.

3.5. Dual detection

It is evident that there is no one detector that is suitable both for quantification and identification with high enough sensitivity. While MS is well suited for detailed identification, it is not suitable for quantification of such a large number of unknown compounds. In other words, it is difficult to address both quantification and identification of MOAH with only one form of detection. If both reliable quantification and identification is to be done in one analysis, dual detection is probably the best approach.

There are already several examples of implementation of dual detection for MOSH/MOAH determination. Combining FID and MS

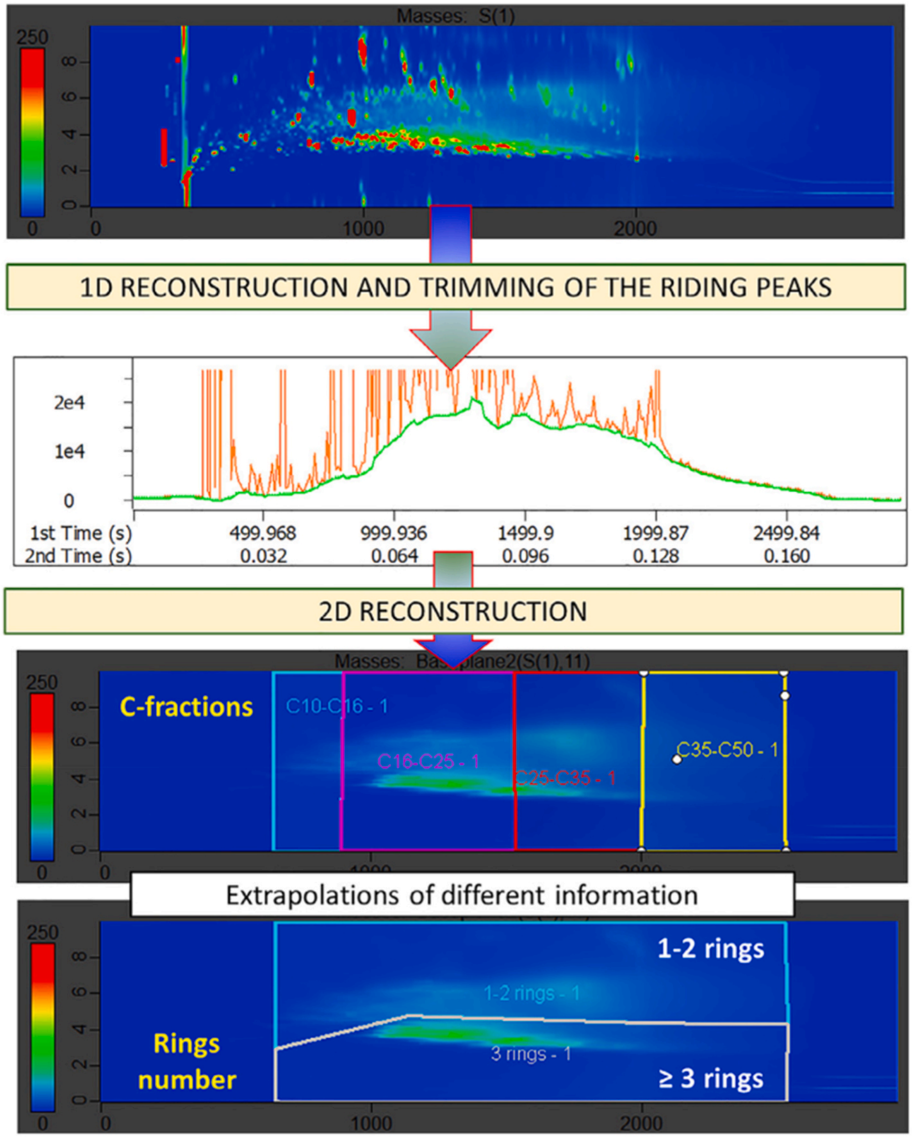

Fig. 10. Illustration of algorithm for trimming interference peaks on a mineral oil hydrocarbon hump in a 2D GC × GC plot. Figure obtained from Bauwens et al. [21] with permission.

allows simultaneous quantification and identification of MOSH/MOAH, as shown by Purcaro et al. [28], Bauwens et al. [25], and Zoccali et al. [35]. For a simpler analysis, FID and VUV can be combined to achieve quantification and information about aromaticity. García-Cicourel et al. [54] used SFC-FID/UV to deconvolute and quantify MOSH/MOAH fractions from mineral oils. In short, combination of detectors that provide complementary quantitative and molecular information would therefore be more useful than only one kind of detector and simpler than performing two different analyses in parallel.

4. Discussion and conclusions

In summary, this review has covered several aspects of MOAH characterization; chromatographic separation, and detection including identification as well as quantification. It should be noted that toxicological knowledge is still lacking, meaning that it remains unknown what performance in terms of LOD/LOQ is required in order to standardize any of these methods in the current situation, the focus should be on research to characterize MOAH and aid toxicological assessment.

To compare different approaches the methods need to be viewed in their entirety, from sample preparation to detection and data analysis. Table 1 summarizes the methods referenced in this work and highlights their strengths and weaknesses. It should be mentioned that although sample preparation was not covered in detail in this review, it is a critical part of an effective method. For all methods listed in Table 1, the sample matrix, especially the fat content, will affect how much can be injected for separation and subsequently what LOD/LOQ can be achieved.

Table 1 lists a number of quantitative as well as qualitative analysis techniques, as well as their performance parameters. For quantification, it is evident that there are several improvements that can be made to the standard HPLC-GC-FID method, to gain more information on the identity of the analytes. While FID remains the most suitable detector for straightforward quantification of the total MOAH content, dual detection with VUV could improve its reliability by aiding deconvolution of MOSH/MOAH in cases of overlap. This could help address issues related to uncertainties in the chromatogram interpretation. Alternatively, SFC-GC-FID/VUV could probably achieve similar results as HPLC-GC-FID/

Table 1

Summary of strengths, weaknesses, and analytical performance of the discussed analytical techniques for MOSH/MOAH characterization. Parameters that are not available in the literature are denoted with N/A. Note that the LOD/LOQ reported for most techniques is very much dependent on sample matrix. The higher the fat content, the more difficult it is to achieve lower LOD/LOQ.

Analytical method	Strengths	Weaknesses	Specificity	Precision	LOD	LOQ	References
HPLC-GC-FID	- Well-established quantitative method - Automated, fully hyphenated	- Difficulty achieving target LOQ - Extensive sample preparation - Chromatogram interpretation - Recognizing interferences	Poor	Uncertainty ~20%	0.1–1 mg/kg	0.25–2 mg/kg	[14–18]
GC-VUV	- Group-type calibration possible, if done correctly - Deconvolution MOSH/MOAH	- VUV not as sensitive or robust as FID - Interferences not deconvoluted - Lack of LC pre-separation increases demands on sample preparation	Compound class	RSD <8%	0.02 mg/mL	0.06 mg/mL	[72]
GC × GC-MS[a]	- Mature technology - Separation of MOAH by ring number and alkylation - Identification with determination of ring and alkylation carbon number - Distinguish interferences - Sensitivity of MS	- Lacking interlaboratory-validation - Not always clear group separation - MS identification still a challenge - Group-type calibration for quantification not possible for large number of unknown compounds	High	N/A	N/A	N/A	[8]
GC × GC-FID/MS[a]	- Dual detection facilitates quantification and identification in one analysis	- Lacking interlaboratory-validation - Not always clear group separation - MS identification still a challenge	High	N/A	~0.2 mg/kg	N/A	[36–38]
LC × GC-FID/VUV	- Clear group-type separation - Quantification of MOAH sub-fractions	- More overlap within groups - Hyphenation not easy, offline or stop-flow	Compound class	N/A	N/A	N/A	[45]
LC × GC-MS	- Clear group-type separation	- More overlap within groups, which could complicate detailed MS analysis - Hyphenation not easy, offline or stop-flow	Compound class	N/A	N/A	N/A	[44]
Multidimensional LC pre-separation[b]	- Separation of MOAH sub-fractions based on aromaticity - Can facilitate both quantification and identification of MOAH sub-fractions in more detail	- Many separation steps, complicated workflow with offline transfer - Risk of sample loss, sample dilution	High	Uncertainty ~20%	N/A	10 mg/kg	[50]
SFC-GC-FID	- Quantitative method - Easier hyphenation than LC-GC	- Similar as LC-GC-FID	Compound class	N/A	N/A	N/A	[42,53]
SFC-FID/UV	- Simple quantitative method - Dual detection facilitates deconvolution MOSH/MOAH and reliable quantification	- Extensive sample preparation may still needed (depending on the sample)	Poor	Repeatability <5%	0.36% MOAH	1.20% MOAH	[53]
SFC × SFC-FID	- More control over selectivity compared to GC × GC - Compatibility with FID and MS	- Instrumentation not commercially available - Not certain how well MOAH would be separated by ring number and alkylation, confirmation by MS needed	High[c]	N/A	N/A	N/A	[55,58]

[a] Both GC × GC-MS and GC × GC-FID/MS require pre-separation of MOSH/MOAH. Fully hyphenated LC-GC × GC is feasible.

[b] Multidimensional LC separation followed by LC-GC-FID for quantitative analysis and GC × GC-MS for identification of different fractions (total MOAH, mono/di-aromatic, tri/poly-aromatic).

[c] Needs to be confirmed with MS detection.

VUV, but on the other hand HPLC is probably an easier choice for many laboratories lacking SFC expertise.

When it comes to qualitative MOAH characterization, two general approaches can be identified: either aiming to maximize separation between all compounds with GC × GC or opting for a group-type analysis with less separation within groups using LC × GC. In both cases, MS is the best detection method, providing the most structural information and the most sensitivity compared to, for example, spectroscopic alternatives. Which approach is the best depends on whether the goal is a detailed characterization (perhaps with identification of specific compounds), or a group-type analysis. A detailed analysis with identification of specific compounds is of course ideal for understanding their toxicity, but also has its limitations. In a mixture as complex as mineral oil, identification of single compounds is exceedingly difficult. As a result, the analyst is forced to limit themselves to relatively few compounds of interest out of the many thousands that can be present in the sample. As pointed out by Lachenmeier et al. [77], being too focused on a few specific compounds can cause the analyst to overlook other toxicologically relevant components of the sample. Therefore, the choice of compounds for a targeted quantitative analysis should be well-informed and based on toxicological knowledge.

As stated in many other recommendations, HPLC-GC × GC-MS shows the most promise for a characterization of MOAH. It can usually provide a good separation that facilitates determination of ring number and degree of alkylation, which is more useful for the purpose of improving our understanding of MOAH toxicity than a clear group separation. Furthermore, several improvements (as detailed below) can be made to the HPLC-GC × GC-MS approach that may facilitate even more detailed MOAH characterization.

In cases when HPLC-GC × GC-MS does not achieve sufficient separation of MOAH, this can be addressed using multiple LC preseparations, further fractionating MOAH into mono-, di-, tri-, and poly-aromatics. Following this fractionation, the GC × GC separations can be optimized to maximize the use of separation space for each compound group. This could further resolve previously overlapping compounds and perhaps facilitate identification of specific compounds, not only ring number and degree of alkylation but also different aromatic cores and types of alkyl chains. However, the downside of this approach is that it is a complicated multi-step procedure that is difficult to automate and may suffer from sample losses and dilution with each fractionation. Method development may prove challenging if each fractionation and GC × GC separation of each fraction are to be optimized. One should also keep in mind that even with this kind of analysis some samples may require extensive preparation to remove fats and enrich the MOAH. Furthermore, an increased separation alone does not necessarily facilitate reliable identification, but there is also room for improvement in the MS analysis.

A standard GC × GC-MS analysis with EI can provide ring number and alkylation, as well as some information about the structure, but has several shortcomings (see Section 3.2). Implementing softer atmospheric ionization techniques (such as APCI, APPI, APLI) in combination with a tandem MS fragmentation spectrum would facilitate a more reliable identification as compared to a simple EI spectrum (possibly with overlap) or selection of a fragment ion. Further research is needed to determine to what extent different MOAH isomers can be distinguished (e.g., type of aromatic core, different alkylation patterns) with tandem MS data. However, accurate identification will remain challenging without MS reference spectra for many MOAH compounds.

SFC × SFC-MS should also be highlighted as a potentially powerful technique for MOAH characterization. The work of Guibal et al. [55] and Petkovic et al. [58] provides a good foundation, but the ability of SFC × SFC to separate MOAH should be explored further with MS detection. In any case, it will take time before any form of SFC becomes widely adopted for MOSH/MOAH determination, because LC- and GC-based techniques are often a more feasible alternative for laboratories that lack SFC instrumentation and/or expertise.

In short, GC × GC-MS with multiple LC fractionations is the most promising approach to detailed MOAH characterization. Although it is unlikely to become a standard interlaboratory-validated MOAH characterization technique, it can be especially useful for research purposes when the time and expertise required for method development and analysis is available. For routine confirmatory analysis of MOAH, HPLC-GC × GC-MS is the best candidate, especially considering that completely automated systems have been developed [25,35,36,38–41,81]. With implementation of atmospheric pressure ionization and tandem MS, it could become more reliable than current GC × GC-MS methods with EI. Ideally, there will also be efforts to perform an interlaboratory-validation of a HPLC-GC × GC-MS method to standardize MOAH characterization.

In conclusion, this review has explored the future prospects of analysis of mineral oil hydrocarbons in foods, showing that there are several alternatives to current standard HPLC-GC-FID and GC × GC-MS methods, both in terms of separation and detection, that could be explored further. MOAH characterization is an excellent example an application where the power of orthogonal multidimensional separations becomes useful for detailed analysis of complex mixtures. Recommendations for MOAH characterization (multiple pre-fractionations prior to GC × GC-MS, adjustments to MS analysis) and improved quantitative analysis (dual detection, SFC alternative to LC) have been given. Hopefully, this work can provide some guidance to further method development that will contribute to our understanding of MOAH toxicity and address current knowledge gaps.

Declaration of competing interest

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

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