Green Analytical Chemistry 4 (2023) 100047

Contents lists available at ScienceDirect

Green Analytical Chemistry

journal homepage: www.elsevier.com/locate/greeac

Validation of the liquid chromatography-comprehensive multidimensional gas chromatography-time-of-flight mass spectrometer/flame ionization detector platform for mineral oil analysis exploiting interlaboratory comparison data

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ARTICLE INFO

Keywords:
Mineral oil hydrocarbons
LC-GC-FID
LC-GC × GC-ToFMS/FID
Vegetable oils
Infant formula
Interlaboratory comparison (ILC)

ABSTRACT

Mineral oils, classified into two main fractions, namely saturated (MOSH) and aromatic hydrocarbons (MOAH), originate from petroleum. Their determination in food is challenging due to the difficulty of isolating them from the matrix and the presence of natural interferences, leading to low reproducibility of the results among different laboratories. Therefore, standardized procedures are highly required to minimize the uncertainty caused by various sources (e.g., integration, interference removal, etc.). However, at present, a few sample preparation procedures have been standardized, while the analytical determination is mainly performed using the hyphenated liquid-gas chromatographic technique coupled with a flame ionization detector (LC-GC-FID). However, LC-GC-FID is still not enough for confirmatory purposes, for which the use of comprehensive 2D GC (GC × GC) has been suggested. Recently, the use of a fully integrated platform for routine and confirmatory purposes has been proposed by Bauwens and co-workers (2022), namely LC-GC × GC-time-of-flight mass spectrometer (ToFMS)/FID.

The aim of this work is to validate the quantification of MOSH and MOAH performed by LC-GC × GC-FID supported by the use of a recently developed integration software. The validation was performed by taking advantage of the participation in several recently organized interlaboratory comparisons organized by the Joint Research Center (to harmonize and validate the method for the determination of MOAH in infant formula products) and by the German Society for Fat Science and the French Technical Institute for the Study and Research of Fats (to improve the standardized European method for MOSH and MOAH in fats, i.e. EN 16995:2017). Data obtained by using LC-GC × GC-FID were in good agreement with those from the ILCs, in terms of recovery, precision, accuracy, and repeatability.

1. Introduction

Mineral oil hydrocarbons (MOH) are complex mixtures consisting of two main classes: I) open-chain, straight and branched alkanes (paraffin), and predominantly alkylated (naphthenes) cycloalkanes, collectively termed MOSH, and II) mostly alkylated aromatic hydrocarbons, termed MOAH. The potential impact of MOH on human health varies widely depending on their composition. In particular, MOSH can accumulate in human tissues and may cause adverse effects in the liver, while MOAH, specifically those with 3–7 aromatic rings, can act as genotoxic carcinogens [1–4].

MOH can enter the food production chain through different routes, such as environmental contamination, industrial food manufacturing, and processing or via transfer from food contact materials [1,2,5,6]. The greatest concern is when unrefined or partially refined mineral oil fractions, thus containing also MOAH, enter the production chain through non-intentional use [1,2,7–10].

The method of choice for MOH analysis in food is a hyphenated liquid chromatographic (LC)-gas chromatographic (GC) system coupled with a flame ionization detector (FID). The method was proposed by Biedermann et al. in 2009 [11] and successively updated until its implementation as the reference method for detecting and quantifying mineral oils in routine analysis [7,12,13]. Nevertheless, using a universal detector, such as the FID, requires the introduction of highly purified fractions for reliable quantification, thus, the removal of the possible interferences is of utmost importance. For this reason, a rather extensive sample preparation step is often required to enrich the extract (e.g., saponification) and remove interferent compounds (e.g., epoxidation or

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https://doi.org/10.1016/j.greeac.2022.100047
Received 19 October 2022; Received in revised form 11 November 2022; Accepted 6 December 2022

purification on aluminum oxide). Such procedures allow for lowering the level of detection/quantification, but at the same time, the extensive manipulation contributes to an increase in the blank level, and the relatively high variability among results from different laboratories [2,14]. The FID is the detector of choice for quantitation, however, it does not provide any confirmatory information, thus weakening the overall outcome of the analysis [15]. To tackle the issue related to the lack of confirmatory information, in 2019 the European Food Safety Authority (EFSA) proposed using GC × GC [16]. Moreover, on top of the analytical challenges, a major source of uncertainty derives from chromatogram interpretation and integration, estimated at around 20% [2,7,8,15–18].

More recently, a unified LC-GC × GC- time-of-flight (ToF)MS/FID platform to perform both routine and confirmatory interpretation in a single analysis has been proposed, along with a dedicated software able to address the particular requirements of MOSH and MOAH integration in two-dimensional (2D) separation [17,19]. The advantages of the 2D separation in terms of chromatographic removal of some interfering peaks, thus providing a more straightforward interpretation, more robust results, accurate quantification, and deeper characterization of the contamination was shown [17].

The aim of this work is to validate the 2D platform for routine analysis, taking advantage of the participation in two interlaboratory comparisons (ILCs). Data using the LC-GC × GC-FID platform was generated on a side and are now compared with the outcomes of the ILCs. The first ILC has been organized by the Joint Research Center (JRC) (referred to as JRC-ILC from now on) in the attempt to harmonize and validate the method for the determination of MOAH content in infant formula (IF) products [20,21]. This action followed the request of the Directorate General for Health and Food Safety (DG SANTE) of the European Commission, after the Rapid Alert System for Food and Feed (RASFF) and the Foodwatch report publication on contaminated IF [22]. At the same time, the German Society for Fat Science (DGF) and the French Technical Institute for the Study and Research of Fats (ITERG) has organized a second ILC (called DGF-ILC from now on) to modify the only available standardized European method (EN 16995:2017, MOSH and MOAH in oils and vegetable fats) [23] to lower the limit of quantification.

2. Material and methods

2.1. Reagents and standards

The MOSH and MOAH internal standards (IS), containing 5-α-cholestane (Cho, 0.6 mg/mL), *n*-C11 (0.3 mg/mL), *n*-C13 (0.15 mg/mL), cyclohexyl cyclohexane (CyCy, 0.3 mg/mL), *n*-pentyl benzene (5B, 0.30 mg/mL), 1-methyl naphthalene (1-MN, 0.30 mg/mL), 2-methylnaphthalene (2-MN, 0.30 mg/mL), tri-tert-butyl benzene (TBB, 0.3 mg/mL) and perylene (Per, 0.6 mg/mL) in toluene, and the MOSH/MOAH retention time standard, containing a standard mixture of *n*-alkanes (C_{10}, C_{11}, C_{13}, C_{16}, C_{20}, C_{24}, C_{25}, C_{35}, C_{40}, and C_{50}), at 50 mg/L each, were kindly provided by Restek (Neukirchen-Vlun, Germany).

Meta-chloroperoxybenzoic acid (mCBPA), aluminum oxide, sodium thiosulfate ($Na_2S_2O_3$), sodium carbonate (Na_2CO_3), sodium sulfate (Na_2SO_4), potassium hydroxide (KOH), ethanol, *n*-hexane, dichloromethane (DCM) were all from Merck-MilliporeSigma (Overijse, Belgium). All solvents were HPLC-grade. Milli-Q water was obtained by the Milli-Q Advantage water purification system (Merck Millipore, Darmstadt, Germany). The glassware was carefully washed and rinsed before use with distilled solvents (acetone and *n*-hexane).

2.2. Samples

A solution of the Shell SN500 mineral oil (high viscosity base oil, Lot number ID 878,338, used to spike some IF samples) at 2.024 g/L in *n*-hexane was provided by JRC, as part of the JRC-ILC. It was sampled directly as a distillation fraction in an oil refinery to obtain a mineral oil product with a large percentage of high molecular weight MOAH.

JRC-ILC: 15 IF powder samples were provided by the European Union Reference Laboratory for Food Contact Materials (EURL-FCM), which organized a collaborative trial study for method validation of the standard operating procedure (SOP, described in Section 2.3.2) drafted by JRC for MOAH determination.

DGF-ILC: for the participation to the DGF-ILC for the revision of EN 16995:2017, ITERG provided the SOP (see Section 2.3.3) and the samples. Eight samples of vegetable oil consisting of refined grapeseed oil (RGO), refined palm olein (RPO), virgin coconut oil (VCO), refined rapeseed oil (RRO), extra virgin olive oil (EVO), spiked cold pressed rapeseed oil (SRO, 7 mg/kg of Gravex 913, mineral oil consisting of 70% MOSH and 30% MOAH), spiked refined sunflower oil (SSO,18 mg/kg of base oil T22), spiked virgin coconut oil (SCO, 5 mg/kg of Gravex 913) were provided with blind replicates of each, for a total of 16 samples to be analyzed in single.

2.3. Sample preparation

All the sample preparation procedures herein summarized follow the detailed SOPs provided by the ILCs' organizers.

2.3.1. Mineral oil Shell SN500

The Shell SN500 mineral oil solution in *n*-hexane (2.024 g/L) was analyzed after dilution to obtain four different MOH concentrations (10.1, 20.2, 60.7, and 202.4 mg/L) [24].

2.3.2. Infant formula samples

IF powder samples were prepared according to the SOP proposed by JRC [25]. Briefly, around 5.0 g of IF powder were reconstituted with 10 mL of milli-Q water pre-warmed at 35 °C, added with 10 μL of IS, and vigorously shaken. Samples were then saponified at 60 °C for at least 30 min and extracted with two aliquots of 15 mL of *n*-hexane. The combined *n*-hexane extracts were washed with 15 mL ethanol/water (1/1, *v/v*) and evaporated to approximately 2 mL.

To remove any remaining lipids after the saponification, sample extracts were purified on a glass column filled with activated silica and Na_2SO_4 on the top. The fraction of interest was collected by eluting 14 mL of DCM. The eluate was then evaporated to around 1 mL and subjected to epoxidation performed by adding mCPBA and shaking intensely for 15 min at 40 °C. The upper phase was recovered and washed with water/ethanol (1/1, *v/v*). The water phase was discarded, and the organic phase was dried with Na_2SO_4, concentrated to 300–500 μL, and injected (50 μL) into the system.

2.3.3. Vegetable oils

The different vegetable oils were analyzed according to the EN 16995 procedure, recently revised [26] and based on the published DGF method [27]. Briefly, 3 g of sample were homogenized with 30 mL of *n*-hexane/ethanol (1/1, *v/v*) along with 20 μL of IS. After 30 min at 60 °C, 10 mL of the upper phase was taken and subjected to saponification for 30 min at 60 °C followed by a double extraction, each with 5 mL of *n*-hexane. The combined extracts were then treated with different purification procedures depending on the fraction (MOSH or MOAH) analyzed. In particular, the MOSH fraction was obtained by purifying the *n*-hexane extract on a glass column filled with a stationary phase consisting of aluminum oxide (10 g), activated silica (3 g), and Na_2SO_4 (1 g). The fraction of interest was collected by eluting 25 mL of *n*-hexane. The MOAH fraction was obtained after extract purification on a glass cartridge filled with a stationary phase consisting of activated silica (3 g) and Na_2SO_4 (1 g). Elution was performed with 15 mL of *n*-hexane/DCM (70/30, *v/v*).

Both the MOSH and MOAH eluates were evaporated under vacuum at 35 °C and the residue was dissolved into 1 mL of *n*-hexane. While MOSH fraction was directly injected (75 μL) into the instrument, MOAH

was subjected to epoxidation, performed by adding mCPBA and stirring for 20 min at 40 °C. After an intense shaking, the organic phase was recovered, dried with Na_2SO_4, and injected (75 μL) into the platform.

2.4. LC-GC × GC-ToFMS/FID analysis

2.4.1. Instrument setting and operating conditions

All the analyses were carried out in a fully integrated LC-GC × GC-ToFMS/FID platform, schematized and described in detail in ref. [19], consisting of an Agilent 1260 Infinity II LC equipped with an isocratic pump G7110B (modified by Axel-Semrau to minimize the dead volumes) and a variable wavelength detector acquiring at 230 nm (Agilent Technologies, Waldbronn, Germany). The GC and GC × GC system consisted of a Pegasus BT 4D GC × GC ToFMS (LECO, St. Joseph, MI, USA) comprising an Agilent 7890A gas chromatograph equipped with a secondary oven, and a quad-jet dual-stage thermal modulator, a ToFMS and a FID detector.

A 250 mm × 2.1 mm i.d. × 5 μm d_p Allure silica HPLC column (Restek, Neukirchen-Vlun, Germany) was used for purification and MOSH and MOAH separation. The two fractions were transferred simultaneously into two parallel 10 m × 0.53 mm retention gap (siltek-treated retention gap from Restek, Neukirchen-Vlun, Germany) connected to an early solvent vapor exit (SVE) before the two sets of analytical columns. Both lines (to the FID and the MS) were equipped with a MXT-1 column (non-polar) of 15 m × 0.25 mm i.d. × 0.1 μm d_f (Restek, Neukirchen-Vlun, Germany) connected to a Select PAH column (mid-polar) of 0.9 m × 0.15 mm i.d. × 0.10 μm d_f. (Agilent Technologies, Waldbronn, Germany). Both secondary columns were located in a single cryogenic modulator and a single secondary oven. For all the details on method conditions the readers are directed to ref. [19].

2.4.2. Data processing and statistical elaboration

Data were acquired and elaborated using the ChromaTOF software (v5.54) for MOSH/MOAH. The hump originating from the MOSH and MOAH contamination was integrated over the C_{10}-C_{50} – carbon range or beyond if required by the specific SOP. The blank subtraction in FID and the trimming of the peaks riding on top of the humps were automatically performed by the software, according to the procedure detailed in ref. [17]. Quantification was performed using the internal standard method: CyCy for the MOSH and both TBB and 2-MN for the MOAH.

3. Results and discussion

As aforementioned in the introduction, several ILCs have been organized since 2020 to harmonize the methods used for MOH analysis, particularly those related to IF and edible oils. Our laboratory participated in these ILCs, providing LC-GC-FID data, as requested by the specific SOPs, and simultaneously acquiring the data using the LC-GC × GC-ToFMS/FID platform. The final elaboration was performed once the software capable of adequately handling the 2D integration [17] had been available, and thus the results were compared with the outcomes of the JRC-ILCs and DGF-ILC [26,28]. From here on in the text, data resulting from the ILCs will be referred to as 1D ILC, and data obtained with the LC-GC × GC-FID platform as 2D.

3.1. LC-GC × GC-FID instrumental validation through the mineral oil shell SN500 JRC-ILC

In 2020 the JRC organized two preliminary ILCs [20,21] to optimize a SOP for MOAH analysis in IF. From these initial trials, besides the need to improve the sample preparation method, emerged the necessity to standardize the integration of the chromatographic hump [29] and to evaluate the instrumental performance. To assess this latter evaluation a pure mineral oil, namely Shell SN500, was provided to all the participants [24]. The sample was delivered in a stock solution diluted in hexane (2.024 g/L) [25] and a simple dilution in *n*-hexane was required to obtain four different concentrations, namely 10.1, 20.2, 60.7, and 202.4 mg/L, before injection into the analytical instrument. Since no sample preparation, other than a simple dilution, was required and considering the absence of interferents, the parameters assessed by this trial were the baseline interpretation, the ISs quantification, and the analytical instrument performance. Evaluating the overall results, the JRC set specific performance to validate the analytical instrument, namely an RSD% smaller than 5% and recovery of the sum of MOSH and MOAH between 92 and 100%. Only six out of 30 participants reported consistent results for the various dilutions. Highly scattered results at low concentrations were provided by most laboratories. Data obtained by using the LC-GC × GC-FID platform showed a C_{50}/C_{20} ratio equal to 0.85, indicating no losses and discrimination during the transfer of the fraction from the LC into the GC, or modulation problems that may cause poor release of the high boiling compounds or poor trapping of the lighter one. The average recovery of the four calibration solutions in the C_{10}-C_{50} range was 98.2% (99.1% for the highest concentration considering the entire hump beyond C_{50}) with a 2.5% of RSD%, fully satisfying the JRC requirements, as pinpointed in **Fig. 1-A**, where the expansion relative to the laboratories that met the performance requirements is reported. The results obtained with the LC-GC × GC-FID showed the highest recovery. The comparison between the 1D ILC approach (data reported in the *x*-axis) and the 2D platform (data reported in the *y*-axis) is reported in **Fig. 1-B**, where the two sets of measurements are plotted along with the theoretical amounts (red line). The coefficient of correlation (R^2=0.9982) indicates that the two approaches are in a positive linear relationship. Furthermore, the two measurement methods are in agreement being the slope of the tendency line very close to 1 (0.97), indicating, therefore, a proper operation of the 2D platform and the integration software.

As an additional goal of the ILC, there was the characterization of the MOSH/MOAH composition of the Shell SN500 mineral oil solution in view of its use to spike different samples of IF for the following ILC. Based on the six best-performing laboratories, the JRC report concluded that the relative composition of the Shell SN500 oil was 60.1 ± 2.1% of MOSH and 34.5 ± 1.2% of MOAH, considering the C_{10}-C_{50} range. The composition calculated with the LC-GC × GC-FID platform was not significantly different (p>0.05), being 62.1 ± 2.7% of MOSH and 36.1 ± 0.8% of MOAH. Details on the distribution of the C-fractions calculated by the different laboratories are reported in **Fig. 2**.

3.2. LC-GC × GC-FID validation on real case samples

3.2.1. Infant formula samples analysis: JRC-ILC

After the evaluation of platform performances by analyzing mineral oil solution in *n*-hexane, an additional ILC was organized to validate the SOP for the analysis of MOAH in IF. In this context, 15 powder IF samples provided by the JRC were analyzed by using the 2D platform.

A comparison of 1D ILC [28] and 2D data is reported in **Table 1**. In particular, MOSH (quantified by using CyCy) and MOAH (quantified by using 2-MN) content, expressed in mg/kg, the standard deviation of repeatability (SD_r) and reproducibility (SD_R), the percentage relative standard deviation of repeatability (RSD_r) and reproducibility (RSD_R), the limit of reproducibility (R), z-score, the absolute difference between the 1D ILC and the 2D mean measured values (Δ_m), the expanded uncertainty (U_Δ) related to 1D data and the TBB/2-MN ratio for the MOAH fraction are reported. The 32 laboratories participating in the ILC were required to provide all the data in duplicate. After outliers removal, a total of about 50 replicates were retained for each sample. The 2D mean values were derived from two replicates analysis (n=2), except for the MOAH fraction of sample IF-01, for which only the value of a single analysis is available (indicated with a * in the table).

Although the main focus of the ILC was the determination of the MOAH, the MOSH fraction, whose separation (offline or online) is described in the SOP, was taken into consideration during the ILC outcome

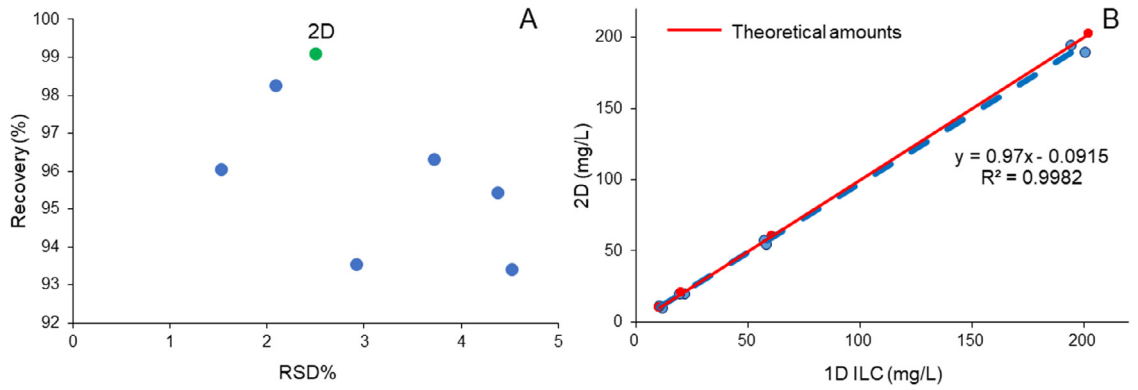

Fig. 1. A) Representation of six results that satisfy JRC requirements in terms of recovery% (y-axis) and RSD% (x-axis). 2D label on a green dot identifies the results obtained using the LC-GC × GC-FID platform. **B)** Comparison between data (sum of MOSH and MOAH) obtained from 1D ILC (x-axis) and measured by using the LC-GC × GC-FID platform (y-axis) for the four Shell SN500 diluted solutions. The red line corresponds to theoretical amounts.

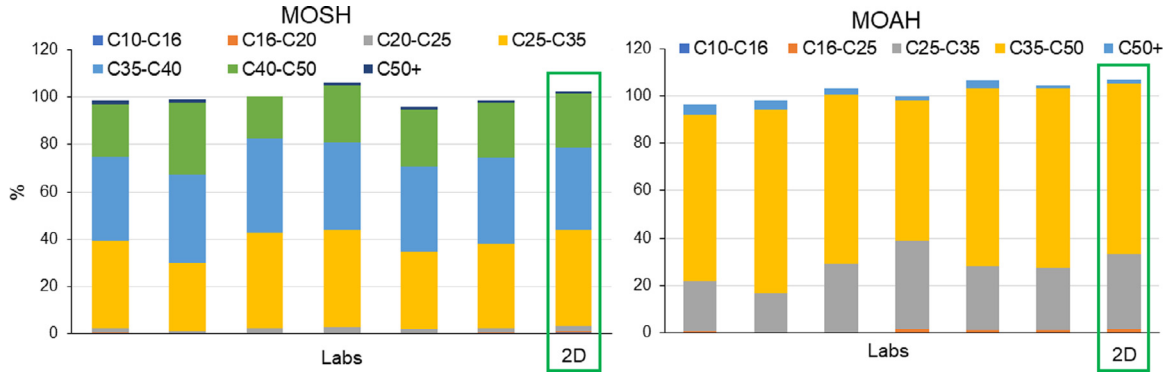

Fig. 2. MOSH and MOAH fractions distribution in the C_{10}-C_{50} range for the Shell SN500 mineral oil. Data as reported by the 6 best-performing laboratories in the JRC-ILC in comparison with the data obtained using the LC-GC × GC-FID platform (2D).

discussion [28]. MOSH content of the 15 IF samples varied from about 5.0 to 19.0 mg/kg, with an RSD_r% below 10% and an RSD_R% in the 13–27% range (average 21%). The MOAH content estimated by 1D ILC data varied from about 0.4 to 5.3 mg/kg, by using 2-MN as IS, with an RSD_r% in the 6–22% range (average of 9.5%) and an RSD_R% in the 13–66% range (average around 28%). During the discussion of the outcomes of the ILC, it emerged that MOAH quantification by using TBB (data not showed) as IS systematically underestimated the MOAH content compared with the quantification by using 2-MN, nevertheless, the difference has not been proven to be significant [28]. The same situation occurred during 2D quantification of the MOAH fractions (MOAH obtained by using TBB as IS are reported in **Supplementary materials - Table S1**), obtaining a TBB/2-MN ratio within the 1.02–1.15 range for all samples. This variability range is within the intermediate precision required by the JRC Guidance published in 2019 [18], which requires a value below 20% or 15% according to the fat content of the food analyzed.

The reproducibility of the results provided by the LC-GC × GC-FID was assessed by comparing the absolute difference between 1D ILC and 2D mean measured values (Δ_m) and the reproducibility limit (R) reported in the ILC results [28] (**Fig. 3A and B**). The reproducibility limit is the value less than or equal to which the absolute difference between two test results obtained under reproducibility conditions may be expected to be with a probability of 95% [30]. In all samples and for both MOSH and MOAH fractions, the maximum acceptable difference set by R was always largely respected. To evaluate the LC-GC × GC-FID method performance, Δ_m was also compared with the respective expanded uncertainty (U_Δ) [31]. In all cases, there is no significant difference between the two measurements since Δ_m is lower than U_Δ, indicating that 2D results perfectly agree with 1D ILC data, taken as reference values. This concept is graphically represented in **Fig. 3C and D**, in which the 2D mean results (green dots) and the 1D ILC values (red dots) are plotted along with the expanded uncertainty (U_Δ) (vertical bars).

Just as a final estimation, the z-score for the 2D results was calculated, obtaining all values between 1 and −1, suggesting a low data dispersion and a high precision (**Table 1**). Nevertheless, it needs to be emphasized that the assigned value is the best available estimate of the true quantity value, but an assumption underlying the z-score is that the uncertainty of the assigned value is negligible [32], a condition not fulfilled in this case where the RSD_R reached values of 66%.

Although the topic of this article is the validation of the LC-GC × GC platform in terms of MOSH and MOAH quantification (using the FID), the complete platform is equipped with a parallel MS detector which allows for a more in-depth investigation of the qualitative composition of the fractions of interest. As an example, the 1D chromatogram of the MOAH fraction of the IF-06 sample along with the 2D plot is reported in **Fig. 4**. Due to the enhanced separation power, the fully integrated LC-GC × GC-ToFMS/FID plots provided a series of additional information compared to 1D chromatograms. Furthermore, the improved separation between the interferents and the MOAH cloud facilitates integration, minimizing the need for extensive interpretation of the chromatogram by the operator. In the same way, the bleeding is not interfering with MOSH or MOAH quantification as it is chromatographically separated [16]. The non-polar × mid-polar GC column set emphasizes the separation of MOAH [33], with a spatial distribution accordingly to the number of aromatic rings, as the retention in the second

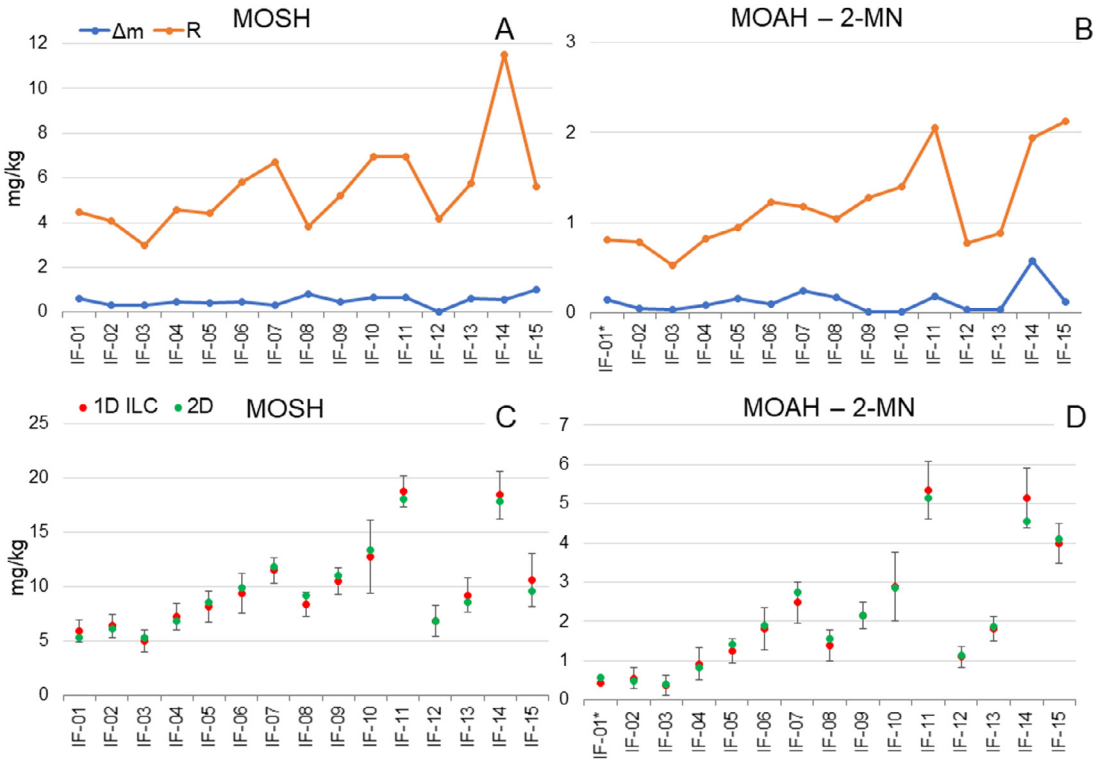

Fig. 3. A-B) Graphical representation of the absolute difference between 1D ILC and 2D mean measured values (Δ_m) and the limit of reproducibility (R) reported in the ILC results. **C-D)** Graphical comparison between the 1D ILC values (red dots) and the 2D average results (green dots). Vertical bars represent the expanded uncertainty (U_Δ). *2D value obtained from a single analysis.

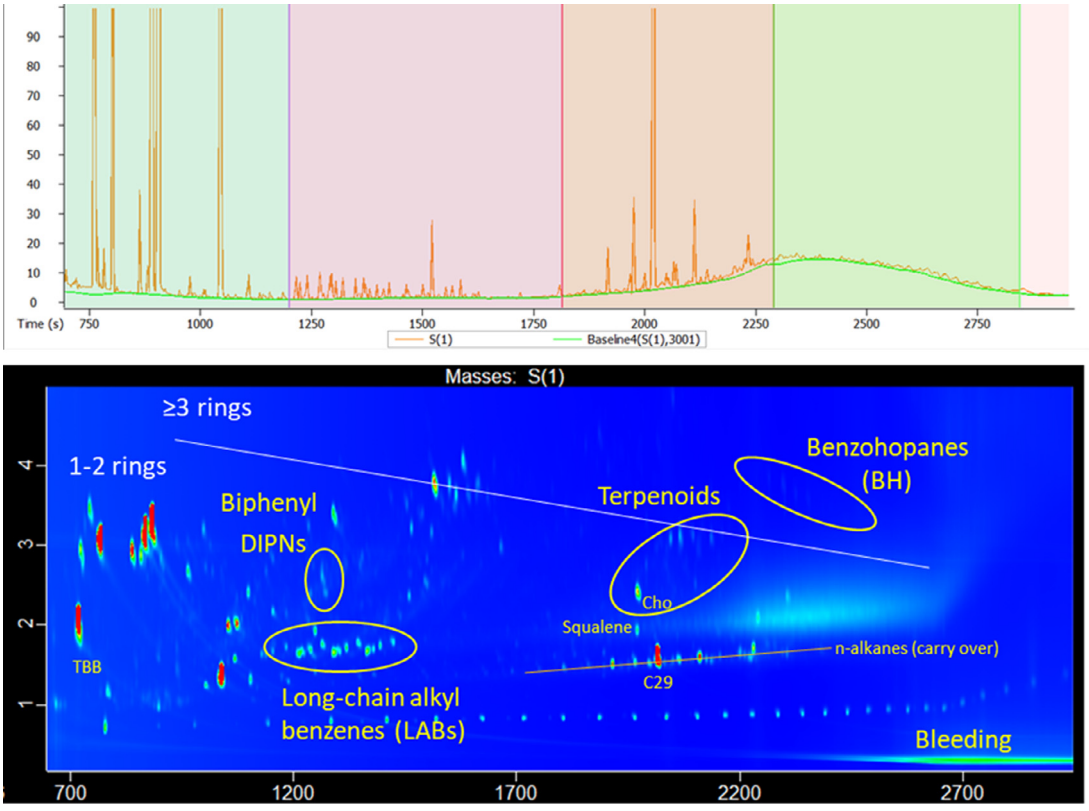

Fig. 4. 1D and 2D plots for the MOAH fraction of the IF-06 sample obtained by using the LC-GC × GC-ToFMS/FID platform.

Table 1
Comparison between the MOSH (upper table) and MOAH (bottom table) data resulting from the JRC-ILC (1D) [28] and those obtained using the LC-GC × GC-FID platform (2D).

Sample ID	1D ILC Average (mg/kg)	SD_r	RSD_r%	SD_R	RSD_R%	R	2D Average (mg/kg)	SD_r	RSD_r%	z-score	Δ_m	U_Δ	TBB/2-MN
MOSH - CyCy													
IF-01	5.90	0.45	7.7	1.60	27.1	4.48	5.30	0.28	5.3	−0.37	0.60	0.99	
IF-02	6.41	0.41	6.3	1.47	22.9	4.07	6.12	0.47	7.7	−0.2	0.29	1.06	
IF-03	4.97	0.35	7.1	1.07	21.6	2.97	5.28	0.53	10.1	0.28	0.30	1.03	
IF-04	7.24	0.47	6.5	1.63	22.6	4.57	6.81	0.53	10.1	−0.27	0.43	1.20	
IF-05	8.13	0.54	6.7	1.58	19.4	4.42	8.53	0.63	7.4	0.25	0.40	1.41	
IF-06	9.37	0.89	9.5	2.08	22.2	5.81	9.84	0.26	2.7	0.23	0.47	1.82	
IF-07	11.50	0.60	5.1	2.40	21	6.70	11.80	0.10	0.6	0.13	0.30	1.20	
IF-08	8.32	0.53	6.4	1.37	16.5	3.85	9.14	0.23	2.5	0.60	0.82	1.11	
IF-09	10.50	0.60	5.5	1.90	17.7	5.20	11.00	0.20	2.1	0.24	0.50	1.20	
IF-10	12.70	0.80	6.5	2.50	19.8	6.90	13.4	2.10	15.5	0.27	0.70	3.40	
IF-11	18.70	0.70	3.5	2.50	13.1	6.90	18.10	0.40	2.4	−0.27	0.70	1.40	
IF-12	6.83	0.67	9.8	1.49	21.8	4.18	6.86	0.30	4.4	0.02	0.03	1.41	
IF-13	9.20	0.75	8.2	2.06	22.4	5.77	8.58	0.39	4.6	−0.3	0.62	1.60	
IF-14	18.40	0.90	5.1	4.10	22.4	11.50	17.9	0.80	4.4	−0.14	0.60	2.20	
IF-15	10.60	0.50	5.1	2.00	18.9	5.60	9.60	1.57	16.4	−0.51	1.01	2.47	
MOAH - 2-MN													
IF-01	0.44	0.07	16.7	0.29	65.5	0.81	0.58*				1.14		1.1
IF-02	0.55	0.12	22.3	0.29	51.7	0.79	0.5	0.09	18.0	−0.18	0.05	0.28	1.03
IF-03	0.37	0.03	9.0	0.19	51.1	0.53	0.4	0.17	42.8	0.17	0.03	0.25	1.13
IF-04	0.92	0.08	8.1	0.29	32.0	0.82	0.83	0.27	32.4	−0.3	0.09	0.41	1.15
IF-05	1.26	0.11	9.1	0.34	27.1	0.95	1.42	0.15	10.5	0.47	0.16	0.3	1.13
IF-06	1.81	0.23	12.8	0.44	24.3	1.23	1.9	0.2	10.3	0.22	0.1	0.54	1.09
IF-07	2.49	0.18	7.3	0.42	16.9	1.18	2.74	0.27	9.8	0.6	0.25	0.52	1.14
IF-08	1.38	0.13	9.8	0.37	27.1	1.05	1.55	0.21	13.7	0.45	0.17	0.4	1.09
IF-09	2.15	0.12	5.7	0.46	21.3	1.28	2.16	0.18	8.4	0.02	0.01	0.35	1.12
IF-10	2.88	0.16	5.5	0.5	17.4	1.4	2.87	0.58	20.3	−0.03	0.02	0.88	1.07
IF-11	5.33	0.35	6.6	0.73	13.7	2.05	5.16	0.16	3.0	−0.24	0.18	0.73	1.06
IF-12	1.10	0.10	9.5	0.28	25.9	0.78	1.14	0.13	11.5	0.14	0.04	0.27	1.04
IF-13	1.82	0.14	7.8	0.32	17.5	0.89	1.86	0.1	5.4	0.13	0.04	0.31	1.06
IF-14	5.15	0.36	7.0	0.69	13.5	1.94	4.57	0.16	3.5	−0.84	0.58	0.76	1.02
IF-15	3.99	0.23	5.7	0.76	19.1	2.13	4.12	0.17	4.2	0.17	0.13	0.52	1.02

* Value obtained by a single analysis.

dimension increased with the ring number. In **Fig. 4** a virtual line separates the compounds with 1 and 2 aromatic rings (below the line) from those with 3 or more (above the line). In the monoaromatic area of the chromatogram, a cluster of well-shaped peaks was present and it was identified as long-chain alkylbenzenes (LABs) [19]. The presence of diisopropyl naphthalenes (DIPNs), a specific indicator for recycled paperboard [5,33], may suggest a migration from the original packaging of the IF [5,34]. The MOAH contamination, represented by the cloud eluted in the high C-fraction window, showed a clear prevalence of 1 or 2 benzene rings. Just before the start of the cloud a well-shaped peak coming from squalene can be detected, along with a series of terpenoid compounds just slightly more retained in the second dimension. Moreover, C_{32}-C_{35} benzohopanes (BH), characterized by the same base peak but different molecular ions of hopanes [34] (mass spectra reported in **Supplementary material – Figure S1**), were identified above the MOAH cloud. Finally, a small carryover of *n*-alkanes, in particular C_{29}, is visible, but as already observed by Biederman and Grob [33], it is beneficial for supporting the C fraction determination, while chromatographically separated from the MOAH fraction.

3.2.2. *Vegetable oil samples analysis: DGF-ILC*

From 2020 to 2022, DGF and ITERG organized a series of ILCs to review the EN 16995:2017 method, specific for MOSH and MOAH analysis in vegetable fats and oils by using an LC-GC-FID system. The final version of the method, containing additional and partially modified processing steps, was validated through an ILC in which 16 vegetable oil samples were dispatched to 39 laboratories, corresponding to 8 oils with blind replicates [26,27]. The outcomes from the ILC (1D) [26] are shown in **Table 2** and were compared with the results obtained by analyzing the same samples by using the LC-GC × GC-FID platform.

MOSH content in samples varied from about 1.4 to 75.0 mg/kg, with an RSD_r% below 20%, and an RSD_R% in the 11–50% range (average 20.6%). The MOAH content estimated by 1D ILC data varied from about 0.4 to 7.0 mg/kg, by using TBB as IS, with an RSD_r% in the 4–34% range (average around 11%) and an RSD_R% in the 11.5–88% range (average around 33%). For both MOSH and MOAH fractions, the virgin coconut oil sample was the least contaminated and had higher RSD_r% and RSD_R% values. For this ILC, TBB was suggested by the organizers as IS MOAH quantification, claiming that having a higher degree of alkylation compared to 2-MN behaves more similarly to the main MOAH fraction constituents found in edible oils. As a control, the ratio of TBB/2-MN was calculated obtaining values ≤1.25 (within the 0.98–1.16 range), as required by the DGF-ILC SOP [26] and similar to the JRC-ILC ones.

The reproducibility of the results obtained using the LC-GC × GC-FID platform was assessed by comparing Δ_m with the R reported in the ILC (**Fig. 5A and B**). In all samples and for both MOSH and MOAH fractions, the maximum acceptable difference set by R was always respected. The calculated Δ_m value was for all samples lower than the U_Δ [31], indicating that 2D results perfectly agree with 1D ILC data, taken as reference values (**Fig. 5C and D**).

As for the JRC-ILC and despite the relatively high RSD_R values (exceeding 50% in some cases) [32], the z-score values were considered as a bare indication of the performance. For MOSH it varied between 1 and −1, suggesting a low data dispersion and a high precision. For the MOAH fraction, two samples, namely RRO and SSO, slightly exceeded the 1-SD range (1.57 and 1.03, respectively) (**Table 2**).

The MOAH fraction of the RRO sample analyzed by LC-GC × GC-FID is reported in the upper plot of **Fig. 6**. The MOAH contamination in the C-fraction window below C_{25} showed a clear prevalence of 1 and

Table 2
Comparison between the data resulting from the DGF-ILC (1D) and those obtained by using the LC-GC × GC-ToFMS/FID platform (2D).

Sample ID	Type of oil	1D ILC Average (mg/kg)	SD_r	RSD_r%	SD_R	RSD_R%	R	2D Average (mg/kg)	SD_r	RSD_r%	z-score	Δ_m	U_Δ	TBB/2-MN
						MOSH - CyCy								
RGO	**Refined grapeseed oil**	74.60	3.70	4.9	8.50	11.4	23.80	72.40	3.00	4.2	−0.25	2.2	8.5	
RPO	**Refined palm olein**	10.20	0.50	4.7	1.90	18.0	5.20	10.10	2.40	23.6	−0.08	0.2	3.5	
VCO	**Virgin coconut oil**	1.35	0.25	18.2	0.68	50.4	1.90	2.43*				1.08		
RRO	**Refined rapeseed oil**	3.23	0.31	9.7	0.78	24.1	2.18	3.53	0.20	5.6	0.38	0.3	0.68	
EVO	**Extra virgin olive oil**	8.45	0.55	6.5	1.25	14.8	3.51	9.33	0.86	9.2	0.70	0.88	1.64	
SRO	**Spiked rapeseed oil**	7.97	0.54	6.8	1.30	16.3	3.63	8.56	0.88	10.3	0.45	0.59	1.65	
SSO	**Spiked sunflower oil**	15.80	1.10	7.0	2.00	12.4	5.50	16.50*				0.7		
SCO	**Spiked virgin coconut oil**	4.78	0.45	9.5	0.83	17.4	2.33	5.51	0.29	5.3	0.87	0.73	0.99	
						MOAH - TBB								
RGO	**Refined grapeseed oil**	7.06	0.29	4.1	1.02	14.5	2.87	6.82	0.33	4.9	−0.24	0.25	0.75	1.16
RPO	**Refined palm olein**	3.06	0.24	7.8	0.85	27.9	2.39	2.97	0.04	1.2	−0.11	0.10	0.48	1.15
VCO	**Virgin coconut oil**	0.42	0.14	33.5	0.37	87.6	1.03	0.91*				0.49		0.98
RRO	**Refined rapeseed oil**	0.99	0.18	18.0	0.54	54.1	1.5	1.84	0.61	33.0	1.57	0.85	0.93	1.15
EVO	**Extra virgin olive oil**	2.37	0.15	6.3	0.66	27.7	1.84	2.83	0.52	18.3	0.69	0.46	0.79	1.11
SRO	**Spiked rapeseed oil**	2.29	0.17	7.6	0.49	21.2	1.36	2.75	0.39	14.2	0.93	0.46	0.65	1.09
SSO	**Spiked sunflower oil**	6.12	0.42	6.9	0.70	11.5	1.97	6.84	0.85	12.4	1.03	0.72	1.46	1.07
SCO	**Spiked virgin coconut oil**	1.99	0.09	4.4	0.34	17.1	0.95	2.33	0.45	19.4	1.00	0.34	0.66	0.98

* Value obtained from a single analysis.

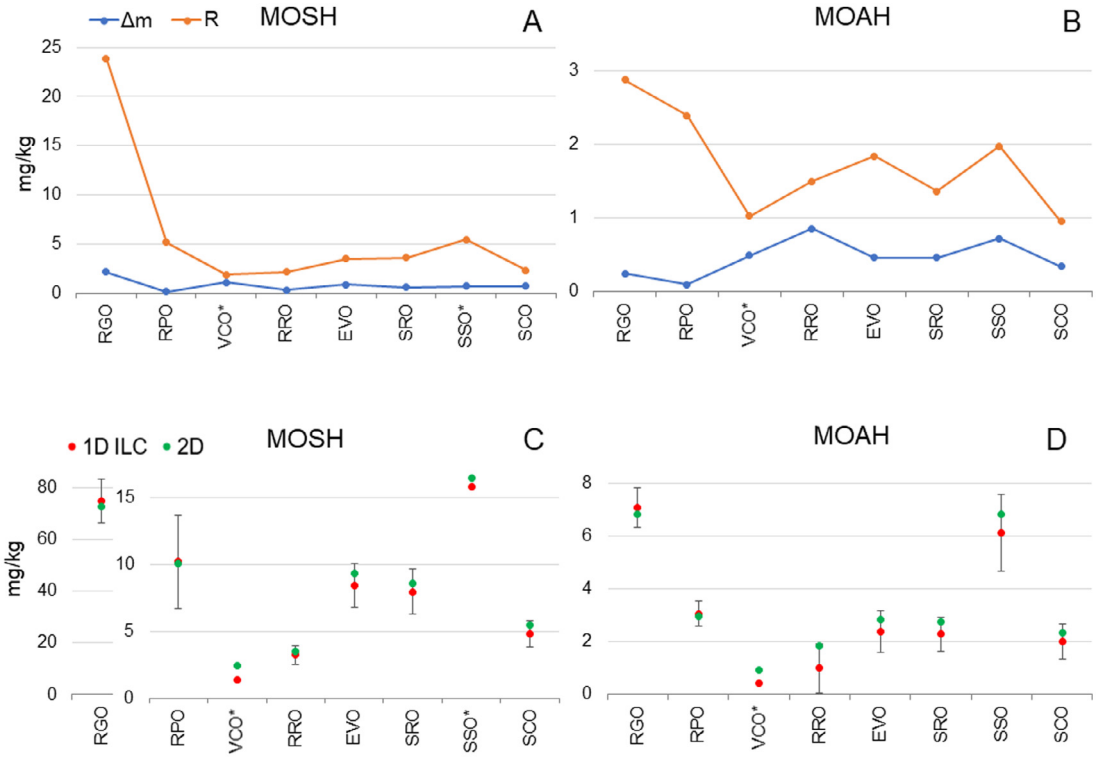

Fig. 5. A-B) Graphical representation of the absolute difference between 1D ILC and 2D mean measured values (Δ_m) and the limit of reproducibility (R) reported in the ILC results. **C-D)** Graphical comparison between the 1D ILC reference values (red dots) and the 2D average results (green dots). Vertical bars represent the expanded uncertainty (UΔ). *2D value obtained from a single analysis.

2 benzene rings. The lower plot in Fig. 6 is related to the same MOAH fraction after the automatic blank subtraction and trimming procedure performed by the dedicated software. As visible, all the well-shaped peaks were efficiently removed, and the remaining cloud consisted of the MOAH to be quantified. Although the trimming parameters are set by the operator, automation of the removal step reduced the variability linked to the manual integration, providing objective parameters that can be reproduced. Interpretation of the interferents is also simplified by the distribution of compounds in the 2D space [17].

3.3. White analytical chemistry considerations

Despite we acknowledge that overall the methods for MOSH and MOAH analysis are still far to be considered green, we tried to compare the routine method with the advanced multidimensional platform, following the principle of white analytical chemistry [35], which gives emphasis to the performance of the method as well. Most of the consideration of the green analytical aspects refers to the solvent consumption, thus to the sample preparation steps. In this comparison this part

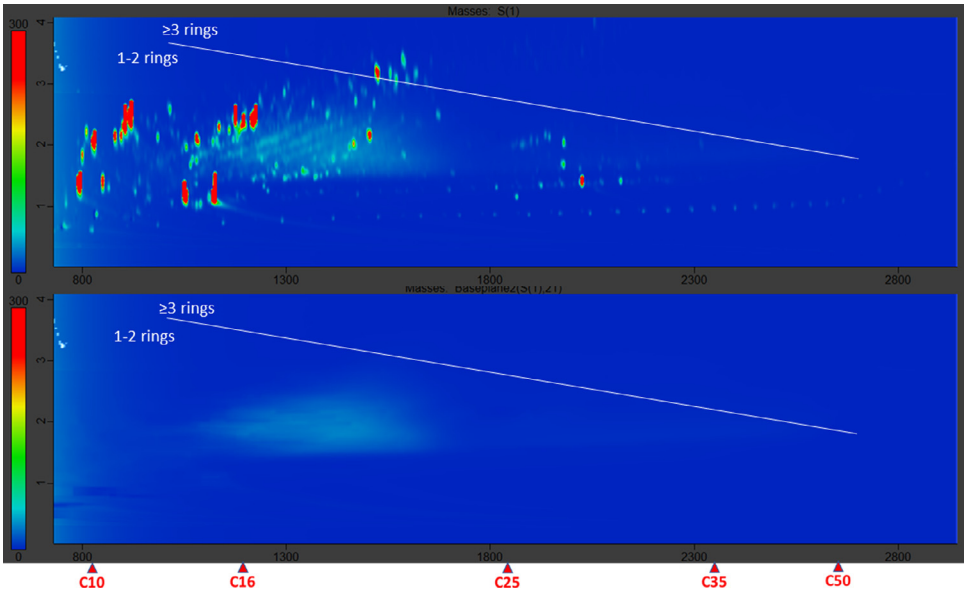

Fig. 6. LC-GC × GC-FID plot of the MOAH fraction of the refined rapeseed oil (RRO) sample before (upper) and after (lower) the automatically blank subtraction and trimming of the peaks riding on top of the hump.

is equivalent, so here the main comparison is based on the number of analyses required to provide both quantification and confirmation of the contamination, and on the overall performance of the two analytical approaches. The fully integrated LC-GC × GC-ToFMS/FID platform enables the separation of MOSH and MOAH, their simultaneous transfer and acquisition with dual detection, in our case FID and MS, in a single analytical run, but two FIDs in parallel can be used thus providing quantification and confirmation of both MOSH and MOAH in GC × GC simultaneously, reducing time and solvent consumption compared with the routine approach that involved the LC-GC-FID analysis possibly followed by an additional confirmatory analysis by GC × GC. Although the percentage of samples needing confirmation depends on the matrix and its complexity, it is difficult to estimate the right number of additional analyses needed. For comparison purposes, we considered only 20% of the samples to undergo confirmatory GC × GC. Therefore, green aspects were evaluated considering only a 20% difference between the two methods, resulting in a total score of 100 *vs* 75 for the LC-GC × GC and LC-GC, respectively.

Regarding red principles, the trueness and precision of LC-GC × GC was shown to be superior to other routine LC-GC methods in the Shell SN500 mineral oil trial. Sensitivity was not assessed in the present study but roughly a two times lower limit of quantification was previously reported for LC-GC × GC [19]. Despite an increase of roughly 10-times has been estimated in general for GC × GC compared to 1D GC, this evaluation refers to a single well-shaped peak. The estimation of the sensitivity in the case of MOSH and MOAH is more complicated being tightly related not only to the signal but mainly to the blank level that is independent of the analytical method but strictly related to the sample preparation manipulation. On one side, the use of GC × GC allows for chromatographic separation of the bleeding from the fraction of interest, thus improving the signal, but on the other side, the signal generated by the hump (or rather a cloud in the 2D space) depends not only on the volatility range (as in 1D) but also on the distribution of all the isomers in the 2D space. Therefore two-times reduction of the limit of quantification is a reasonable general estimation for both MOSH and MOAH. Concerning the scope of application, although not developed in this work, it is important to point out an additional advantage of the LC-GC × GC platform, which is the possibility to quantify sub-classes separately (e.g. 1–2 rings vs ≥3 rings MOAH) as shown in [19], thus providing an enhanced characterization useful for toxicological evaluation and thus extending the scope of application beyond simple quantification. These considerations lead to a final score of 100 *vs* 65 for the LC-GC × GC and LC-GC, respectively.

Finally, regarding the practical aspect (blue principles), the main differences are related to the cost and time efficiency, as the operator skills required to manage the LC-GC and GC × GC separately are equivalent to those required to run the integrated LC-GC × GC platform. A final score of 83.3 *vs* 62.5 was estimated for the LC-GC × GC and LC-GC, respectively.

All these aspects lead to a final white score of 94.4 and 67.5 for the LC-GC × GC and LC-GC, respectively.

5. Conclusions

In the present work, the performance of the LC-GC × GC-ToFMS/FID platform in terms of MOSH and MOAH quantification was successfully validated by comparing the data with those resulting from different ILCs. Three different kinds of samples were tested, namely a solution of mineral oil in hexane, powder IF, and vegetable oils of various origins. The first trial allowed to validate the instrumental platform regardless of the sample manipulation and, thus, extra variability related to the operator experience. For all samples, independently of the more or less laborious sample preparation expressly required by the ILCs SOPs, the data obtained using the 2D platform were in total agreement with those resulting from the ILCs. In particular, good results were obtained in terms of recovery, precision, accuracy, and repeatability, confirming the possibility of using the 2D platform not only as a confirmatory method but also to reliably quantify MOSH and MOAH fractions in different matrices. The availability of dedicated software that automatically performs blank subtraction and interference peak trimming allows for reduced variability during integration.

Finally, from an evaluation of the white analytical aspects, the LC-GC × GC-FID platform performed superior to the LC-GC-FID, mainly thanks to the expanded scope deriving from the separation of subclasses, along with the superior analytical performance and cost-efficiency resulting from the merging of routine and confirmatory methods in a single platform. Nevertheless, the overall methods (sample preparation and analytical determination) remain very laborious and would be benefit from innovative approaches towards greener aspects, which we acknowledge that at the moment cannot be a priority respect to the urgent necessity to fill the remaining gaps for reliability and robustness of the actual analytical methods.

Funding

This work is supported by Fonds de la Recherche Scientifique Belgique (FNRS) (CDR projects-MOHPlatform, J.0170.20).

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.

Data Availability

Data will be made available on request.

Acknowledgments

GP and GB thank LECO and Restek for their support. This article is based upon work from the Sample Preparation Study Group and Network, supported by the Division of Analytical Chemistry of the European Chemical Society.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.greeac.2022.100047.

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