Assessing the environmental and overall performance of gas chromatographic analyses. Development of a comprehensive evaluation framework and application to routine chiral analyses of fragrances as a case study

Gaia Bechis [a], Bastien Raccary [b], Elise Sarrazin [c], Elise Corbi [c], Christophe Peres [b], Nathalie David [c], Carlo Bicchi [a], Cecilia Cagliero [a], *

[a] *Department of Drug Science and Technology, University of Turin, 10125, Turin, Italy*
[b] *Le Labo Durable, 89 rue des Poissonniers, 75018, Paris, France*
[c] *Chanel, Laboratoire Recherche et Analyses Parfums, 135 Avenue Charles de Gaulle, 92521, Neuilly-sur-Seine, Cedex, France*

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ABSTRACT

Enantioselective gas chromatography is used in fragrance quality control laboratories to authenticate the origin of raw materials and detect possible frauds or adulterations of perfumes. These laboratories must contend with increasing attention to environmental sustainability, quality standards that require accurate and reliable measurements, and practical considerations such as productivity, costs, and simplicity of methods. Quantitative tools enabling a global evaluation of all these aspects are therefore required. In the first part of the study, a GC-MS method for the chiral recognition of a set of odorants was developed and speeded up. The improvement in environmental footprint associated with fast GC was then quantitatively evaluated using AGREE. This tool allowed a rapid comparison of environmental impacts between different analytical methods, but, despite a very different energy consumption, showed few differences in the final score of the developed methods. Therefore, a multi-criteria approach based on the RGB model, for the first time specifically dedicated to GC analytical methods, was developed. It accurately accounts for the contribution of GC and the need to limit the consumption of energy and toxic solvents while maintaining analytical performance and adequate laboratory productivity. The template can be adapted to analyses with a different scope by changing the analytical performance criteria and the reference threshold of the method. The global assessment of the methods developed showed that fast GC improves the greenness and the productivity of a laboratory, and lowers costs while maintaining adequate analytical performance making the approach not only green but also sustainable.

1. Introduction

Like in life science, chirality is crucial in fragrance chemistry (Brenna et al., 2003). Biosynthesis of natural odorants is generally stereo-guided, so chiral analysis has been used for many decades to authenticate the origin of natural raw materials for quality control purposes (Cagliero et al., 2017). However, chirality also impacts sensory evaluation. Enantiomers can differ in odor quality and in

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odor intensity (Brenna et al., 2003,Cagliero et al. 2017,Koppenhoefer et al., 1994). The core fragrance ingredient Hedione® (methyl dihydrojasmonate) is a *cis* and *trans* blend of two pairs of enantiomers. But, the *cis* pair is known to be more powerful, and within the *cis* pair, the (*1R,2S*)-enantiomer is the strongest (odor threshold of 15 ppb) and most pleasant (with intensely floral, jasmine-like, extremely long-lasting notes). So, chiral ingredients can have a major impact to provide newness and originality to fragrance creations. As a consequence, in the context of an illegal fake scent boom, enantiomeric recognition represents a major tool to authenticate fragrances and demonstrate counterfeits.

Gas chromatography (GC), especially in combination with mass spectrometry (MS), is the technique of choice to analyze volatiles. However, enantiomer separation requires stationary phases with a chiral selector in their structure able to interact differently with each enantiomer of the investigated chiral compound(s). Cyclodextrin derivatives are the most popular chiral stationary phases available for enantioselective-GC in the fragrance field (Cagliero et al., 2016,Cagliero et al. 2017,Cagliero et al., 2021). Several studies have also shown that fast GC can successfully be used for chiral recognition with cyclodextrins as chiral selectors by optimizing column dimensions and analytical conditions (Bicchi et al., 2010,Cagliero et al., 2012). However, this technique has not yet been applied in a multipurpose context aiming at authenticating both fragrance raw materials and finished products.

In recent years, industry and quality control laboratories have dealt with increasing regulatory and public attention to environmental sustainability. As part of the European Green Deal for the European Union, the Commission has clearly committed to address climate- and environment-related challenges (European Commission). Special attention is paid to the "Sustainable Chemicals Strategy", which addresses not only the safety of the end products, but also of their entire life cycle (European Commission). Analytical chemistry is present at every stage of product development and throughout the life of a product, and therefore the environmental impact of analysis must be addressed (Raccary et al., 2022a). Since the introduction of the concept of Green Analytical Chemistry (GAC) (Anastas 1999), the analytical community has made great efforts to develop and apply GAC principles (Gałuszka et al., 2013), including the creation of tools and metrics to assess the greenness of applied analytical methods. They can guide chemists toward more sustainable practices, although each tools adopts its own calculations and criteria. One of the latest tools is the Analytical GREENness calculator (AGREE) (Pena-Pereira et al., 2020), which evaluates the compliance of an analytical method with the twelve principles of the GAC. On the other hand, the Life Cycle Assessment (LCA) approach provides quantitative and holistic information on the potential environmental impacts of analytical chemistry methods throughout their life cycle. However, despite the fact that LCA is a relevant framework (Raccary et al., 2022b), conducting LCA is time-consuming, requires expertise, and cannot currently be used routinely (ISO-14040 2006,Raccary, Loubet, Peres and Sonnemann 2022a). At the same time, industrial quality control laboratories must also deal with the multiplication of norms and quality standards that require accurate and reliable measurements, as well as practical considerations such as productivity, cost, and simplicity of the methods. A set of tools has been developed to critically and globally evaluate analytical methods by balancing considerations of a method's greenness with its analytical efficiency and "productivity" (Nowak et al., 2020). The White Analytical Chemistry (WAC) approach (Nowak et al., 2021) can be considered an extension of the 12 principles of GAC. It evaluates the quality of methods in terms of analytical efficiency, greenness and safety, and practical and economic aspects. For each aspect, four parameters are proposed, to each of which a score is assigned, and a global score is calculated to measure the overall compliance of the method to all principles. A "white" method is a balanced analysis method that fully satisfies all parameters. One of the strengths of this approach is the selection of predefined principles and the equal importance given to each of the three main aspects. However, these points could also limit the outcome of the results regarding specific analytical applications, such as routine chiral analysis of fragrances.

When it comes to evaluate the greenness of a method, great attention is often given to sample preparation, since it is believed to be the analytical phase to have the most impacts on the environment, especially when GC is used as separation technique. GC is considered a relatively environmentally friendly alternative to other chromatographic techniques, because it uses inert gasses as mobile phases (Napolitano-Tabares et al., 2021). However, it involves extensive energy consumption and in most cases either the use of nonrenewable gas as helium, or hydrogen, whose production is still almost entirely based on fossil fuels. Some attempts were made to improve sustainability in GC (Armenta and de la Guardia 2016,Cagliero et al., 2023,Napolitano-Tabares et al. 2021,Plotka et al., 2013). They focused primarily on: i) miniaturization, ii) replacing helium with hydrogen (that, as mentioned above, is not always better for sustainability), iii) increasing the separation capability to reduce the number of analyses required, and finally, iv) reducing analysis time. However, the number of studies in this regard is still limited, and a quantitative assessment of the environmental impacts of GC and fast GC analyses has never been performed. Recently, a first attempt was made by Nowak and collaborators to calculate the actual energy consumption and carbon footprint of different analytical techniques (including GC-MS), but it was mainly based on literature data and the energy consumption of a model method (Nowak et al., 2023a).

The aim of this study was: i) to develop sustainable chiral recognition methods suitable for authentication controls of both fragrances and fragrance ingredients and ii) to develop a metric tool enabling to evaluate the overall performance of a GC method. Particular attention was therefore paid to the chromatographic step and on the impact of fast GC analyses on the greenness and reliability of the methods, comparing, in this specific case study, the performance of the proposed methods with a reference method included in the European Pharmacopeia. In particular, a new comprehensive evaluation framework, based on RGB (Red-Blue-Green) additive color model (Nowak and Koscielniak 2019), was developed to evaluate whether the proposed analytical methods can be considered "sustainable", i.e. a suitable compromise between limited energy and toxic solvent consumption, high analytical performance and an adequate laboratory productivity.

2. Materials and methods

2.1. Samples and chemicals

Ethanol (EtOH), cyclohexane and a standard mixture of *n*-Alkanes (from *n*-7 to *n*-30 at a concentration of 1 mg/mL), were obtained from Merck (Milan, Italy). EtOH was used as dilution solvent for the fragrance samples. At the same time the alkane standard mixture was diluted in cyclohexane at a concentration of 0.1 mg/mL and applied for linear retention indices (I^T) calculation.

A set of racemic standards from the Authors' collection for a total of 27 chiral pairs (Table 1) were selected as target analytes. In particular, stock solutions of each standard were prepared diluting the pure compounds in cyclohexane at the concentration of 10 mg/mL. These stock solutions were used to prepare the following mixtures diluted at the concentration of 0.2 mg/mL in cyclohexane: mixture 1: isobornyl acetate, linalyl acetate, α-terpinyl acetate, methyl jasmonate; mixture 2: linalool, α-terpineol, citronellol; mixture 3: α-pinene, β-pinene, limonene; mixture 4: menthone, isomenthone, carvone, α-ionone; mixture 5: hydroxycitronellal, cyclamen aldehyde, Cetalox®; mixture 6: acetate citronellyl, Hedione® trans > cis, muscone; mixture 7: Hedione® cis > trans, rose oxide, Muscenone®.

A set of six model perfumes, kindly provided by Chanel company (Chanel, Neuilly-sur-Seine), were analyzed. The fragrance samples were diluted 1:20 in EtOH before analysis.

2.2. Instruments

GC-MS analyses were carried out on a Shimadzu GC-MS system, consisting of a Shimadzu GC2010 gas chromatograph coupled to a Shimadzu QP2010 Plus mass spectrometer (Shimadzu, Milan, Italy). A MultiPurpose Sampler MPS2 (Gerstel, Mülheim a/d Ruhr, Germany) was adopted as autosampler.

The energy consumption was measured with a Zhurui PR10 power meter plug (Zhurui, China).

2.3. Analysis conditions

Separation of chiral compounds was achieved using capillary columns coated with cyclodextrin derivatives as stationary phases. All columns were provided by MEGA (MEGA S. r.l., Legnano (MI), Italy).

Four chiral selectors were tested adopting columns with a conventional geometry (25 m length x 0.25 mm d_c x 0.25 mm d_f). The stationary phases were the following: i) 30% 2^{I-VII}-*O*-ethyl-3^{I-VII}-*O*-ethyl-6^{I-VII}-*O*-*tert*-butyldimethylsilyl-β-cyclodextrin diluted in PS086 (*i.e.,* MEGA-DEX DET-Beta), ii) 30% 2^{I-VII}-*O*-methyl-3^{I-VII}-*O*-pentyl-6^{I-VII}-*O*-methyl-β-cyclodextrin column diluted in PS086 (*i.e.* MEGA-DEX DMP-Beta), iii) 30% 2^{I-VII}-*O*-acetyl-3^{I-VII}-*O*-acetyl-6^{I-VII}-*O*-*tert*-butyldimethylsilyl-β-cyclodextrin column diluted in PS086 (*i.e.* MEGA-DEX DAC-Beta) and iv) 30% 2^{I-VII}-*O*-methyl-3^{I-VII}-*O*-methyl-6^{I-VII}-*O*-*tert*-butyldimethylsilyl-β-cyclodextrin column diluted in PS086 (*i.e.* MEGA-DEX DMT-Beta).

The analysis conditions with these columns were as follows: injection temperature: 220 ˚C, carrier gas: helium, flow: 1.0 mL/min (pressure 39.9 kPa), injection mode: split, split ratio: 20:1, injection volume: 1 μL. The oven temperature program was: from 50.0 ˚C to 220 ˚C (5 min) at 2 ˚C/min.

Different dimensions were also tested for the MEGA-DEX DET-Beta CD columns: a) 15 m × 0.18 mm d_c x 0.18 mm d_f. Analysis conditions: injection temperature: 220 ˚C, carrier gas: He, flow: 0.72 mL/min (pressure 77.7 kPa), injection mode: split, split ratio: 20:1, injection volume:1 μL. Oven temperature program: from 50.0 ˚C to 220 ˚C (5 min) at 3.7 ˚C/min and b) 10 m × 0.10 mm d_c x 0.10 mm d_f. Analysis conditions: injection temperature: 220 ˚C, carrier gas: He, flow: 0.4 mL/min (pressure 250.8 kPa), injection mode: split, split ratio: 50:1, injection volume:1 μL. Oven temperature program: from 50.0 ˚C to 220 ˚C (5 min) at 5 ˚C/min.

For all analyses, the MS operative conditions were as follows: transfer line: 230 ˚C, ion source temperature: 200 ˚C. The MS operated in electron impact ionization mode (EI) at 70 eV with a scan rate of 666 μ/s, and mass range of 35–350 m/z.

The identification was carried out by spectral similarity match estimated over commercial and in-house databases. In addition, the enantiomer stereochemistry was confirmed through authentic enantiomeric standards and I^T comparison with an in-house database of retention indexes with a tolerance of ± 3 (Cagliero et al. 2017, Liberto et al., 2008). The retention indices were calculated as:

$$I^T = 100i\frac{t_{R(X)} - t_{R(M_{(n)})}}{t_{R(M_{(n+i)})} - t_{R(M_{(n)})}} + 100n$$

where t_R is the retention time, *i* is the difference in the number of carbon atom of the two hydrocarbons bracketing the analyte's retention time, *X* is the analyte, and $M_{(n)}$ and $M_{(n+i)}$ the two hydrocarbons with *(n)* and *(n + i)* carbon numbers.

For Hedione®, the enantiomer stereochemistry was established on the MEGA-DEX DMT-Beta column using the elution order reported by Werkhoff et al. (Werkhoff, et al., 2002) with the same chiral selector; the enantiomeric excess found on one of the investigated fragrances was used to establish the enantiomer elution order on the other columns.

The separation number (Δ*s*) was calculated as:

$$\Delta s = \frac{(t_{R(A)} - t_{R(b)})}{(\sigma_A + \sigma_B)/2}$$

where t_R is the retention time, σ is the standard deviation of the peak width, A is the first eluting peak ((*R*)-α-pinene) and B is the last eluting peak ((3Y,5E)-3-Methyl-5-cyclopentadecen-1-one) of the reference standard mixture (Blumberg 2011).

Table 1
List of the chiral compounds tested.

#	Chiral compounds	#	Enantiomers
1	Limonene	1A	(*S*)-Limonene
		1B	(*R*)-Limonene
2	Hydroxycitronellal	2A	(X)-Hydroxycitronellal
		2B	(Y)-Hydroxycitronellal
3	Rose oxide	3A	(*2R,4S*)-cis Rose oxide
		3B	(*2S,4R*)-cis Rose
		3C	(*2R,4R*)-trans Rose oxide
		3D	(*2S,4S*)-trans Rose oxide
4	Linalool	4A	(*R*)-(−)-Linalool[
		4B	(*S*)-(+)-Linalool
5	Linalyl acetate	5A	(*R*)-(−)-Linalyl acetate
		5B	(*S*)-(+)-Linalyl acetate
6	α-Pinene	6A	(*1R*)-(+)-α-Pinene
		6B	(*1S*)-(−)-α-Pinene
7	β-Pinene	7A	(*1R*)-(+)-β-Pinene
		7B	(*1S*)-(−)-β-Pinene
8	Citronellol	8A	(*S*)-Citronellol
		8B	(*R*)-Citronellol
9	Isomenthone	9A	(+)-(1R,4R)-Isomenthone
		9B	(−)-(1S,4S)-Isomenthone
10	Menthone	10A	(−)-Menthone
		10B	(+)-Menthone
11	α-Ionone	11A	(*S*)-(−)α-Ionone
		11B	(*R*)-(+)-Ionone
12	Cetalox®	12A	(−)-Naphtho[2,1-*b*]furan,dodecahydro-3a,6,6,9a-tetramethyl
		12B	(+)-Naphtho[2,1-*b*]furan,dodecahydro-3a,6,6,9a-tetramethyl
13	α-Terpinyl acetate	13A	X-α-Terpinyl acetate
		13B	Y-α-Terpinyl acetate
14	Muscenone®	14A	(3X,4E)- 3-Methyl-4-cyclopentadecen-1-one
		14B	(3Y,4E)- 3-Methyl-4-cyclopentadecen-1-one
		14C	(3X,5E)- 3-Methyl-5-cyclopentadecen-1-one
		14D	(3Y,5E)- 3-Methyl-5-cyclopentadecen-1-one
		14E	(3S,5Z)- 3-Methyl-5-cyclopentadecen-1-one
		14F	(3R,5Z)- 3-Methyl-5-cyclopentadecen-1-one
15	Isobornyl acetate	15A	(X)- Isobornyl acetate
		15B	(Y)- Isobornyl acetate
16	α-Terpineol	16A	(*S*)-(−)- α-Terpineol
		16B	(*R*)-(+)- α-Terpineol
17	Cyclamen aldehyde	17A	(X)- Cyclamen aldehyde
		17B	(Y)- Cyclamen aldehyde
18	Methyl jasmonate	18A	(*1R,2R*)-(−)- Methyl jasmonate

Table 1 (*continued*)

#	Chiral compounds	#	Enantiomers
		18B	(*1S,2S*)-(+)- Methyl jasmonate
		18C	(*1R,2S*)-(+)- Methyl epijasmonate
		18D	(*1S,2R*)-(−)- Methyl epijasmonate
19	Methyl dihydrojasmonate (Hedione®)	19A	(−)-(*1R,2R*)- Methyl dihydrojasmonate
		19B	(+)-(*1S,2S*)- Methyl dihydrojasmonate
		19C	(+)-(*1R,2S*)- Methyl dihydrojasmonate (= Paradisone®)
		19D	(−)-(*1S,2R*)- Methyl dihydrojasmonate
20	Acetate citronellyl	20A	(*R*)- Acetate citronellyl
		20B	(*S*)- Acetate citronellyl
22	Muscone	21A	(−)-Muscone
		21B	(+)-Muscone
22	Carvone	22A	(*R*)-Carvone
		22B	(*S*)-Carvone

2.4. Data elaboration

The software used for data acquisition and processing was GCMSsolution® 4.30 (Shimadzu, Milan, Italy).

Excel (Microsoft Office, v.2016) was used for the RGB model calculation following and properly adapting the tool developed by Nowak et al. (Nowak and Koscielniak 2019). The Analytical GREENess calculator (AGREE v0.4 2020) (Pena-Pereira et al., 2020) was applied for the calculation of the greenness score of the methods.

3. Results and discussion

3.1. Optimization of the chromatographic method for the chiral recognition of odorants

A fragrance consists of 50–250 raw materials and is thus a complex mixture of volatile substances (Sarrazin, 2017). The first part of the study aimed at developing a GC method to separate the enantiomers, isomers and diastereoisomers of chiral key odorants commonly found in fragrances for a total of 27 chiral pairs (Table 1). They can either be of natural or synthetic origin and the enantiomer of most of them have different odor qualities (Table S1). Conventional columns (25 m × 0.25 mm d_c, 0.25 mm d_f) coated with four cyclodextrin derivatives (see Paragraph 2.3) were first tested as chiral selectors to determine which offered the best separation and separated the highest number of the investigated chiral compounds. Indeed, there is no cyclodextrin derivative characterized by universal enantioselectivity, since the separation depends on the difference of interaction energy between each enantiomer and the chiral selector. The four cyclodextrin chiral selectors tested are those most commonly used in the flavor and fragrance industry and have already been chosen to build-up a library of linear retention indices to identify the enantiomers of a set chiral compounds in the flavor and fragrance field (Liberto et al. 2008).

Table 2 summarizes retention indices and resolutions of the target analytes with the four cyclodextrin-based stationary phases investigated.

The results show that the DET-Beta column separates most of the enantiomers of the chiral compounds under investigation. Only five critical racemates are not separated, that are α-terpinyl acetate, carvone, hydroxycitronellal, muscone, and (5Z)-3-methyl-5-cyclopentadecen-1-one. DMP-Beta separates 16 out of the 27 racemates, but it is highly complementary to DET-Beta, since only hydroxycitronellal is not separated on both columns. This compound is separated on DAC-Beta, which, however, does not separate other 10 racemates. Finally, the DMT-Beta column separates 19 out of 27 racemates, but no advantages are observed in terms of complementarity to DET-Beta. The DET-Beta column was therefore selected for the following speeding-up of the analytical method and evaluation of the environmental and global impact of the analyses. However, to note is that at least two stationary phases (DET-Beta and DMP-Beta) should be used for a full investigation of the whole set of target analytes.

The Es-GC-pattern of an authentic fragrance analyzed on the conventional DET-Beta column is shown in Fig. 1a, while its enantiomeric composition in terms of percent enantiomeric composition (EC%) is listed in Table 3.

3.2. Speeding-up of the chiral analyses

A limitation of using cyclodextrins as chiral selectors in Es-GC is the long analysis time due to the low temperature rate required for enantiomer separation with conventional columns. However, the Fast GC approach involving reduced column length and inner diameter, and/or increasing flow rate can successfully be applied to Es-GC. This not only leads to shorter analysis times, but also to a lower enantiomer elution temperature due to the shorter column length, without losing efficiency, and data consistency and in some case improving enantioselectivity because the separation is thermodynamically driven (Bicchi et al. 2010; Cagliero et al. 2012). Therefore, two DET-Beta columns with lower dimensions were tested, a 15 m × 0.18 mm d_c, 0.18 mm d_f (DET-Beta 0.18) and a

Table 2

Target and reference ions, linear retention indices and resolutions on the four chiral stationary phases. Legend: DET-Beta - 30% 2[I-VII]-O-ethyl-3[I-VII]-O-ethyl-6[I-VII]-O-tert-butyldimethylsilyl-β-cyclodextrin in PS086, DMP-Beta - 30% 2[I-VII]-O-methyl-3[I-VII]-O-pentyl-6[I-VII]-O-methyl-β-cyclodextrin in PS086, DMT-Beta 30% 2[I-VII]-O-methyl-3[I]–[VII] –O-methyl-6[I-VII]-O-tert-butyldimethylsilyl-β-cyclodextrin in PS086 and DAC-Beta - 30% 2[I-VII]-O-acetyl-3[I-VII]-O-acetyl-6[I-VII]-O-tert-butyldimethylsilyl-β-cyclodextrin in PS086; N.S.: not separated.

COMPOUNDS	CONF[a]	TARGET (REF.) IONS	DET-Beta I^T[b]	R_s[c]	DMP-Beta I^T[b]	R_s[c]	DMT-Beta I^T	R_s[c]	DAC-Beta I^T[b]	R_s[c]
Limonene	(S)	68.00 (69.00–93.00)	1057	6.0	1061	2.7	1082	3.7	1050	N.S.
	(R)		1073		1068		1096			
Hydroxy-citronellal	X	59.00 (43.00–71.00)	1374	N.S.	1439	N.S.	1449	0.5	1644	1.2
	Y						1450		1648	
Rose oxide	(2R,4S) cis	69.00 (139.00–41.00)	1113	1.2	1122	1.8	1144	N.S.	1176	N.S.
	(2S,4R) cis		1116		1126					
	(2R,4R) trans		1132	1.6	1154	N.S.	1159	3.1	1195	N.S.
	(2S,4S) trans		1137				1166			
Linalool	(R)	71.00 (93.00–41.00)	1174	6.3	1212	4.3	1203	3.4	1302	1.1
	(S)		1189		1223		1213		1304	
Linalyl acetate	(R)	93.00 (43.00–80.00)	1232	2.5	1243	N.S.	1257	N.S.	1301	0.6
	(S)		1238						1303	
α pinene	(R)	93.00 (92.00–91.00)	921	0.8	929	2.9	968	4.6	917	0.6
	(S)		924		936		984		919	
β pinene	(+)	93.00 (41.00–69.00)	945	3.7	975	1.0	1010	1.0	968	0.3
	(−)		955		978		1014		970	
Citronellol	(R)	69.00 (41.00–67.00)	1323	1.0	1368	N.S.	1357	N.S.	1381	1.5
	(S)		1325						1385	
Isomenthone	(+)	112.00 (69.00–41.00)	1147	8.5	1202	N.S.	1220	6.4	1262	2.0
	(−)		1169				1236		1266	
Menthone	(−)	112.00 (69.00–41.00)	1167	2.4	1226	N.S.	1232	1.7	1275	2.0
	(+)		1173				1238		1280	
α Ionone	(S)	121.00 (93.00–43.00)	1410	3.6	1438	6.6	1455	1.8	1520	4.6
	(R)		1421		1456		1465		1533	
Cetalox	(−)	221.00 (97.00–137.00)	1753	3.6	1807	2.4	1774	5.5	1798	0.3
	(+)		1766		1816		1794		1800	
α-terpenyl acetate	X	121.00 (93.00–43.00)	1350	N.S.	1380	0.8	1377	12.1	1397	3.3
	Y				1382	1.2	1409	N.S.	1406	
Muscenone®	(3X,4E)-3-methyl-4-cyclopentadecen-1-one	55.00 (67.00–41.00)	1855	0.4	1908		1856		1887	N.S.
	(3Y,4E)-3-methyl-4-cyclopentadecen-1-one		1858		1912					
	(3X,5E)-3-methyl-5-cyclopentadecen-1-one	68.00 (81.00–41.00)	1873	0.1	1930	N.S.	1874	0.9	1898	N.S.
	(3Y,5E)-3-methyl-5-cyclopentadecen-1-one		1875				1877			
Muscenone®	(3S,5Z)-3-methyl-5-cyclopentadecen-1-one	68.00 (81.00–41.00)	1889	N.S.	1942	N.S.	1884	0.04	1913	N.S.
	(3R,5Z)-3-methyl-5-cyclopentadecen-1-one						1885			
Isobornyl acetate	X	95.00 (43.00–93.00)	1221	1.0	1271	1.5	1260	1.1	1319	N.S.
	Y		1224		1275		1264			
α Terpineol	(S)	59.00 (93.00–121.00)	1296	5.0	1362	N.S.	1339	4.6	1393	1.5
	(R)		1309		1366		1354		1398	
Cyclamen aldehydes	X	133.00 (105.00–91.00)	1551	1.1	1570	1.1	1581	0.3	1617	1.1
	Y		1555		1573		1583		1621	
Methyl jasmonate	X	83.00 (41.00–151.00)	1684	10.7	1738	6.4	1719	7.7	1816	N.S.
	Y		1718		1760		1746			
	X-epi		1693	9.9	1721	17.5	1705	14.9	1800	10.5
	Y-epi		1723		1780		1755		1845	
Hedione	(−)-(1R,2R)	83.00 (82.00–153.00)	1687	4.0	1734	4.0	1711	4.3	1816	N.S.
	(+)-(1S,2S)		1698		1746		1725			
	(+)-(1R,2S)-Paradisone	83.00 (82.00–156.00)	1719	0.5	1770	2.0	1741	1.7	1841	0.9
	(−)-(1S,2R)		1721		1776		1747		1844	
Acetate citronellyle	(3S)-(−)	81.00 (69.00–43.00)	1363	1.2	1375	N.S.	1374	0.085	1430	1.4
	(3R)-(+)		1367				1375		1433	
Muscone	(−)	55.00 (85.00–41.00)	1868	N.S.	1926	0.7	1869	N.S.	1899	N.S.
	(+)				1929					
Carvone	(R)	82.00 (54.00–108.00)	1321	N.S.	1345	2.3	1377	N.S.	1453	2.5
	(S)				1353				1462	

[a] CONF. = configuration. X,Y: configuration not assigned.

[b] I^T = linear retention index.
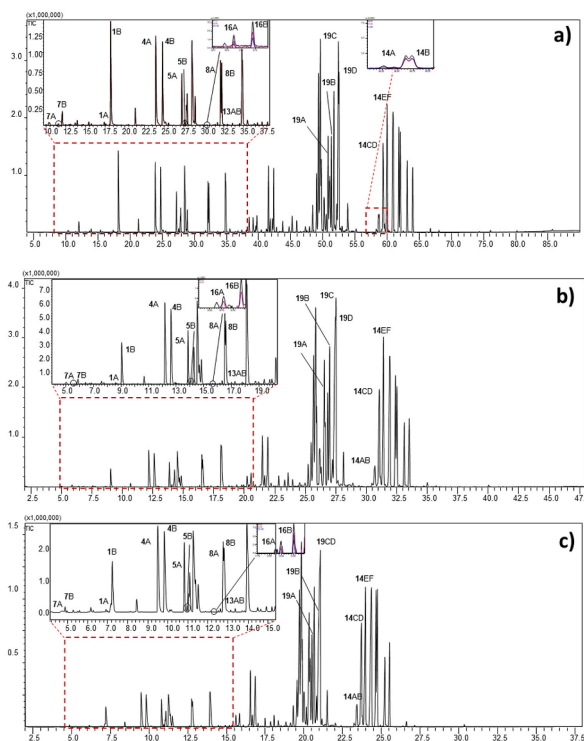
[c] R_s = enantiomeric resolution.

Fig. 1. GC-MS profile of the reference fragrance on a) 25 m × 0.25 mm d_c x 0.25 mm d_f; b) 15 m × 0.18 mm d_c x 0.18 mm d_f; c) 10 m × 0.10 mm d_c x 0.10 mm d_f 30% 2^{I-VII}-*O*-ethyl-3^{I-VII}-*O*-ethyl-6^{I-VII}-*O*-*tert*-butyldimethylsilyl-β-cyclodextrin in PS086. Compound peak numbers refer to Table 1.

Table 3
Enantiomeric composition of the chiral compounds detected in the reference fragrance obtained on DET-Beta columns with different dimensions.

	ENANTIOMERIC COMPOSITION (EC%[a])		
	DET-Beta (0.25 mm d_c)	DET-Beta (0.18 mm d_c)	DET-Beta (0.10 mm d_c)
(*R*)-Linalyl acetate	91.6	91.2	91.5
(*S*)-Linalyl acetate	8.4	8.8	8.5
(*R*)-Linalool	52.4	52.2	51.2
(*S*)-Linalool	47.6	47.8	48.8
(*S*)-α-Terpineol	28.2	29.6	31.5
(*R*)-α-Terpineol	71.8	70.4	68.45
(*R*)-Citronellol	49.8	48.3	47.3
(*S*)-Citronellol	50.2	51.7	52.7
(*R*)-α-Pinene	67.3	65.5	N.S.[b]
(*S*)-α-Pinene	32.7	34.45	
(+)-β-Pinene	8.1	7.8	Not calculable
(−)-β-Pinene	91.9	92.2	
(*S*)-Limonene	4.2	4.9	4.2
(*R*)-Limonene	95.8	95.1	95.8
(3X,4E)-3-Methyl-4-cyclopentadecen-1-one	49.6	48.1	46.2
(3Y,4E)-3-Methyl-4-cyclopentadecen-1-one	50.3	51.1	53.78
(3X,5E)-3-Methyl-5-cyclopentadecen-1-one	58.4	N.S.[2]	N.S.[2]
(3Y,5E)-3-Methyl-5-cyclopentadecen-1-one	41.5		
(−)-(*1R,2R*) trans Methyl dihydrojasmonate	51.6	55.6	53.9
(+)-(*1S,2S*) trans Methyl dihydrojasmonate	48.4	44.34	46.1
(+)-(*1R,2S*) cis Methyl dihydrojasmonate	63.0	61.23	64.0
(−)-(*1S,2R*) cis Methyl dihydrojasmonate	37.0	38.7	35.9

[a] Enantiomeric composition $EC\% = \frac{E_{1/2}}{E_1 + E_2} \times 100$

[b] N.S. = not separated.

10 m × 0.10 mm d_c, 0.10 mm d_f (DET-Beta 0.10) column. They were first applied to a mixture of standards and then to real-world samples.

The analysis conditions for the two narrower-bore columns were translated from the original method using an appropriate GC method translation software (Agilent), based on the approach proposed by Klee and Blumberg (2002). The flow was decreased to 0.72 and 0.4 mL/min and the temperature rate increased to 3.7 °C/min and 5 °C/min, for the DET-Beta 0.18 and DET-Beta 0.10 columns, respectively. At the same time, the split ratio was decreased to 50:1 for the DET-Beta 0.10 column because of the limited column capacity. The analysis time was reduced from 90 min for the DET-Beta 0.25–48 min and 38 min for the DET-Beta 0.18 and DET-Beta 0.10, respectively, while keeping the same chromatographic performances. As shown in Table S2 that compares the retention indices for each target enantiomer obtained with the DET-Beta columns with different dimensions. The retention indices differ from 0 unit, for ((S)- and (R)-limonene, to a maximum of 4 units for (R)-linalool, hydroxycitronellal, *cis*-hedione, patchouli alcohol, menthone and isomenthone, carvone, α-ionone, and isobornyl acetate. The separation capability of the three columns on the reference standard mixture was also determined through the separation measure, Δs, defined as the number of consecutive non-overlapping σ-intervals within the time interval (R)-α-pinene - (3Y,5E)-3-methyl-5-cyclopentadecen-1-one (first and last eluting peaks). The results showed a very similar separation capacity for the DET-Beta 0.25 and DET-Beta 0.18 columns (Δs = 1132 and Δs = 1031, respectively) and a slightly lower peak capacity with the DET-Beta 0.10 column (Δs = 767), which was due to a not proportional reduction of the peak width in relation to the decrease of the retention time difference. However, in terms of enantioseparation, similar resolution values are obtained on the three columns investigated (Table S3). In general, slightly lower resolutions are obtained with the columns with a narrower inner diameter and shorter length but the (baseline) separation is always maintained, with the exception of α-pinene and 3-methyl-5-cyclopentadecen-1-one whose resolution is poor with the conventional column as well. Moreover, the elution order of the two enantiomers is maintained on the three columns.

The analysis of authentic fragrances has shown that the method translation approach enables to obtain perfectly superimposable chromatographic patterns. The chromatographic profiles of the reference fragrance with DET-Beta 0.25 (a), DET-Beta 0.18 (b) and DET-Beta 0.10 (c) are shown in Fig. 1, while the enantiomeric composition calculated with the three columns is reported in Table 3. The results show that the analysis time can drastically be reduced with the DET-Beta 0.10 column, while maintaining the enantiomer separation of the fragrance components and an accurate evaluation of the enantiomeric composition.

The actual applicability of the methods developed and the outcome that can be obtained with chiral analysis in a fragrance quality control laboratory were then tested by analyzing six authentic perfumes. The enantiomeric composition results were consistent for the three columns studied (data not shown).

3.3. Evaluation of the greenness of chiral analyses

As mentioned in the introduction, the reduction of the analysis time is commonly considered as one of the most promising approaches to reduce the environmental impact of GC analyses. However, experimental data in this respect have never been published. This part of the study reports an evaluation on how the greenness is influenced by miniaturizing the column dimensions and speeding-up the analyses time. AGREE (Pena-Pereira et al., 2020) was selected between the available metric tools, since it comprehensively evaluates the compliance of an analytical method with the twelve principles of the Green Analytical Chemistry (GAC), and it is user-friendly, being therefore suitable for calculations in a routine quality control laboratory. The methods proposed with the DET-Beta 0.25, DET-Beta 0.18 and DET-Beta 0.10 were compared to that reported in the European Pharmacopoeia for the quality control of the lavender essential oil that suggests to monitor the enanantiomeric composition of linalool, borneol and linalyl acetate (European Phamacopoeia), taken as an example of an official method reporting the chiral analysis of real-world samples. The analysis conditions of the reference method are reported in the Supplementary Information.

Fig. 2 shows the comparison of the results from AGREE for the reference method (a) and the proposed methods (b-d). Some criticisms of the reference method were highlighted, as its final score is 0.55 on a scale of 0–1 (1 is the best score, and 0 the worst). The low score is mainly related to (i) the degree of integration, since the measurements are performed at-line (principle 3), (ii) the amount of waste generated and the toxicity of the solvent used, since the Pharmacopeia recommends preparing 10 mL of solution and to dilute the essential oil in pentane (principles 7 and 11), (iii) the analysis throughput, which is related to a relatively long analysis time (65 min) and a low number (two) of chiral compounds monitored (principle 8), and (iv) the energy consumption, which is 0.88 kWh for each analysis (principle 9). For the other parameters, good results are obtained because the method does not require sample preparation, since the samples are directly injected after dilution. The AGREE score drastically increases (above 0.7)
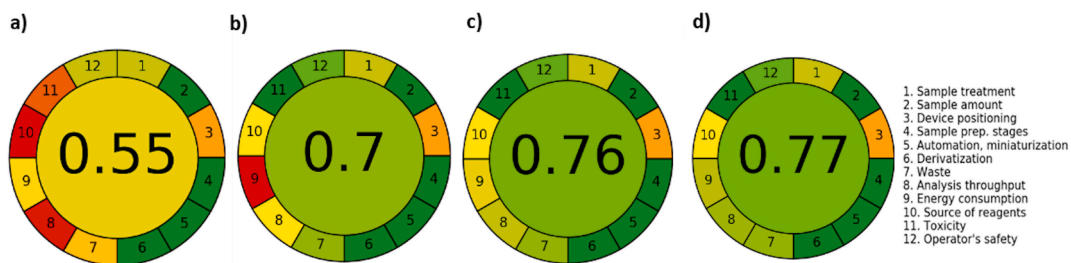

Fig. 2. AGREE scores calculated for the reference methods (a) and for the methods developed with the DET-Beta 0.25 (b), DET-Beta 0.18 (c) and DET-Beta 0.10 (d) columns.

1. Sample treatment
2. Sample amount
3. Device positioning
4. Sample prep. stages
5. Automation, miniaturization
6. Derivatization
7. Waste
8. Analysis throughput
9. Energy consumption
10. Source of reagents
11. Toxicity
12. Operator's safety

with the methods developed in this study, which can therefore be considered more compliant to the 12 principles of GAC. The degree of integration remains critical, since the samples are not collected and diluted online with the analysis, as well as the use of non-renewable reagents, since helium is used as a carrier gas (principle 10). The comparison of the results of the three methods shows that, apart from the analysis throughput, the main parameter that distinguishes the developed methods is the energy consumption for each analysis, which was calculated to be 1.53 kWh for the analyses performed with the DET-Beta 0.25 column, 0.73 kWh for the analyses performed with DET-Beta 0.18, and 0.63 kWh for the analyses performed with DET-Beta 0.10. The difference in the final score of the three methods is minimal (0.07) and it is highlighted because the energy consumption was measured with a current measuring plug. AGREE also allows to simply select the most energy-intense technique used in the method, setting a default score of 0 for GC-MS. Indeed, GC-MS is usually considered an energy-consuming analytical system, but it is essential to solve the complexity of the analyzed matrices and it is fundamental to consider that energy consumption can be drastically reduced with fast GC. In conclusion, AGREE enables a quick comparison of the greenness between different analytical methods, but it has some limitations. In fact, this tool does not consider cases where sample preparation is not required and it is not sensitive enough when two methods relying on the same analytical technique are compared. In addition, it does not take into account the analytical performance of the methods, as well as the costs and productivity associated with the analysis, which could be assessed by metric tools that evaluate the global performance of the methods.

3.4. Global assessment of chiral analyses with RGB model

The RGB model (Nowak and Koscielniak 2019) was used for the global assessment of the performance of the developed methods. This model inspired the concepts behind WAC and its associated metric tool, but it is more flexible in selecting parameters to be evaluated and in assigning their relative weights, and thus it is easier to be adapted to both the scope of the analysis and the objectives to be achieved. The name RGB is derived from the three primary colors that correspond to the three primary parameters of any analytical method. The red color represents the analytical performance of the method, the green color concerns its safety and greenness (in agreement with GAC principles), and the blue color refers to its productivity and practical effectiveness, including criteria such as methodological complexity, time and cost. An overall method score (called *method brilliance*) is calculated by combining the results of the three attributes, also taking into account the relative importance that the user attributes to each of them. In addition, a color depending on whether one of the three attributes predominates or not is assigned to the evaluated method.

An RGB template (Fig. 3) was created for the global evaluation of the methods to determine the chiral composition of fragrances. In particular, the selection of criteria for the "red" attribute was based on the need to adequately separate enantiomers of a racemate, accurately identify them, and correctly determine their relative composition. The criteria for the "green" and "blue" attributes were modulated considering the prevailing importance of GC in these analyses. Since improving the greenness of the analysis is the main objective of this study, a higher relative weight (w = 6) is assigned to the green attribute, while a relative weight of 4 is given to red and blue attributes. The assignment of a scale for rating each criterion is another fundamental step in the creation of the template. Nowak and Koscielniak (2019) proposed to determine a Low Acceptable Value (LAV), *i.e.*, a value above which the results can be con-

Fig. 3. RGB model template. Legend: LAV - Low Acceptable Value, LSV - Low Satisfactory Value, HSV- Highest Satisfactory Value. [a] consumption of helium per analysis, [b] hazard score calculated based on the number of hazards and their category according to European Regulation (EC) No. 1272/2008 (see paragraph 3.4 for details), [c] consumption of energy to carry out 15 analyses in 24 h, [d] need of replacement of consumables (column, liner, septum, …).

sidered "acceptable" (with a score of 33.3 on a scale of 1–100), and a Low Satisfactory Value (LSV), *i.e.,* a value above which the results can be considered "satisfactory" (score 66.6). In addition to these two thresholds, we added a new value, the Highest Satisfactory Value (HSV), which represents an optimal value to be obtained when no other methods provide better results (maximum score, 100). Specifically, we selected as LAVs the results that can be obtained with the reference method of the Pharmacopeia and as LSVs we decided to fix a "high" target, i.e. the best results that can currently be obtained (i.e., the results obtained with the DET-Beta 0.25 column in terms of analytical performance and the results obtained with the DET-Beta 0.10 column for the green and blue attributes). The HSVs for the redness criterion were selected considering that the aim of this study is to accurately determine the enantiomeric composition of all 27 chiral pairs, while for greenness and blueness, the consumption associated with GC analysis was calculated by setting the HSVs to the lowest possible energy and gas carrier (hydrogen) consumptions achieved with the current GC technology, *i.e.,* when the instrument is simply switched on (standby method).

Based on the above considerations, the following criteria were fixed to evaluate the analytical performance of the methods: (i) the number of compounds separated with a resolution that allowed their correct quantification, (ii) the precision in the evaluation of enantiomeric composition (evaluated by the maximum relative standard deviation for five determinations in fragrance samples performed on different days), (iii) the accuracy of the linear retention indices (determined by comparing the I^Ts obtained on the studied column to those listed in the reference library), (iv) the precision of the I^Ts (measured by their maximum difference on the investigated column on five determinations in different days). The highest relative weight was given to the first criterion (w = 4), followed by criterion ii (w = 3), criterion iii (w = 2) and criterion iv (w = 1). In evaluating the greenness of the methods, the highest importance (w = 4) was given to the energy consumption for each analysis (kWh), measured taking into account both the heating and cooling step and all the equipment used for the analysis (GC, MS, autosampler, PC). Another point of concern for GC (in particular GC-MS) is the use of helium as a carrier gas, which is not comprehensively taken into account in the previously published tools: the consumption of non-renewable gas (helium) or gas produced from non-renewable sources (hydrogen, in some cases) should be minimized or suppressed to reduce the environmental footprint of the analyses. Instrument manufacturers are indeed moving in the direction of replacing helium with hydrogen (possibly from non-fossil sources) also in GC-MS. The second criterion for the green parameter was thereby the amount of non-renewable carrier gas used for each analysis. The third criterion of the green attribute was the consumption of reagents in sample preparation through the determination of the total amount of reagents used (excluding carrier gas) every 10 analyses. The last "green" criterion considered the toxicity of the chemicals used. A hazard score was assigned to each reagent, taking into account both the number of hazards and their category according to European Regulation (EC) No. 1272/2008 (European Parliament). The total hazard score is obtained by multiplying the number of hazards in category I by 1, those in category II by 0.8, those in category III by 0.6, and those in category IV by 0.4. A similar approach has been recently proposed by Nowak and co-workers (Nowak et al., 2023b), while previous tools, as Analytical Eco-Scale (Gałuszka et al., 2012), took only into account the number of hazards, which meant rating in the same way dichloromethane and ethanol which have both one hazard (CMR - carcinogenic, mutagenic, or toxic vs. inflammable). Finally, the practical and economic aspects were considered for the blueness of the methods, following the suggestions of Nowak et al. for the WAC approach (Nowak et al., 2021). In terms of costs, energy and gas consumption were considered, as these are the items that mostly change depending on the method used. Regarding energy consumption, it is essential to mention that the calculation was performed considering a timeframe of 24 h. Still, the number of analyses was fixed at 15, since reducing the length of analyses does not mean to increase their number. High importance (w = 3) in terms of productivity was also given to time efficiency. At the same time, another critical issue to consider is the practical effectiveness of a method, especially in the context of quality control. Indeed, the blue attribute must also consider the need for specific or advanced instruments and operator skills to manage the analysis system (requirements), and, finally, the instrument maintenance.

The RGB results for the three methods developed in this study are detailed in the supplementary material (Figs. S1–S3) and summarized in Fig. 4. Generally, the method developed on the DET-Beta 0.25 column (Fig. S1) predominates in the red attribute, indicating that its main strength is its analytical performance. The overall evaluation of the method shows a method brilliance (MB) of only 25%, because, although the color score (CS) in terms of redness is 69.4% (very satisfactory), the green CS is only 11.4% (due to a very high energy consumption) and the blue CS is 29.3% (due to high cost and low time efficiency). The method developed on the DET-Beta 0.18 column (Fig. S2) shows a more balanced performance on the three attributes (final color gray) and the MB increases to 60.3%, as the value for the red color slightly decreases to 64.5%, but the values for green and blue increase to 59.8% and 57.1%, respectively. These two attributes improve even further with the method developed on the DET-Beta 0.10 column (Fig. S3), which has the best overall performance with a MB of 63.9%. The final color of the method is green, as all environmental criteria are fully met, while a slight decrease in analytical performance (still fully compliant with quality requirements) is observed. Considering the performance of the methods for each attribute, it can be observed that all the developed methods show acceptable performance, with the method on the DET-Beta 0.25 outperforming the others in terms of number of separated compounds and precision in I^Ts, but the methods developed on the narrower inner diameter and shorter columns show even higher performance in terms of precision of the enantiomeric ratio (Fig. 4A). Regarding greenness (Fig. 4B), the three methods are equivalent concerning the amount and toxicity of reagents used. Indeed, sample preparation is not required and only ethanol is used as a dilution solvent. However, major differences are seen with respect to energy and helium consumption for the analysis. The method developed on the DET-Beta 0.25 column requires much more energy than the reference method and its final score on this criterion is therefore 1. Moreover, it requires a larger amount of carrier gas, not only because the analysis time is longer, but also because the flow rate for this column is 1 mL/min, while, for the DET-Beta 0.18 and DET-Beta 0.10 columns, it is 0.72 mL/min and 0.4 mL/min, respectively. The same trend in energy and gas consumption is observed for the blueness attribute (Fig. 4C). The productivity of the three methods is also very different, as only 15 analyses per day can be performed with the DET-Beta 0.25 column, while the method developed with the DET-Beta 0.10 column enables up to 38 analyses. The three methods are almost equivalent in terms of instrument maintenance and requirements, but it is im-

Fig. 4. Comparison of RGB scores obtained for each criterion in terms of redness (a), greenness (b) and blueness (c) for the investigated columns. Legend: LAV - Low Acceptable Value, LSV - Low Satisfactory Value, HSV- Highest Satisfactory Value, man./month – maintenance/month, int. – intermediate, adv. – advanced.

portant to emphasize that the DET-Beta 0.10 column reaches pressures up to 250.8 kPa, a pressure that not all GC systems can achieve (in particular those of the previous generations).

In general, the overall assessment of the three methods shows that narrower bore and shorter columns can successfully be used in routine controls dealing with chiral recognition of fragrance compounds, as they allow correct enantiomeric determination (providing therefore accurate information about the quality of the analyzed sample) while improving environmental impact and laboratory productivity. The use of the DET-Beta 0.10 column allows to obtain the highest total score, but its main limitation is the need to use dedicated instruments enabling to apply high pressures. Therefore, the DET-Beta 0.18 column can be considered a good candidate for routine use in quality control in all laboratories.

4. Conclusions

The RGB model developed in this study provides, for the first time, a global assessment of gas chromatographic methods by accurately considering the contribution of GC and the potential improvements associated with the use of narrower and shorter columns and speeding-up of analyses in terms of environmental impact. Moreover, it evaluates the "sustainability" of a GC method, since it combines the assessment of the environmental impact of a method (that provides an ecological outcomes) with the evaluation of its analytical performance (ensuring accurate results in terms of product quality with a consequent social impact) and an evaluation of the method productivity (therefore measuring its economic impact). The template is user-friendly and can be adapted to analyses with a different scope by changing the analytical performance criteria and reference values of the method. Since the selection of principles and thresholds in the original RGB model was non strictly defined (due to the broad scope of the tool), this study also provides guidance for the selection of criteria and reference thresholds for GC analyses.

The overall assessment of the methods developed in this study shows that the use of short and narrow bore columns with fast temperature rates not only speeds up GC analyses, but also improves the greenness, increases laboratory productivity, and lowers costs while maintaining the same analytical performance as conventional methods, even for chiral analyses. This approach can therefore be considered sustainable and used in routine quality control laboratories. Further environmental improvements are expected by replac-

ing helium with hydrogen from non-fossil sources and by reducing energy consumption (e.g., by using micro GC or Low Thermal Mass- LTM devices in conventional GC systems).

Finally, it is important to note that the proposed framework allows a semi-quantitative comparison between different methods. For a quantitative assessment of the environmental impact of GC methods, LCA is more appropriate because it quantitatively estimates the impact on global warming (for example). Further efforts are therefore needed to make LCA more user-friendly and/or to set simplified or dedicated versions to make it applicable in routine quality control laboratories.

Author contributions

Gaia Bechis: Investigation, Data Curation, Conceptualization, Writing - Original Draft, Bastien Raccary: Conceptualization, Writing - Review & Editing, Elise Sarrazin: Conceptualization, Resources, Project administration, Writing - Review & Editing, Elise Corbi: Conceptualization, Writing - Review & Editing, Christophe Peres: Conceptualization, Writing - Review & Editing, Nathalie David: Conceptualization, Resources, Writing - Review & Editing, Carlo Bicchi: Conceptualization, Writing - Review & Editing and Cecilia Cagliero: Methodology, Conceptualization, Supervision, Project administration, Writing - Review & Editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Gaia Bechis reports financial support was provided by Chanel SAS.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scp.2023.101217.

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