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Article

In-Vial Micro-Matrix-Solid Phase Dispersion for the Analysis of Fragrance Allergens, Preservatives, Plasticizers, and Musks in Cosmetics

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Abstract: Fragrance allergens, preservatives, plasticizers, and synthetic musks are usually present in cosmetic and personal care products formulations and many of them are subjected to use restrictions or labeling requirements. Matrix solid-phase dispersion (MSPD) is a very suitable analytical technique for the extraction of these compounds providing a simple, low cost sample preparation, and the possibility of performing both extraction and clean-up in one step, reducing possible contamination and analyte losses. This extraction technique has been successfully applied to many cosmetics ingredients allowing obtaining quantitative recoveries. A new very simple micro-MSPD procedure performing the disruption step in a vial is proposed for the gas chromatography-mass spectrometry (GC-MS) analysis of 66 chemicals usually present in cosmetics and personal care products. The method was validated showing general recoveries between 80% and 110%, relative standard deviation (RSD) values lower than 15%, and limits of detection (LODs) below 30 $ng \cdot g^{-1}$. The validated method was applied to a broad range of cosmetics and personal care products, including several products intended for baby care.

Keywords: cosmetics; micro-matrix solid-phase dispersion; fragrance allergens; preservatives; plasticizers; musks; gas chromatography-mass spectrometry (GC-MS)

1. Introduction

Fragrances and preservatives are common ingredients in cosmetics and personal care products. Fragrances provide nice and attractive scents and preservatives are used to prevent microbial growth because the aqueous nature of many personal care products is an optimal medium for microbial growth. European legislation [1] requires the monitoring of 26 volatile compounds, the so-called potentially allergen substances (PAS) or fragrance allergens. Their presence must be indicated in the list of ingredients when their concentrations exceed 0.01% for rinse-off products, and 0.001% for leave-on products. Of these 26 substances, 24 are chemically defined volatile compounds whereas the other two are natural moss extracts. One of these 24 fragrance allergens, lyral®, was recently proposed to be transferred to the Annex III (list of substances which cosmetic products must not contain except subject to restrictions) to Annex II (list of substances prohibited in cosmetic products). Also, pinene and methyleugenol were included in the referred study; pinene is proposed to be labelled when its concentration exceeds 0.01% for rinse-off products, and 0.001% for leave-on products, whereas methyleugenol has been banned in cosmetics and personal care products for some years, and now it is included in Annex III.

Parabens are the most frequently used preservatives (their maximum concentration in cosmetics and personal care products is 0.4% for a single ester and 0.8% for mixture of esters). Its extended use is due to their broad antimicrobial spectrum and low cost [2,3]. Although these compounds are not mutagenic agents, recent studies have reported that certain parabens have been associated with genotoxicity, allergies and may also act as antiandrogens [4–6]. In recent years, another preservative, phenoxyethanol, is increasing its use as substitute of parabens. According to the European regulation [1], the maximum concentration permitted for this compound is 1% regardless of its use. However, a recent study reported by the France National Agency for Security of Medicaments (ANSM) proposed not using phenoxyethanol in products intended for children under 3 years and to reduce the maximum permitted concentration (0.4%) in other personal care products [7]. Triclosan (2,4,4′-trichloro-2′-hydroxydiphenyl ether) and the bromine-containing preservative bronidox, are also preservatives present in personal care products. Their maximum permitted concentrations according European legislation is 0.3% and 0.1%, respectively. IPBC (iodopropynyl butylcarbamate) is not permitted in products for children under 3 years of age, except in bath products, shower gels and shampoo. The antioxidants butylated hidroxyanisole (BHA) and butylated hydroxytoluene (BHT) can be used without restrictions.

Synthetic musks are other chemical compounds usually present in personal care products under the term “fragrance” or “parfum”. Synthetic musks are used as an alternative for natural musks. The European regulation has forbidden the use of three nitromusks: musk ambrette, musk moskene and musk tibetene due to their bioaccumulative properties [8]. Another two nitromusks (musk ketone and musk xylene) are allowed with restrictions [1].

Plasticizers (phthalates and adipates) are used in cosmetic and personal care formulations as solvents, fixer of fragrances, and to promote skin penetration. Diethyl phthalate (DEP) can be present in personal care products as solvent of the synthetic musk galaxolide. However, the European Commission on Endocrine Disruption has listed DEP as a Category 1 priority substance [9]. Other six phthalates (dibutyl phthalate (DBP), dimethoxyethyl phthalate (DMEP), diisopentyl phthalate (DIPP), dipentyl phthalate (DPP), benzylbutyl phthalate (BBP) and di(2-ethylhexyl) phthalate (DEHP)) were forbidden as ingredients in cosmetics and personal care products due to their possible carcinogenic and mutagenic effects in human health. Adipates (1,6-dimethylhexanedioate (DMA), 1,6-diethylhexanedioate (DEA) and di(2-ethylhexyl) adipate (DEHA)) are permitted without restrictions.

In order to guarantee product safety, the development of analytical methods is mandatory in cosmetic quality control. In this way, several analytical methods to determine fragrance allergens, preservatives, plasticizers, and/or musks in cosmetics and personal care products have been reported. A summary of the more recent extraction and analysis techniques for the analysis of these compounds in different cosmetic matrices can be found in recent reviews [10–13].

Matrix solid-phase dispersion (MSPD) is a very suitable analytical technique for the extraction of contaminants in environmental and other matrices [14] as well as to determine fragrances, preservatives, plasticizers and musks in cosmetic samples. This technique is primarily used because of its flexibility and selectivity providing efficient and low cost extractions; the possibility of performing extraction and clean-up in one step is one of their main advantages [15–21]. Also, its miniaturizing allows reducing the amount of sample, reagents and solvents required. MSPD combines different aspects of several analytical techniques, performing sample disruption while dispersing the components of the sample on and into a solid support, thereby generating a chromatographic material that possesses a particular character for the extraction of compounds from the dispersed sample [15]. This extraction technique allowed obtaining quantitative recoveries for many cosmetic ingredients [16,19,20,22]. For very volatile compounds such as pinene and limonene, that are easily lost during extraction processes [23], MSPD can constitute a good alternative to lower analyte losses [20].

The aim of the present study is to compare the performance of two micro-MSPD procedures, performing the sample disruption in mortar and also in vial, for the gas chromatography-mass spectrometry (GC-MS) analysis of 66 compounds including fragrance allergens, preservatives, plasticizers, and musks, usually present in cosmetics and personal care products. All these families of compounds are subjected to restrictions according international regulation.

2. Experimental Section

2.1. Chemicals, Materials and Samples

The analyzed compounds, their chemical names, Chemical Abstract Services (CAS) numbers, suppliers, purity of the standards and European legislation restrictions are also shown in Table 1. Deuterated methyl-4-hydroxybenzoate-2,3,5,6-d_4 (MeP_d_4; 98atom% D), benzyl_d_7 alcohol (98atom% D) and di-(2-ethylhexyl)phthalate-3,4,5,6-d_4 (DEHP_d4; 98atom% D) used as surrogate standard, were obtained from C/D/N Isotopes (Quebec, Canada), Aldrich (St. Louis, MO, USA), and Fluka Chemie GmbH (Steinheim, Germany), respectively. 2,4,6-trichlorobiphenyl (PCB-30) used as internal standard was provided by Dr. Ehrenstorfer (Augsburg, Germany).

Table 1. Target compounds: chemical names, suppliers, purity, CAS and European restrictions.

Fragrance Allergens	Chemical Names	Purity (%)	CAS	Maximum Concentration Permitted [1]
Pinene	Bicyclo[3.1.1]hept-2-ene, 2,6,6-trimethyl	≥99 [b]	80-56-8	n.r
Limonene [a]	(4R)-1-Methyl-4-(1-methylethenyl)cyclohexene	97 [b]	5989-27-5	n.r
Benzyl alcohol [a]	Benzene methanol	≥99 [b]	100-51-6	1% (as preservative)
Linalool [a]	3,7-Dimethyl-1,6-octadien-3-ol	97 [b]	78-70-6	n.r
Methyl-2-octynoate [a]	Methyl heptin carbonate	≥99 [b]	111-12-6	n.r
Citronellol [a]	(±)-3,7-Dimethyoct-6-en-1-ol	95 [b]	106-22-9	n.r
Citral [a]	3,7-Dimethyl-2,6-octadienal	95 [b]	5392-40-5	n.r
Geraniol [a]	3,7-Dimethyl-(2E)-2,6-octadien-1-ol	≥96 [b]	106-24-1	n.r
Cinnamal [a]	3-Phenyl-2-propenal	≥93 [b]	104-55-2	n.r
Hydroxycitronellal [a]	7-Hydroxy-3,7-dimethyloctanal	≥95 [b]	107-75-5	1%
Anise alcohol [a]	4-Methoxybenzyl alcohol	98 [b]	105-13-5	n.r
Cinnamyl alcohol [a]	3-Phenyl-2-propen-1-ol	98 [b]	104-54-1	n.r
Eugenol [a]	2-Methoxy-4-(2-propenyl)-phenol	99 [b]	97-53-0	n.r
Methyleugenol [a]	1,2-Dimethoxy-4-(2-propenyl)-benzene	99 [b]	93-15-2	0.01% (fine fragrance); 0.004% (eau de toilette); 0.002% (fragrance cream); 0.0002% (other leave-on products); 0.001% (rinse-off products)
Isoeugenol [a]	2-Methoxy-4-(1-propenyl)phenol	98 [b]	97-54-1	0.02%
Coumarin [a]	2H-1-benzopyran-2-one	≥99 [b]	91-64-5	n.r
α-isomethyl ionone [a]	3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1yl)-3-buten-2-one	≥85 [b]	127-51-5	n.r
Lilial® [a]	2-(4-*tert*-Butylbenzyl)propionaldehyde	≥90 [b]	80-54-6	n.r
Amyl cinnamal[a]	2-Benzylideneheptanal	97 [b]	122-40-7	n.r
Lyral® [a,g]	Hydroxyhexyl-3-cyclohexene carboxaldehyde	≥97 [b]	31906-04-4	n.r
Amylcinnamyl alcohol [a]	2-Pentyl-3-phenylprop-2-en-1-ol	≥85 [b]	101-85-9	n.r
Farnesol [a]	3,7,11-trimethyldodeca-2,6,10-trien-1-ol	95 [b]	4602-84-0	n.r
Hexylcinnamal [a]	2-Benzylideneoctanal	≥95 [b]	101-86-0	n.r

Table 1. *Cont.*

	Chemical Names	Purity (%)	CAS	Maximum Concentration Permitted [1]
Benzyl benzoate [a]	Phenylmethyl benzoate	≥99 [b]	120-51-4	n.r
Benzyl salicylate [a]	Benzyl-2-hydroxybenzoate	≥99 [b]	118-58-1	n.r
Benzyl cinnamate [a]	3-Phenyl-2-propenoic acid phenylmethyl ester	99 [b]	103-41-3	n.r
Preservatives				
Bronidox	5-Bromo-5-nitro-1,3-dioxane	≥99 [c]	30007-47-7	0.1% (rinse-off products)
Phenoxyethanol (phEtOH)	2-Phenoxyethanol	99 [c]	122-99-6	1%
Methyl paraben (MeP)	Methyl 4-hydroxibenzoate	99 [b]	99-76-3	0.4% as acid (for single ester) 0.8% as acid (for mixtures of esters)
BHA	Butylated hidroxyanisole	98.5 [c]	25013-16-5	n.r
BHT	Butylated hydroxytoluene	99 [c]	128-37-0	n.r
Ethyl paraben (EtP)	Ethyl 4-hydroxybenzoate	99 [b]	120-47-8	0.4% as acid (for single ester) 0.8% as acid (for mixtures of esters)
Isopropyl paraben (iPrP) *	Isopropyl 4-hydroxybenzoate	≥99 [b]	4191-73-5	0.4% as acid (for single ester) 0.8% as acid (for mixtures of esters)
Propyl paraben (PrP)	Propyl 4-hydroxybenzoate	99 [b]	94-13-3	0.4% as acid (for single ester) 0.8% as acid (for mixtures of esters)
IPBC	Carbamic acid, butyl-3-iodo-2-propynyl ester	97 [c]	55406-53-6	Prohibited in products for children under 3 years, except in bath products. Prohibited in oral and lip products. 0.02% (rinse-off products); 0.01% (leave-on products); 0.0075% (deodorants).
Isobutyl paraben (iBuP) *	Isobutyl 4-hydroxybenzoate	≥97 [b]	4247-02-3	0.4% as acid (for single ester) 0.8% as acid (for mixtures of esters)
Butyl paraben (BuP)	Butyl 4-hydroxybenzoate	99 [b]	94-26-8	0.4% as acid (for single ester) 0.8% as acid (for mixtures of esters)

Table 1. *Cont.*

	Chemical Names	Purity (%)	CAS	Maximum Concentration Permitted [1]
Triclosan	2,4,4′-Trichloro-2′-hydroxydiphenyl ether	≥97 [c]	3380-34-5	0.3% (toothpastes, hand soaps, shower gels, deodorants, face powders and blemish concealers, nail products); 0.2% (mouthwashes)
Benzyl paraben (BzP) *	Benzyl hydroxybenzoate	99 [b]	94-18-8	0.4% as acid (for single ester) 0.8% as acid (for mixtures of esters)
Plasticizers				
DMA	1,6-Dimethylhexanedioate	99 [c]	627-93-0	n.r
DEA	1,6-Diethylhexanedioate	99 [c]	141-28-6	n.r
DMP	Dimethyl phthalate	98 [c]	131-11-3	n.r
DEP	Diethyl phthalate	98 [b]	84-66-2	n.r
DIBP	Diisobutyl phthalate	99 [f]	84-69-5	n.r
DBP	Dibutyl phthalate	99 [b]	84-74-2	Prohibited
DMEP	Dimethoxyethyl phthalate	94 [f]	117-82-8	Prohibited
DPP	Dipentyl phthalate	99.2 [b]	131-18-0	Prohibited
BBP	Benzylbutyl phthalate	98 [b]	85-68-7	Prohibited
DEHA	Di(2-ethylhexyl) adipate	98.5 [c]	103-23-1	n.r
DIHP	Diisoheptylphthalate	99 [b]	41451-28-9	n.r
DEHP	Di(2-ethylhexyl) phthalate	99.5 [c]	117-81-7	Prohibited
DCHP	Diclohexyl phthalate	99 [b]	84-61-7	n.r
DPhP	Diphenyl phthalate	98 [b]	84-62-8	n.r
DNOP	Di-noctyl phthalate	≥ 98 [d]	117-84-0	n.r
Musks				
Cashmeran	1,1,2,3,3-Pentamethyl-2,5,6,7-tetrahydroinden-4-one	≥ 95 [f]	33704-61-9	n.r
Celestolide	4-Acetyl-6-tert-butyl-1,1-dimethylindane	≥ 98 [f]	13171-00-1	n.r
Phantolide	6-Acetyl-1,1,2,3,3,5-hexamethylindan	≥ 98 [f]	15323-35-0	2% (leave-on products)

Table 1. *Cont.*

	Chemical Names	Purity (%)	CAS	Maximum Concentration Permitted [1]
Musk Ambrette	6-tert-Butyl-3-methyl-2,4-dinitroanisole	99 [f]	83-66-9	Prohibited
Traseolide	5-Acetyl-3-isopropyl-1,1,2,6-tetramethylindane	99 [f]	68140-48-7	n.r
Galaxolide	1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta(g)-2-benzopyran	55.5 [b]	1222-05-5	n.r
Musk Xylene	1-tert-Butyl-3,5-dimethyl-2,4,6-trinitrobenzene	100 ng·mL^{-1} [c]	81-15-2	Prohibited in oral products. 1.0% (fine fragrance); 0.4% (eau de toilette); 0.03% (other products)
Tonalide	6-Acetyl-1,1,2,4,4,7-hexamethyltetralin	98 [f]	1506-02-1	Prohibited in oral products. 0.2% (rinse-off products) 0.1% (leave-on products, except: 1% hydroalcoholic products; 2.5% fine fragrance; 0.5% fragrance cream)
Musk Moskene	1,1,3,3,5-Pentamethyl-4,6-dinitro-2H-indene	≥99 [f]	116-66-5	Prohibited
Musk Tibetene	1-tert-Butyl-3,4,5-trimethyl-2,6-dinitrobenzen	≥99 [f]	145-39-1	Prohibited
Ambrettolide	17-Oxacycloheptadec-6-en-1-one	≥ 97 [b]	7779-50-2	n.r
Musk Ketone	4-tert-Butyl-3,5-dinitro-2,6-dimethyl acetophenone	≥98 [b]	81-14-1	Prohibited in oral products. 1.4% (fine fragrance) 0.56% (eau de toilette) 0.042% (other products)

[a] The presence of the substance must be indicated in the list of ingredients when its concentration exceeds 0.001% (leave-on products) and 0.01% (rinse-off products); [b] Sigma Aldrich Chemie GmbH (Steimheim, Germany); [c] Fluka Chemie GmbH (Steimheim, Germany); [d] Supelco Analytical (Bellefonte, PA, USA); [e] LGC Standards GmbH (Wesel, Germany); [f] Dr. Ehrenstorfer (Ausburg, Germany); [g] Is proposed to be excluded completely from cosmetics and personal care products; n.r: no restricted by EC No 1223/2009. * Banned from 30 July 2015.

Ethyl acetate was provided by Sigma-Aldrich Chemie GmbH (Steinheim, Germany). Florisil (60–100 mesh) was purchased from Supelco Analytical (Bellefonte, PA, USA) and anhydrous sodium sulphate (99%) from Panreac (Barcelona, Spain).

Individual stock solutions were prepared in acetone, isooctane or methanol. Further dilutions and mixtures were prepared in acetone or ethyl acetate. Solutions were stored in amber glass vials at −20 °C. All solvents and reagents were of analytical grade.

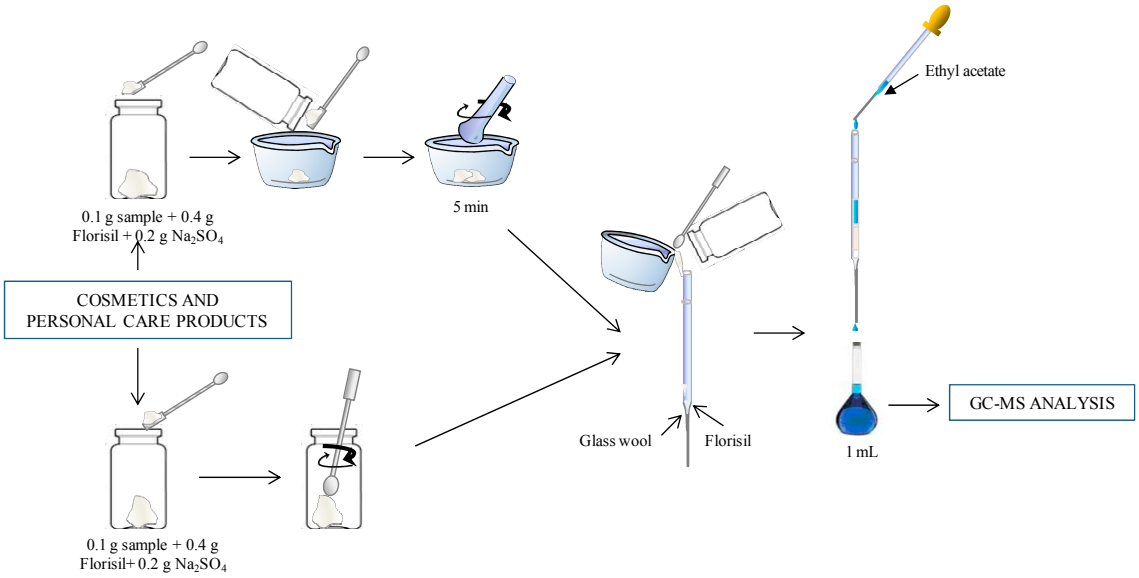
Metallic, glass, and ceramic materials; sorbents (Florisil and sodium sulphate anhydrous) and the glass wool for laboratory use (Sigma-Aldrich) were baked at 230 °C for 12 h before use to eliminate possible phthalate contamination. All materials were allowed to cool down wrapped with aluminum foil and Florisil and sodium sulphate anhydrous in desiccator.

Samples of cosmetics and personal care products from national and international brands were obtained from local sources. They included leave-on and rinse-off products such as shampoo, shower gel, body milk, sunblock, among others, including products intended for babies. Until their analysis, samples were kept in their original containers at room temperature.

2.2. Micro-Matrix Solid-Phase Dispersion (MSPD)

Cosmetic samples (0.1 g) were exactly weighted into a 10-mL glass vial and spiked with 25 μL of each surrogate solution (10 $\mu g \cdot mL^{-1}$) containing benzyl alcohol-d_7, MeP-d_4, PrP-d_4 and DEHP-d_4. Then, the sample was gently blended with 0.2 g of a drying agent (anhydrous Na_2SO_4), and 0.4 g of the dispersing sorbent (Florisil), into the vial or in a porcelain mortar, using a glass rod or a porcelain pestle, respectively, until a homogeneous mixture was obtained (*ca*. 5 min). The mixture was transferred into a glass Pasteur pipette (approximately 150 mm), with a small amount of glass wool at the bottom, containing 0.1 g of Florisil (to obtain a further degree of fractionation and sample clean-up). Finally, a small amount of glass wool was placed on top of the sample before compression with a spatula. Elution with ethyl acetate was made by gravity flow, collecting the extract into a 1 mL volumetric flask. Then, 12.5 μL of PCB-30 internal standard solution (1 $\mu g \cdot mL^{-1}$) was added. The micro-MSPD extracts diluted when necessary were directly analyzed by GC-MS. Fortified samples were spiked with 20 μL of the corresponding acetone solution of the target compounds to get the desired final concentration and submitted to the same process described above. The optimization of the experimental conditions (amount of sample, solvent, dispersant and volume elution) has been described elsewhere [19,20]. Figure 1 illustrates the described micro-MSPD process.

Figure 1. Micro-matrix-solid-phase-dispersion (MSPD) procedure.



2.3. Gas Chromatography-Mass Spectrometry (GC-MS) Analysis

The analysis was performed using an Agilent 7890A (GC)-Agilent 5975C inert MSD with triple axis detector and an Agilent 7693 autosampler from Agilent Technologies (Palo Alto, CA, USA). The temperatures of the transfer line, the quadrupole and the ion source were set at 290, 150 and 230 °C, respectively. Electronic impact (EI) was used as ionization technique. The system was operated by Agilent MSD ChemStation E.02.00.493 software.

Separation was performed on a ZB-5 capillary column (30 m × 0.25 mm i.d. (internal diameter), 0.25 μm film thickness) obtained from Phenomenex (Torrance, CA, USA). Helium (purity 99.999%) was employed as carrier gas at a constant column flow of 1.0 mL·min^{-1}. The GC oven temperature was programmed from 60 °C (held 1 min) to 100 °C at 8 °C min^{-1}, to 150 °C at 20 °C·min^{-1}, to 200 °C at 25 °C·min^{-1} to 220 °C at 8 °C·min^{-1} and 30 °C·min^{-1} to 290 (held 10 min). After 1 min, the split valve was opened (75 mL·min^{-1}), and the injector temperature was kept at 260 °C. The injection volume was 1 μL. The electron multiplier was set at a nominal value of 1553 V.

3. Results and Discussion

3.1. GC-MS Performance

The chromatographic conditions were optimized to achieve an efficient separation of 66 target compounds frequently used in cosmetics and personal care products: 26 fragrance allergens, 13 preservatives, 15 plasticizers (phthalates and adipates) and 12 musks. For GC-MS analysis, the mass spectra detector (MSD) was operated in the selected ion monitoring (SIM) mode, monitoring three ions per compound. Table 2 shows the quantification and identification ions, and the retention time of the compounds. Chromatograms of a standard solution containing 200 ng·mL^{-1} of target compounds (DIHP, 400 ng·mL^{-1}) are shown in Figure 2.

Table 2. Retention time, quantification and identification ions.

Key	Target Compounds	Retention Time (min)	Quantification and Identification Ions	Key	Target Compounds	Retention Time (min)	Quantification and Identification Ions
1	Pinene	5.23	77 (27), **93** (100), 121 (13)	34	Lyral®	12.45	79 (74), 93 (78), **136** (100)
2	Limonene	6.85	**68** (100), 93 (76),121 (25)	35	iBuP	12.49	93 (12), **121** (100), 138 (58)
3	Benzyl alcohol	6.90	77 (73), 79 (115), **108** (100)	36	Farnesol	12.63/12.93	**69** (100), 93 (27), 107 (15)
4	Linalool	7.77	**71 (100)** ,93 (84) ,121 (24)	37	Amylcinnamyl alcohol	12.64	91(88), 115 (60), **133** (100)
5	Methyl-2-octynoate	8.87	79 (66), **95** (100) ,123 (73)	38	BuP	12.93	**121** (100), 138 (84), 194 (6)
6	Bronidox	9.03	85 (27), 107 (49), **135** (100)	39	Celestolide	13.03	173 (22), **229** (100), 244 (44)
7	PhEtOH	9,09	77 (28), **94** (100), 138 (31)	40	Hexylcinnamal	13.31	**129** (100), 145 (51), 216 (40)
8	Citronellol	9.12	**69** (100) ,95 (49) ,109 (18)	41	Phantolide	13.53	187 (11), **229** (100), 244 (24)
9	DMA	9.23	101 (72), 111 (77), **114** (100)	42	Benzyl benzoate	13.58	77 (28), 91 (47), **105** (100)
10	Citral	9.27/9.51	**69** (100), 94 (17), 109 (10)	43	Ambrette	14.53	**253** (100), 254 (13), 268 (35)
11	Geraniol	9.36	**69** (100), 93 (18) ,111 (6)	44	Traseolide	14.74	43 (41), **215** (100), 258 (14)
12	Cinnamal	9.56	77 (35), 103 (50), **131** (100)	45	DIBP	14.84	57 (12), **149** (100), 223 (6.8)
13	Hydroxycitronellal	9.62	**59** (100), 71 (13) , 81 (43)	46	Galaxolide	14.84	213 (23), **243** (100), 258 (20)
14	Anise alcohol	9.64	109 (77), 121 (55), **138** (100)	47	Xylene	14.96	43 (62), 57 (16), **282** (100)
15	Cinnamyl alcohol	9.82	**92** (100), 105 (53), 115 (54)	48	Tonalide	14.99	43 (48), **243** (100), 258 (26)
16	Eugenol	10.21	103 (28),131 (27),**164** (100)	49	Benzyl salicylate	15.08	65 (11), **91** (100), 228 (12)
17	DEA	10.30	**111** (100), 128 (63), 157 (81)	50	Moskene	15.40	**263** (100), 264 (20), 278 (8.9)
18	Methyleugenol	10.47	147 (31), 163 (29), **178** (100)	51	Ambrettolide	16.23	**67** (100), 81 (98), 96 (89)
19	Isoeugenol	10.54/10.82	103(22), 131 (20), **164** (100)	52	Tibetene	16.33	43 (33), **251** (100), 266 (28)
20	MeP	10.78	93.0 (21), **121** (100), 153 (35)	53	DBP	16.46	**149** (100), 150 (9), 223 (4.9)
21	Coumarin	10.82	90 (42), 118 (110), **146** (100)	54	Ketone	16.99	191 (24), 294 (26), **279** (100)
22	DMP	10.83	77 (13), 194 (66), **163** (100)	55	DMEP	17.10	**59** (100), 104 (18), 149 (29)
23	BHA	11.03	137 (63), **165** (100), 180 (51)	56	Benzyl cinnamate	18.59	**91** (100), 131 (90), 192 (63)
24	α-isomethyl ionone	11.05	107 (58), **135** (100), 150 (61)	57	Triclosan	18.78	218 (93), **288** (100), 290 (93)
25	BHT	11.24	177 (8), **205** (100), 220 (25)	58	BzP	18.98	91 (46), **121** (100), 228 (21)
26	EtP	11.24	**121** (100), 138 (21), 166 (18)	59	DPP	19.12	71 (16), **149** (100), 237 (5.6)
27	Cashmeran	11.26	135 (43), **191** (100), 206 (57)	60	BBP	20.49	**91** (53), 149 (100), 206 (24)

Table 2. *Cont.*

Key	Target Compounds	Retention Time (min)	Quantification and Identification Ions	Key	Target Compounds	Retention Time (min)	Quantification and Identification Ions
28	Lilial®	11.36	131 (39), 147 (40), **189** (100)	61	DEHA	20.69	112 (26), **129** (100), 147 (21)
29	iPrP	11.45	**121** (100), 138 (39), 180 (14)	62	DIHP	21.07	149 (100), 223 (7), **265** (52)
30	DEP	11.82	**149** (100), 150 (12), 177 (24)	63	DCHP	21.53	55 (19), **149** (100), 167 (31)
31	PrP	11.99	**121** (100), 138 (58), 180 (7)	64	DEHP	21.54	167 (30), **149** (100), 279 (10)
32	Amyl cinnamal	12.31	115 (89), **129** (100), 145 (57)	65	DPhP	21.65	77 (19), 153 (4), **225** (100)
33	IPBC	12.34	100 (15), **165** (100), 182 (50)	66	DNOP	22.71	**149** (100), 223 (22), 279 (6.2)

The GC-MS method performance parameters for the 66 target compounds are summarized in Table 3. Regarding the instrumental linearity, the method exhibited a direct proportional relationship between the amount of each analyte and the chromatographic response. Calibration standards in ethyl acetate were prepared covering a concentration range from 10 to 1000 ng·mL^{-1} (anise alcohol, cinnamyl alcohol, amylcinnamyl alcohol, triclosan, and musk ketone, 20–1000 ng·mL^{-1}; IPBC, 50–1000 ng·mL^{-1}; di-iso-heptyl-phthalate (DIHP), 100–4000 ng·mL^{-1}; and farnesol, 250–1000 ng·mL^{-1}). Correlation coefficients $R \geq 0.9915$ were generally obtained. Method precision was studied within-a-day (n = 3) and among-days (n = 6) at 250 ng·mL^{-1} (other concentration levels, 50, 500 and 1000 ng·mL^{-1} were calculated, data not shown). Relative standard deviation (RSD) values ranged from 1.7% to 9.5% for intra-day analysis, and between 1.8 and 10% for inter-day analysis. Instrumental detection limits (IDLs) were in all cases calculated as the concentration giving a signal-to-noise of three (S/N = 3) since none of the target compounds were detected in the solvent chromatographic blanks and they were at the low ng·mL^{-1} with values in general below 6 ng·mL^{-1} (farnesol, IPBC, and DIHP, 70 ng·mL^{-1}, 10 ng·mL^{-1}, and 24 ng·mL^{-1}, respectively). The phthalate DIHP is complex mixtures of isomers, and the chromatographic signal is composed of several chromatographic peaks.

Figure 2. Selected ion monitoring (SIM) chromatogram of a standard mixture of the target compounds (200 ng·mL^{-1}; di-iso-heptyl-phthalate (DIHP), 400 ng·mL^{-1}).

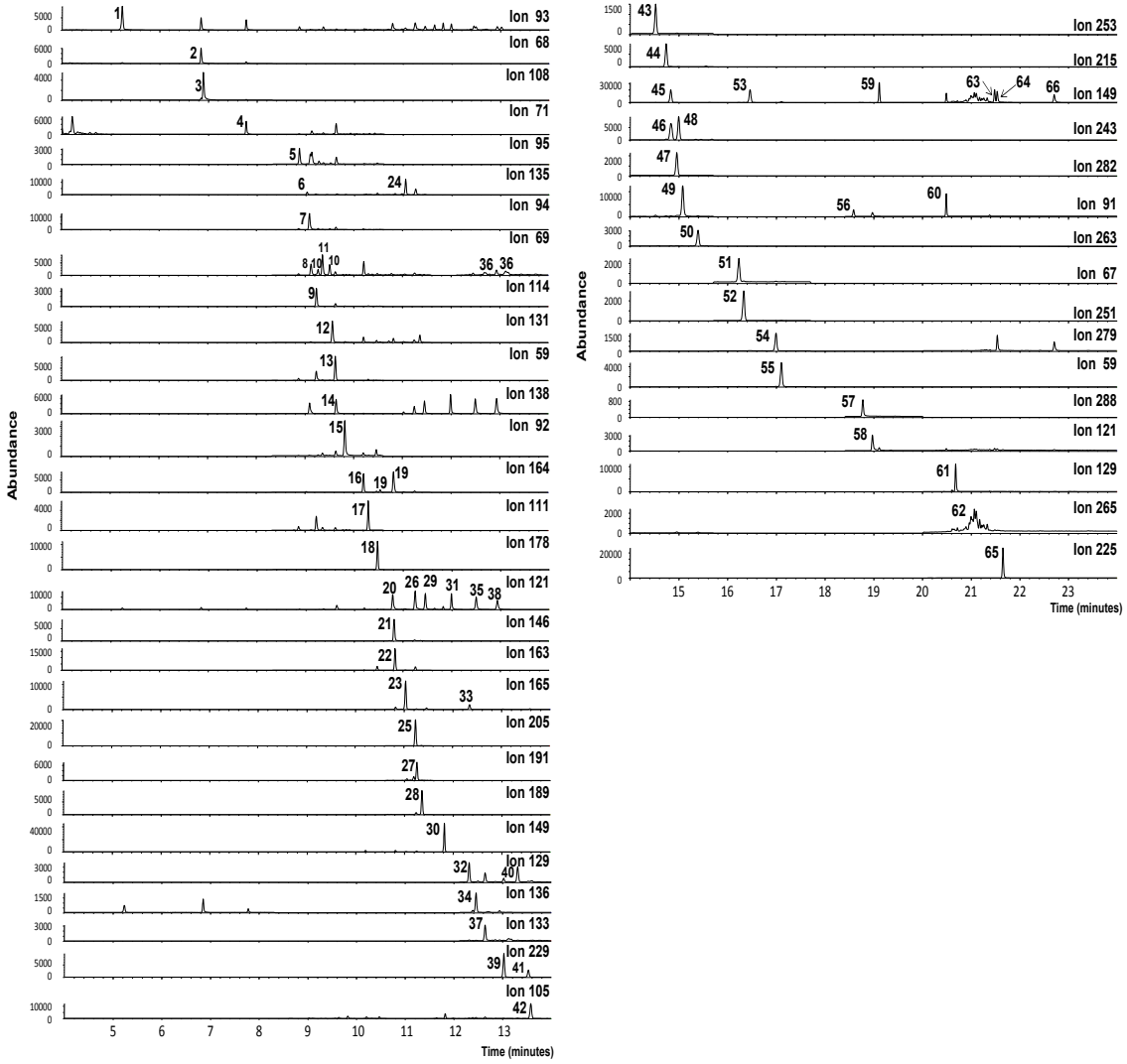


Table 3. Quality parameters of the method.

Fragrance Allergens	Correlation coefficient (*R*)	IDL ($ng \cdot mL^{-1}$)	LOD (%, w/w × 10^4)	LOQ (%, w/w × 10^4)	Intra-Day Precision (RSD, %) [a]	Inter-Day Precision (RSD, %) [b]
Pinene	0.9997	1.02	0.0169	0.0563	1.8	1.8
Limonene	0.9993	0.99	0.0213	0.0709	2.5	2.1
Benzyl alcohol	0.9980	2.03	0.0232	0.0773	3.0	5.5
Linalool	0.9984	2.10	0.0260	0.0866	4.0	3.8
Methyl-2-octynoate	0.9969	2.75	0.0275	0.0916	4.6	5.0
Citronellol	0.9965	2.78	0.0313	0.1042	5.6	4.6
Citral	0.9973	2.80	0.0400	0.1332	5.2	4.3
Geraniol	0.9969	3.05	0.0400	0.1332	5.1	5.2
Cinnamal	0.9984	2.97	0.0300	0.0990	3.4	3.2
Hydroxycitronellal	0.9972	1.93	0.0197	0.0656	4.7	4.2
Anise alcohol	0.9972	4.04	0.0404	0.1345	4.0	3.9
Cinnamyl alcohol	0.9965	5.28	0.0528	0.1758	3.3	3.8
Eugenol	0.9964	1.91	0.0210	0.0693	5.0	4.7
Methyleugenol	0.9982	1.97	0.0197	0.0656	2.8	2.4
Isoeugenol	0.9976	2.95	0.0309	0.1029	3.7	3.5
Coumarin	0.9997	2.00	0.0220	0.0733	1.7	2.1
α-isomethyl ionone	0.9985	0.96	0.0118	0.0393	3.4	3.0
Lilial®	0.9984	1.05	0.0196	0.0653	3.5	2.8
Amyl cinnamal	0.9963	2.20	0.0320	0.1066	4.4	4.1
Lyral®	0.9937	2.40	0.0240	0.0799	4.6	5.5
Amylcinnamyl alcohol	0.9930	6.04	0.0604	0.2011	4.3	4.1
Farnesol	0.9978	70.0	0.7000	2.331	4.3	2.3
Hexylcinnamal	0.9954	3.01	0.0301	0.1002	5.0	4.2
Benzyl benzoate	0.9986	2.10	0.0343	0.1142	3.1	2.7
Benzyl salicylate	0.9926	2.93	0.0293	0.0976	5.2	4.9
Benzyl cinnamate	0.9945	2.93	0.0293	0.0976	4.1	3.3

Table 3. *Cont.*

Preservatives	Correlation coefficient (R)	IDL ($ng \cdot mL^{-1}$)	LOD (%, w/w × 10^4)	LOQ (%, w/w × 10^4)	Intra-Day Precision (RSD, %) [a]	Inter-Day Precision (RSD, %) [b]
Bronidox	0.9977	2.61	0.0261	0.0869	1.8	3.2
PhEtOH	0.9967	2.34	0.0234	0.0779	4.6	4.4
MeP	0.9972	2.02	0.0300	0.0999	4.2	5.3
BHA	0.9984	1.7	0.0170	0.0566	4.5	4.8
BHT	0.9990	0.53	0.0053	0.0176	3.1	2.6
EtP	0.9974	2.87	0.0375	0.1249	3.3	3.7
iPrP	0.9972	2.80	0.0380	0.1265	4.7	4.4
PrP	0.9956	2.92	0.0292	0.0972	5.2	5.3
IPBC	0.9956	10.0	0.150	0.4995	1.7	4.4
iBuP	0.9941	2.94	0.0310	0.1032	5.1	5.2
BuP	0.9942	3.02	0.0302	0.1006	4.4	5.4
Triclosan	0.9915	5.95	0.0595	0.1981	4.8	5.7
BzP	0.9942	5.90	0.0590	0.1947	5.0	7.9
Plasticizers						
DMA	0.9994	0.90	0.0090	0.0299	1.8	2.1
DEA	0.9992	1.20	0.0260	0.0866	3.6	3.0
DMP	0.9996	0.47	0.0096	0.0319	2.5	2.1
DEP	0.9996	0.70	0.0070	0.0233	3.0	3.0
DIBP	0.9992	1.30	0.0203	0.0676	4.2	3.6
DBP	0.9990	0.75	0.0075	0.0250	4.4	3.9
DMEP	0.9991	2.00	0.0375	0.1238	4.3	4.3
DPP	0.9982	0.17	0.0064	0.0213	4.6	4.8
BBP	0.9976	2.00	0.0342	0.1139	2.5	3.6
DEHA	0.9974	0.93	0.0261	0.0869	3.0	6.7
DIHP	0.9989	24	0.4000	1.332	9.5	10

Table 3. *Cont.*

Plasticizers	Correlation coefficient (R)	IDL ($ng \cdot mL^{-1}$)	LOD (%, w/w × 10^4)	LOQ (%, w/w × 10^4)	Intra-Day Precision (RSD, %) [a]	Inter-Day Precision (RSD, %) [b]
DEHP	0.9976	0.95	0.0300	0.0999	3.9	6.3
DCHP	0.9990	0.70	0.0200	0.0666	6.3	5.4
DPhP	0.9990	0.45	0.0307	0.1022	3.6	5.2
DNOP	0.9966	0.40	0.0092	0.0306	1.7	3.0
Musks						
Cashmeran	0.9996	0.60	0.0300	0.0999	3.7	3.0
Celestolide	0.9983	0.25	0.0026	0.0866	5.0	4.2
Phantolide	0.9983	0.52	0.0087	0.0289	4.5	4.3
Ambrette	0.9965	2.00	0.0300	0.0999	3.6	4.4
Traseolide	0.9970	0.80	0.0126	0.0419	5.0	4.8
Galaxolide	0.9995	0.83	0.0216	0.0719	3.6	2.8
Xylene	0.9946	2.05	0.0293	0.0976	4.1	4.3
Tonalide	0.9992	0.83	0.0162	0.0539	4.7	3.9
Moskene	0.9933	1.72	0.0480	0.1598	2.6	4.3
Tibetene	0.9964	1.90	0.0196	0.0652	4.2	4.0
Ambrettolide	0.9990	2.13	0.1200	0.3996	3.8	3.5
Ketone	0.9954	3.20	0.0706	0.2351	5.4	4.5

[a] $n = 3$. Calculated for 250 $ng \cdot mL^{-1}$; [b] $n = 6$. Calculated for 250 $ng \cdot mL^{-1}$

3.2. Analytical Method Performance

Complete method quality parameters were evaluated using real cosmetic samples and the results are shown in Tables 4 and 5. In this way, recovery studies were carried out by applying the optimized method to two samples spiked at three levels of concentration: 2, 10 and 20 $\mu g \cdot g^{-1}$. These samples are a regenerating cream (leave-on) and a shampoo (rinse-off); they were selected for recoveries studies since the leave-on sample was labeled as perfume-free and preservative-free, and the rinse-off sample was almost free of the target compounds (only contained MeP, BHT, and PrP). In any case, previous analyses of the samples showed the presence of some of the target compounds, and these initial concentrations were taken into account to calculate the recoveries. Recoveries were higher than 90% for the most of the studied compounds (see Tables 4 and 5 for leave-on and rinse-off samples, respectively) regardless of using vial or mortar for the MSPD disruption step. In the case of the most volatile compounds, pinene recovery was 70% and 35%, for leave-on and rinse-of samples, respectively; and for limonene, recovery presented an average value of 75% employing a vial, whereas lower recoveries were obtained employing a mortar. Recovery study was extended to three other cosmetic matrices (shampoo, sunblock product, body milk) that were fortified at 10 $\mu g \cdot g^{-1}$. Results are presented in Table 6, and demonstrate the quantitative recovery of the compounds. Precision was evaluated attaining RSD values generally lower than 10% (see also Tables 4 and 5).

Figure 3 shows a comparison of the results obtained using vial or mortar for the micro-MSPD for a real leave-on sample containing 23 target analytes (hands cream). Obtained responses are equivalent employing mortar or vial for the disruption step, excluding pinene and limonene for which responses were higher using vial. Limits of detection (LODs) were calculated as the compound concentration giving a signal-to-noise ratio of three (S/N = 3). As shown in Table 3, LOD values for the fragrance allergens ranged from 0.0118 to 0.0604 $\mu g \cdot g^{-1}$ (excluding farnesol, 0.700 $\mu g \cdot g^{-1}$), for preservatives, these values were between 0.0053 and 0.0595 $\mu g \cdot g^{-1}$ (excluding IPBC) and for plasticizers and musks LODs values ranged from 0.0026 to 0.1200 (excluding DIHP).

Therefore, the proposed micro-MSPD method using a vial instead of a mortar for the disruption and dispersion step can be considered suitable for the determination of fragrance allergens, preservatives, musks, and plasticizers in cosmetic and personal care products. It is highly recommended to decrease losses of most volatile fragrances such as pinene and limonene during sample preparation. For these compounds, the increase of temperature in the mortar disruption step is unfavorable for their quantitative extraction, whereas for in-vial disruption the generated heat is lower, and the most volatile compounds can be extracted lossless; also, in-vial disruption reduces extraction steps, providing a quicker extraction procedure.

Table 4. Recoveries of fragrance allergens, preservatives, plasticizers and musks in a leave-on sample (regenerating cream) fortified at three concentration levels, analyzed by the proposed method μMSPD-GC-MS.

Fragrance Allergens	Recoveries (%, RSD)					
	2 μg·g^{-1}		10 μg·g^{-1}		20 μg·g^{-1}	
	Mortar	Vial	Mortar	Vial	Mortar	Vial
Pinene	23.2 (6.4)	63.1 (3.9)	23.5 (0.24)	71.8 (13)	34.0 (0.87)	72.6 (4.3)
Limonene	51.7 (2.0)	73.8 (1.1)	56.7 (7.1)	79.5 (11)	57.8 (0.016)	78.6 (10)
Benzyl alcohol	97.3 (0.76)	97.3 (1.3)	98.6 (0.80)	90.4 (7.9)	113 (0.15)	110 (1.9)
Linalool	105 (0.67)	82.5 (0.11)	96.7 (10)	89.3 (14)	107 (0.17)	100 (13)
Methyl-2-octynoate	87.8 (1.7)	85.2 (2.9)	97.5 (10)	86.7 (14)	112 (0.90)	95.4 (11)
Citronellol	101 (4.0)	89.3 (11)	97.6 (8.1)	93.1 (13)	110 (0.53)	94.8 (10)
Citral	99.0 (3.7)	104 (1.8)	97.5 (14)	112 (14)	112 (1.1)	101 (10)
Geraniol	114 (1.6)	82.5 (7.7)	82.0 (5.6)	81.7 (7.6)	102 (0.14)	92.7 (10)
Cinnamal	90.5 (4.5)	87.8 (0.74)	91.5 (12)	84.5 (13)	104 (0.88)	96.2 (6.6)
Hydroxycitronellal	81.9 (1.7)	80.1 (0.60)	101 (11)	97.8 (2.9)	114 (0.052)	101 (11)
Anise alcohol	93.8 (4.5)	92.2 (2.6)	96.2 (13)	87.4 (13)	111 (0.67)	101 (6.3)
Cinnamyl alcohol	96.3 (5.6)	87.3 (13)	94.0 (9.6)	87.2 (15)	110 (0.83)	98.8 (13)
Eugenol	87.2 (5.2)	83.0 (4.0)	93.8 (8.7)	89.2 (15)	105 (0.96)	98.7 (12)
Methyleugenol	85.8 (0.15)	83.6 (3.1)	95.5 (11)	86.7 (14)	109 (1.3)	98.7 (8.4)
Isoeugenol	80.9 (15)	100 (12)	114 (9.6)	109 (14)	87.2 (1.0)	89.4 (9.1)
Coumarin	91.1 (0.61)	85.2 (2.7)	95.5 (14)	87.3 (11)	109 (0.23)	100 (2.7)
α-isomethyl ionone	83.6 (6.2)	86.3 (0.78)	95.7 (11)	89.6 (12)	108 (0.82)	101 (7.4)
Lilial®	84.5 (3.3)	83.2 (1.4)	97.0 (11)	88.8 (15)	110 (1.7)	98.2 (10)
Amyl cinnamal	89.3 (4.4)	89.5 (7.8)	94.3 (5.2)	85.8 (4.3)	111 (3.5)	95.9 (15)
Lyral®	99.3 (11)	83.0 (12)	104 (6.9)	94.3 (5.4)	114 (2.8)	95.4 (14)
Amylcinnamyl alcohol	108 (10)	95.2 (12)	104 (7.4)	95.9 (3.9)	112 (3.1)	102 (15)
Farnesol	<LOQ	<LOQ	104 (2.7)	97.1 (7.6)	109 (7.5)	86.8 (7.5)
Hexylcinnamal	87.7 (1.8)	107 (0.12)	107 (4.5)	103 (5.1)	115 (3.8)	97.3 (11)
Benzyl benzoate	88.7 (7.6)	90.8 (6.9)	98.3 (14)	90.8 (12)	111 (0.16)	104 (4.9)
Benzyl salicylate	105 (3.1)	109 (13)	97.9 (14)	90.7 (13)	112 (1.9)	106 (2.8)
Benzyl cinnamate	94.5 (1.8)	102 (0.27)	102 (15)	94.2 (12)	112 (10)	108 (1.6)

Table 4. *Cont.*

Preservatives	Recoveries (%, RSD)					
	2 µg·g^{-1}		10 µg·g^{-1}		20 µg·g^{-1}	
	Mortar	Vial	Mortar	Vial	Mortar	Vial
Bronidox	92.1 (1.3)	88.0 (4.4)	95.6 (12)	87.3 (13)	108 (0.89)	100 (10)
PhEtOH	96.0 (3.8)	91.6 (0.87)	102 (12)	92.1 (13)	109 (0.91)	97.1 (11)
MeP	95.5 (4.2)	90.2 (6.4)	97.3 (11)	93.6 (15)	107 (1.7)	96.6 (11)
BHA	72.8 (6.6)	80.2 (1.2)	104 (9.4)	104 (13)	99.3 (0.53)	97.7 (7.3)
BHT	82.3 (0.16)	81.4 (0.33)	116 (0.83)	115 (12)	108 (0.67)	105 (6.9)
EtP	96.7 (10)	83.9 (15)	103 (13)	95.2 (14)	112 (0.36)	102 (10)
iPrP	100 (4.7)	91.0 (6.5)	100 (10)	93.2 (14)	109 (1.1)	98.2 (11)
PrP	111 (5.2)	87.5 (14)	99.3 (9.6)	97.5 (7.8)	109 (2.0)	94.3 (13)
IPBC	106 (15)	83.0 (12)	88.4 (1.6)	101 (4.5)	113 (4.0)	89.0 (16)
iBuP	113 (9.4)	92.6 (14)	103 (12)	95.2 (2.2)	111 (1.4)	98.5 (11)
BuP	96.8 (7.9)	82.0 (6.7)	99 (9.2)	88.9 (2.7)	110 (2.5)	95.2 (15)
Triclosan	109 (14)	112 (3.4)	100 (13)	107 (9.1)	111 (11)	108 (12)
BzP	105 (14)	92.6 (1.5)	111 (13)	111 (6.8)	117 (11)	111 (8.4)
Plasticizers						
DMA	93.9 (7.0)	105 (12)	116 (9.8)	108 (8.5)	103 (0.60)	97.5 (3.1)
DEA	87.5 (0.038)	81.4 (2.8)	95.4 (15)	87.5 (12)	111 (0.22)	100 (5.2)
DMP	81.5 (3.6)	83.3 (0.53)	98.2 (15)	90.5 (9.4)	109 (0.77)	102 (0.33)
DEP	79.3 (5.2)	83.1 (0.81)	96.1 (13)	87.2 (12)	110 (0.36)	101 (2.8)
DIBP	83.1 (1.2)	95.0 (2.1)	98.4 (14)	88.7 (14)	111 (0.88)	101 (3.2)
DBP	91.0 (6.5)	94.8 (3.3)	100 (14)	92.1 (8.8)	114 (2.5)	110 (3.6)
DMEP	90.3 (6.8)	103 (7.2)	107 (12)	99.2 (12)	114 (3.7)	108 (0.82)
DPP	96.8 (11)	98.3 (0.40)	101 (14)	96.3 (10)	110 (6.6)	107 (2.6)
BBP	89.7 (3.5)	83.7 (0.35)	92.0 (16)	86.7 (8.9)	103 (0.34)	96.9 (4.2)
DEHA	83.9 (7.8)	84.5 (2.7)	87.8 (14)	85.2 (8.5)	86.4 (0.87)	95.0 (0.76)

Table 4. *Cont.*

Plasticizers	Recoveries (%, RSD)					
	2 µg·g^{-1}		10 µg·g^{-1}		20 µg·g^{-1}	
	Mortar	Vial	Mortar	Vial	Mortar	Vial
DIHP	104 (5.3)	102 (1.1)	106 (6.3)	88.4 (6.0)	96.9 (6.2)	93.7 (5.1)
DEHP	98.1 (3.6)	81.1 (0.73)	93.3 (13)	92.4 (4.8)	101 (8.8)	96.4 (3.1)
DCHP	88.5 (2.4)	92.0 (5.1)	93.0 (12)	87.5 (6.4)	105 (2.4)	102 (3.4)
DPhP	84.9 (4.6)	84.4 (1.3)	90.5 (0.61)	84.3 (8.6)	102 (0.29)	96.9 (4.2)
DNOP	87.1 (1.2)	88.4 (2.8)	89.0 (15)	84.1 (9.2)	103 (3.6)	98.5 (2.2)
Musks						
Cashmeran	87.4 (2.0)	82.5 (9.5)	98.0 (13)	89.1 (13)	110 (1.5)	103 (7.2)
Celestolide	81.8 (5.7)	82.9 (0.80)	94.6 (9.9)	87.4 (3.1)	109 (1.9)	96.9 (9.0)
Phantolide	86.3 (4.9)	90.4 (0.67)	102 (10)	94.3 (3.4)	115 (3.3)	102 (11)
Ambrette	86.8 (9.3)	83.7 (14)	93.8 (0.23)	104 (7.1)	115 (6.1)	91.5 (6.2)
Traseolide	88.1 (7.6)	90.7 (3.3)	99.4 (9.4)	91.0 (4.5)	114 (2.6)	97.9 (10)
Galaxolide	88.9 (0.27)	94.7 (0.52)	103 (15)	95.3 (13)	114 (1.4)	105 (3.3)
Xylene	81.1 (12)	82.1 (5.6)	68.3 (2.1)	79.1 (2.6)	93.3 (3.1)	80.0 (6.2)
Tonalide	83.1 (1.4)	88.4 (0.72)	87.5 (14)	83.1 (8.2)	101 (0.92)	96.4 (1.4)
Moskene	89.8 (13)	86.1 (15)	93.5 (7.3)	83.2 (4.4)	114 (3.7)	94.6 (15)
Tibetene	103 (8.1)	109 (3.8)	100 (14)	93.0 (13)	115 (3.6)	111 (2.6)
Ambrettolide	96.0 (5.6)	111 (7.9)	106 (1.1)	107 (12)	113 (3.0)	108 (8.8)
Ketone	101 (14)	109 (6.1)	104 (10)	97.9 (15)	114 (5.9)	109 (6.9)

Table 5. Recoveries of fragrance allergens, preservatives, plasticizers and musks in a rinse-off sample (shampoo) fortified at three concentration levels, analyzed by the proposed method μMSPD-GC-MS.

Fragrance Allergens	Recoveries (%, RSD)					
	2 μg·g^{-1}		10 μg·g^{-1}		20 μg·g^{-1}	
	Mortar	Vial	Mortar	Vial	Mortar	Vial
Pinene	4.08 (12)	20.8 (0.59)	5.13 (0.38)	36.5 (1.2)	9.5 (6.9)	36.8 (9.4)
Limonene	28.2 (11)	64.7 (2.1)	28.1 (7.5)	75.8 (15)	38.9 (5.7)	65.9 (14)
Benzyl alcohol	113 (9.3)	90.8 (13)	85.7 (1.7)	92.2 (1.5)	105 (8.7)	102 (8.9)
Linalool	81.3 (9.3)	114 (6.9)	85.4 (3.6)	109 (2.5)	95.5 (14)	88.7 (0.53)
Methyl-2-octynoate	92.4 (2.8)	83.2 (5.2)	94.0 (6.7)	101 (5.6)	106 (11)	88.5 (15)
Citronellol	108 (1.4)	114 (5.0)	90.9 (5.0)	99.1 (3.8)	100 (14)	102 (6.8)
Citral	100 (3.0)	107 (10)	83.3 (6.4)	103 (7.0)	103 (12)	97.7 (4.3)
Geraniol	109 (4.0)	94.9 (13)	90.4 (11)	102 (3.4)	93.9 (13)	92.6 (0.44)
Cinnamal	105 (3.6)	89.1 (11)	88.5 (5.3)	94.2 (0.88)	103 (7.2)	96.0 (15)
Hydroxycitronellal	100 (14)	82.1 (5.0)	80.1 (2.7)	83.7 (4.7)	89.9 (12)	87.6 (3.7)
Anise alcohol	112 (8.5)	90.1 (15)	86.6 (2.4)	97.1 (0.76)	101 (10)	91.7 (9.3)
Cinnamyl alcohol	113 (7.9)	83.4 (15)	87.6 (4.3)	97.7 (0.40)	97.9 (13)	95.5 (13)
Eugenol	106 (3.5)	88.6 (13)	87.5 (1.9)	99.1 (1.2)	98.6 (10)	92.1 (15)
Methyleugenol	110 (10)	94.3 (1.5)	96.4 (1.2)	102 (0.33)	104 (4.4)	95.9 (10)
Isoeugenol	87.9 (10)	83.8 (6.9)	107 (2.6)	119 (0.42)	96.2 (5.0)	92.7 (10)
Coumarin	111 (12)	90.1 (3.8)	89.7 (1.7)	97.1 (3.5)	104 (1.7)	97.8 (7.9)
α-isomethyl ionone	110 (10)	97.4 (0.76)	94.4 (0.84)	98.4 (1.2)	103 (4.3)	93.4 (6.5)
Lilial®	106 (12)	91.7 (2.3)	88.2 (0.10)	93.3 (4.1)	98.9 (5.3)	88.3 (12)
Amyl cinnamal	112 (5.8)	106 (9.2)	102 (3.6)	109 (4.1)	108 (11)	102 (16)
Lyral®	105 (1.7)	112 (9.0)	89.2 (1.2)	99.4 (2.3)	98.8 (11)	82.6 (4.9)
Amylcinnamyl alcohol	113 (8.3)	118 (5.5)	98.8 (1.8)	114 (1.0)	112 (7.7)	113 (12)
Farnesol	<LOQ	<LOQ	97 (3.2)	111 (6.8)	95.0 (15)	108 (8.4)
Hexylcinnamal	108 (1.2)	105 (5.5)	105 (3.1)	111 (4.7)	108 (9.5)	104 (11)
Benzyl benzoate	111 (11)	98.4 (1.5)	92.3 (1.6)	103 (0.42)	104 (3.1)	97.6 (5.6)

Table 5. *Cont.*

Fragrance Allergens	Recoveries (%, RSD)					
	2 µg·g^{-1}		10 µg·g^{-1}		20 µg·g^{-1}	
	Mortar	**Vial**	**Mortar**	**Vial**	**Mortar**	**Vial**
Benzyl salicylate	116 (1.2)	113 (3.7)	80.8 (0.51)	102 (4.5)	111 (8.4)	104 (10)
Benzyl cinnamate	102 (12)	102 (2.1)	102 (5.4)	113 (3.9)	119 (4.4)	116 (3.3)
Preservatives						
Bronidox	104 (2.8)	90.4 (11)	94.4 (3.2)	97 (5.3)	101 (7.7)	95.9 (16)
PhEtOH	112 (10)	90.5 (2.1)	91.7 (3.1)	94 (5.5)	98.4 (12)	92.6 (11)
MeP [a]	n.c	n.c	n.c	n.c	n.c	n.c
BHA	106 (12)	98.4 (1.3)	105 (5.7)	110 (1.1)	100 (3.1)	100 (8.3)
BHT [a]	n.c	n.c	n.c	n.c	n.c	n.c
EtP	112 (1.0)	103 (1.7)	102 (2.5)	102 (0.32)	110 (3.9)	108 (10)
iPrP	118 (3.2)	114 (15)	102 (1.1)	110 (3.4)	111 (6.8)	113 (7.4)
PrP [a]	n.c	n.c	n.c	n.c	n.c	n.c
IPBC	113 (8.7)	97.7 (14)	103 (8.0)	117 (0.50)	111 (16)	95.4 (7.9)
iBuP	94.1 (15)	103 (2.4)	104 (2.9)	109 (2.3)	111 (0.13)	113 (8.4)
BuP	115 (1.0)	110 (1.6)	108 (2.7)	114 (2.4)	116 (1.6)	113 (10)
Triclosan	87.0 (6.9)	84.4 (6.1)	81.7 (6.7)	91 (7.8)	118 (6.4)	113 (11)
BzP	87.3 (11)	104 (9.5)	81.4 (2.0)	112 (1.7)	104 (12)	103 (11)
Plasticizers						
DMA	98.6 (5.5)	95.1 (2.7)	104 (0.65)	72.4 (0.65)	104 (1.3)	96.6 (9.4)
DEA	101 (5.5)	81.3 (6.9)	94.8 (1.6)	92.8 (1.1)	103 (4.0)	91.8 (11)
DMP	109 (12)	87.9 (1.5)	95.4 (2.7)	94.2 (0.72)	103 (1.4)	95.0 (7.6)
DEP	105 (7.0)	92.2 (0.34)	102 (2.5)	100 (0.20)	101 (3.2)	100 (8.6)
DIBP	115 (4.9)	93.3 (2.7)	94.1 (2.4)	102 (0.64)	98.9 (4.6)	102 (10)
DBP	117 (12)	109 (0.69)	91.5 (2.0)	108 (1.7)	105 (5.9)	110 (9.3)
DMEP	112 (10)	100 (1.6)	112 (7.9)	119 (4.9)	113 (2.3)	112 (8.7)
DPP	113 (11)	88.4 (4.1)	94.7 (4.2)	107 (0.56)	114 (3.9)	115 (5.9)

Table 5. *Cont.*

Plasticizers	Recoveries (%, RSD)					
	2 µg·g^{-1}		10 µg·g^{-1}		20 µg·g^{-1}	
	Mortar	Vial	Mortar	Vial	Mortar	Vial
BBP	114 (5.6)	115 (2.2)	101 (5.4)	108 (2.4)	117 (3.0)	119 (0.20)
DEHA	96.9 (9.1)	105 (7.0)	101 (6.6)	108 (8.5)	112 (1.0)	107 (2.8)
DIHP	98.5 (1.4)	102 (7.9)	98.1 (1.7)	102 (3.4)	99.2 (6.8)	113 (7.3)
DEHP	116 (2.3)	93.4 (3.5)	103 (4.5)	101 (4.6)	109 (4.4)	103 (5.2)
DCHP	116 (8.7)	107 (0.94)	107 (6.9)	107 (1.5)	112 (10)	114 (0.43)
DPhP	116 (11)	105 (1.5)	95.9 (6.9)	104 (3.2)	113 (1.1)	108 (2.2)
DNOP	118 (4.4)	87.8 (8.3)	96.1 (6.5)	106 (0.48)	111 (2.3)	120 (4.4)
Musks						
Cashmeran	112 (8.9)	101 (1.8)	113 (0.77)	99 (1.2)	103 (4.0)	96.8 (11)
Celestolide	113 (12)	115 (1.1)	114 (0.99)	107 (0.47)	104 (4.0)	101 (6.8)
Phantolide	109 (10)	107 (3.4)	113 (1.4)	111 (4.2)	102 (10)	103 (14)
Ambrette	118 (6.4)	104 (10)	118 (6.7)	118 (11)	100 (10)	106 (10)
Traseolide	113 (10)	104 (7.3)	95.2 (1.4)	102 (3.8)	103 (9.2)	100 (12)
Galaxolide	113 (13)	100 (2.6)	106 (2.0)	98.9 (0.011)	101 (4.0)	97.2 (8.0)
Xylene	118 (2.9)	111 (8.2)	101 (5.6)	88.9 (14)	104 (7.1)	114 (4.3)
Tonalide	117 (16)	113 (2.6)	90.7 (0.77)	89.8 (1.3)	101 (5.4)	98.0 (7.6)
Moskene	111 (15)	96.7 (3.6)	109 (4.0)	105 (10)	103 (16)	96.0 (7.3)
Tibetene	112 (12)	108 (5.7)	111 (1.7)	99.0 (6.2)	104 (10)	100 (16)
Ambrettolide	115 (3.8)	111 (3.5)	99.3 (1.3)	101 82.7)	104 (6.1)	108 (14)
Ketone	79.6 (4.5)	114 (13)	93.5 (0.75)	109 (4.0)	117 (8.0)	113 (11)

[a] n.c: not calculated since initial sample concentration is higher than the spiked level. MeP, BHT, and PrP: 22, 21, and 10 µg·g^{-1}, respectively.

Table 6. Recovery study in different cosmetic matrices. Spike level: 10 μg·g^{-1}.

Fragrance Allergens	Recoveries (%, RSD)					
	S3 [a]		S6 [a]		S8 [a]	
	Mortar	Vial	Mortar	Vial	Mortar	Vial
Pinene	4.2 (7.3)	72.1 (1.5)	11.2 (3.1)	74.0 (0.013)	21.2 (11)	74.3 (4.1)
Limonene	35.4 (5.6)	90.3 (1.7)	81.3 (3.1)	77.0 (2.1)	57.1 (2.5)	93.0 (0.87)
Benzyl alcohol	115 (6.9)	109 (0.19)	114 (4.2)	91.2 (10)	113 (0.51)	116 (0.38)
Linalool	102 (4.5)	117 (0.021)	n.c	n.c	n.c	n.c
Methyl-2-octynoate	106 (10.4)	93.0 (3.4)	94.9 (8.6)	81.3 (9.7)	103 (3.7)	113 (6.1)
Citronellol	89.8 (13)	101 (2.8)	110 (3.8)	100 (2.2)	90.0 (2.1)	100 (2.8)
Citral	113 (7.1)	105 (6.7)	115 (5.0)	94.2 (4.0)	107 (2.9)	108 (8.1)
Geraniol	80.4 (13)	93.4 (1.9)	107 (7.8)	92.4 (4.1)	91.2 (8.1)	98.2 (9.7)
Cinnamal	98.8 (9.4)	103 (2.8)	106 (7.4)	98.2 (4.6)	101 (2.4)	108 (2.5)
Hydroxycitronellal	108 (12)	102 (6.8)	93.6 (6.3)	81.0 (7.4)	112 (6.1)	111 (6.8)
Anise alcohol	98.3 (13)	101 (4.2)	95.4 (5.2)	96.1 (6.2)	83.3 (6.6)	104 (0.041)
Cinnamyl alcohol	81.7 (15)	96.9 (6.7)	112 (11)	91.4 (8.8)	106 (8.7)	109 (3.5)
Eugenol	100 (11)	95.4 (4.2)	115 (10)	92.1 (3.6)	101 (6.1)	109 (5.9)
Methyleugenol	100 (8.3)	110 (0.45)	96.4 (6.5)	96.1 (4.9)	100 (3.5)	106 (3.7)
Isoeugenol	102 (9.9)	93.0 (2.9)	114 (15)	82.5 (5.3)	86.2 (3.3)	95.2 (0.45)
Coumarin	107 (11)	118 (0.62)	95.8 (2.1)	81.0 (1.5)	91.3 (1.3)	97.1 (0.52)
α-isomethyl ionone	98.4 (7.5)	104 (1.9)	96.8 (3.7)	94.6 (0.24)	98.8 (3.1)	103 (2.5)
Lilial®	99.2 (8.6)	98.1 (1.2)	97.2 (4.5)	85.0 (0.055)	96.3 (3.7)	102 (4.2)
Amyl cinnamal	106 (10)	107 (0.82)	105 (8.1)	96.4 (3.6)	98.7 (4.5)	106 (4.2)
Lyral®	115 (7.3)	98.0 (1.5)	85.8 (12)	82.0 (11)	112 (6.7)	114 (7.5)
Amylcinnamyl alcohol	104 (10)	98.3 (6.7)	109 (9.7)	96.5 (9.4)	111 (4.3)	111 (9.1)
Farnesol	92.3 (13)	95.0 (0.29)	97.2 (1.8)	95.9 (13)	109 (8.5)	106 (12)
Hexylcinnamal	107 (14)	119 (0.29)	n.c	n.c	105 (5.9)	112 (5.9)
Benzyl benzoate	102 (9.0)	105 (0.43)	101 (2.4)	95.4 (1.2)	107 (3.8)	113 (5.1)
Benzyl salicylate	112 (10)	115 (6.9)	n.c	n.c	113 (3.5)	114 (4.3)
Benzyl cinnamate	115 (6.7)	116 (0.14)	113 (9.0)	112 (0.40)	113 (6.1)	115 (4.8)

Table 6. *Cont.*

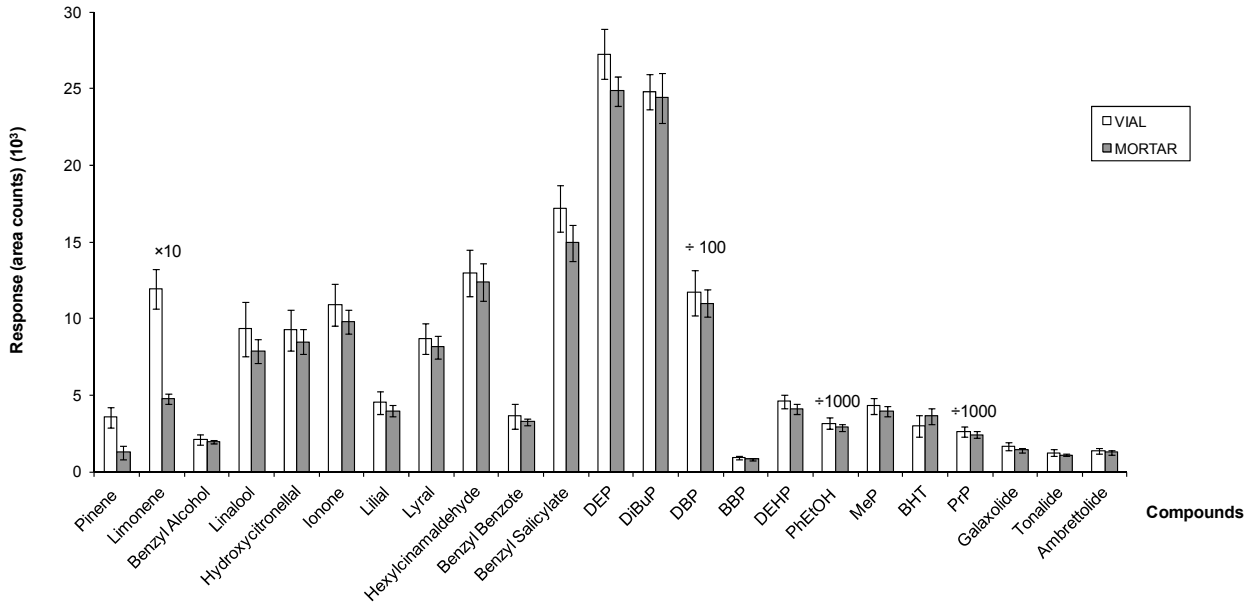
Preservatives	Recoveries (%, RSD)					
	S3 [a]		S6 [a]		S8 [a]	
	Mortar	Vial	Mortar	Vial	Mortar	Vial
Bronidox	93.9 (7.5)	101 (2.7)	106 (5.2)	108 (0.94)	105 (0.72)	95.0 (5.2)
PhEtOH	n.c	n.c	n.c	n.c	n.c	n.c
MeP	112 (11)	100 (7.7)	n.c	n.c	n.c	n.c
BHA	99.1 (9.6)	94.2 (0.89)	109 (6.2)	83.2 (0.91)	93.1 (3.1)	102 (2.7)
BHT	98.4 (3.1)	92.0 (0.040)	n.c	n.c	91.2 (3.4)	100 (3.2)
EtP	108 (7.7)	92.0 (9.8)	n.c	n.c	n.c	n.c
iPrP	105 (11)	114 (8.5)	114 (6.3)	115 (1.2)	94.9 (3.9)	103 (3.8)
PrP	115 (8.7)	115 (1.14)	n.c	n.c	n.c	n.c
IPBC	106 (14)	84.2 (10)	101 (7.4)	113 (15)	110 (18)	114 (10)
iBuP	105 (13)	111 (5.3)	n.c	n.c	112 (9.6)	106 (1.4)
BuP	103 (14)	107 (0.79)	n.c	n.c	107 (13)	103 (6.8)
Triclosan	119 (5.8)	96.0 (3.0)	114 (3.3)	106 (13)	104 (8.8)	110 (3.5)
BzP	96.0 (14)	108 (7.9)	95.1 (2.8)	116 (9.0)	110 (10)	102 (3.5)
Plasticizers						
DMA	105 (8.1)	105 (1.1)	97.0 (3.7)	84.0 (2.8)	95.1 (0.59)	98.2 (3.1)
DEA	108 (6.5)	100 (2.9)	104 (5.2)	96.1 (2.4)	105 (4.6)	113 (5.4)
DMP	96.4 (7.6)	104 (1.8)	95.0 (5.8)	88.3 (2.0)	95.2 (0.75)	101 (1.5)
DEP	97.8 (7.4)	107 (0.41)	n.c	n.c	n.c	n.c
DIBP	97.6 (10)	104 (0.24)	100 (2.5)	88.2 (1.5)	96.4 (2.5)	102 (3.1)
DBP	109 (8.4)	115 (1.1)	108 (4.4)	98.7 (2.1)	106 (3.2)	112 (4.1)
DMEP	113 (8.7)	119 (5.8)	98.2 (7.0)	103 (3.0)	107 (7.9)	114 (4.9)
DPP	108 (7.3)	108 (0.93)	112 (3.7)	101 (0.82)	114 (2.7)	115 (2.2)
BBP	97.3 (8.1)	97 (1.9)	109 (3.6)	86.0 (0.94)	103 (4.8)	110 (0.74)
DEHA	112 (6.9)	83 (3.3)	83.1 (4.1)	80.2 (1.7)	96.4 (4.9)	103 (0.70)
DIHP	113 (6.6)	115 (4.6)	108 (7.3)	107 (15)	101 (10)	89.0 (1.5)

Table 6. *Cont.*

Plasticizers	Recoveries (%, RSD)					
	S3 [a]		S6 [a]		S8 [a]	
	Mortar	Vial	Mortar	Vial	Mortar	Vial
DEHP	114 (13)	93 (1.3)	99.2 (4.4)	90.3 (2.2)	105 (2.1)	112 (2.1)
DCHP	113 (14)	96 (0.80)	94.0 (8.6)	88.5 (1.5)	97.2 (8.5)	97.2 (7.5)
DPhP	112 (7.6)	102 (0.13)	115 (3.0)	92.0 (5.9)	102 (3.1)	108 (3.1)
DNOP	102 (8.1)	114 (0.88)	113 (2.8)	100 (0.31)	114 (1.5)	113 (2.4)
Musks						
Cashmeran	98.4 (8.6)	96.0 (0.32)	93.0 (7.0)	88.3 (1.6)	97.2 (2.4)	103 (2.5)
Celestolide	102 (8.5)	103 (1.0)	93.5 (6.9)	93.5 (1.6)	98.0 (4.8)	105 (5.0)
Phantolide	100 (8.1)	102 (1.1)	96.4 (4.4)	93.9 (1.0)	101 (4.8)	107 (4.4)
Ambrette	92.0 (13)	84.2 (13)	113 (6.3)	112 (15)	112 (10)	113 (11)
Traseolide	98.8 (10)	100 (2.3)	105 (7.7)	101 (0.10)	105 (5.3)	113 (4.9)
Galaxolide	98.0 (10)	102 (0.72)	n.c	n.c	n.c	n.c
Xylene	88.2 (9.2)	--	111 (8.9)	--	86.0 (5.5)	97.4 (7.4)
Tonalide	98.4 (10)	98.0 (0.83)	81.0 (2.6)	84.0 (2.2)	n.c	n.c
Moskene	93.0 (12)	89.1 (11)	109 (11)	103 (15)	98.2 (8.1)	103 (8.6)
Tibetene	107 (10)	105 (4.4)	111 (11)	106 (7.8)	104 (7.1)	109 (7.9)
Ambrettolide	114 (13)	101 (0.98)	94.4 (10)	86.2 (4.8)	80.1 (10)	93.2 (3.5)
Ketone	109 (11)	99.0 (7.4)	109 (13)	114 (3.7)	108 (9.5)	115 (10)

[a] See initial concentration in Table 7. n.c: not calculated since initial sample concentration is higher than the spiked level.

Figure 3. Comparative results between in vial or mortar μ-MSPD for a leave-on sample (hands cream).



3.3. Application to Real Samples

Finally, the validated method was applied to the analysis of 18 real cosmetic and personal care products, including five rinse-off (shower gel, shampoos and baby liquid soap) and 13 leave-on (sunblock, after sun, body milk, hands cream, deodorants, among others) products, which represent a wide variety of personal care products. Results are shown in Table 7. Forty-eight of the 66 targets were found in the samples, with a minimum of 12 and a maximum of 28 compounds in each sample, at global concentrations ranging from 0.043% to 1.6%. It is worthy to note that the sample containing more targets is a baby body care lotion (sample S16).

3.3.1. Fragrance Allergens

Twenty-two of the 26 fragrance allergens were found in the analyzed samples. Linalool was detected in 83% of the samples at concentration values up to 0.1%. Also limonene, coumarin, benzyl alcohol, and benzyl salicylate were found in many samples at concentrations below 800 $\mu g \cdot g^{-1}$. Other fragrance allergens were detected in 2–12 samples. It is remarkable the presence of farnesol at high concentrations (>0.2%) in two leave-on samples (S12 and S13). Regarding the number of compounds per sample, three leave-on samples (S7, S16 and S18) contained 15 target allergens. In the other samples, the number of compounds was 3–12.

Table 7. Analysis of target compounds in rinse-off and leave-on cosmetic samples (% w/w $\times 10^4$) [a].

Fragrance Allergens	Rinse-off Samples [b]					Leave-on Samples [b]												
	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**	**S11**	**S12**	**S13**	**S14**	**S15**	**S16**	**S17**	**S18**
Pinene	-	0.777	-	1.18	-	-	2.24	-	-	-	1.51	-	0.972	0.396	1.40	0.881	0.426	0.0800
Limonene	266	148	-	283	-	0.446	199	-	152	-	11.0	1.31	163	222	53.2	14.3	2.73	6.38
Benzyl alcohol	4.00	-	-	-	3.32	3.06	7.55	-	2.50	2.93	31.2	3.76	17.9	-	-	6.14	0.698	27.5
Linalool	666	84.6	-	172	-	27.3	358	17.2	369	101	161	252	178	1024	255	228	-	26.4
Methyl-2-octynoate	60.4	-	-	-	-	-	-	105	24.7	-	-	-	72.0	-	-	-	-	-
Citronellol	25.0	-	-	-	-	-	79.6	-	-	1.45	45.3	234	-	63.1	-	58.0	7.75	13.2
Citral	-	-	-	13.6	-	-	8.84	-	10.5	6.28	-	-	-	-	6.50	-	-	-
Geraniol	90.2	19.1	-	44.5	-	-	167	-	-	2.83	23.1	10.3	-	-	37.2	41.1	-	17.3
Cinnamal	-	-	-	-	-	-	-	-	-	-	-	-	-	4.73	-	1.14	-	-
Hydroxycitronellal	-	-	2.08	-	-	0.212	33.1	-	-	-	57.4	-	-	1.29	-	18.3	52.0	1.00
Anise alcohol	-	-	-	-	-	0.155	-	23.6	-	-	-	-	-	-	-	-	-	-
Cinnamyl alcohol	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	12.4	9.23	6.42
Eugenol	-	-	-	-	-	2.67	-	-	-	-	-	1.66	31.8	40.5	-	-	3.63	0.114
Coumarin	30.8	3.44	6.89	9.55	-	0.460	11.8	-	16.6	-	-	113	21.0	557	3.25	-	1.79	20.3
α-isomethyl ionone	3.32	-	-	-	-	0.297	31.5	-	48.5	-	36.5	-	-	136	-	89.9	167	31.8
Lilial®	-	7.83	1.36	-	-	0.843	30.8	-	172	-	14.0	331	491	2.79	233	82.4	-	-
Amyl cinnamal	-	116	-	-	-	-	-	-	-	7.34	-	-	-	-	-	-	-	-
Lyral®	-	-	-	-	-	-	108	-	-	-	211	-	-	-	-	58.1	41.1	10.7
Farnesol	-	-	-	-	-	-	-	-	-	-	-	2924	2188	-	-	-	-	-
Hexylcinnamal	-	-	-	-	-	12.9	29.6		27.4		115	393	885	4.37	0.475	60.2	-	74.5
Benzyl benzoate	-	0.316	-	5.88	0.380	0.452	5.66	-	-	-	7.63	1.53	-	0.789	1.28	4.21	14.1	8.28
Benzyl salicylate	-	2.48	-	524	0.355	12.4	4.29	-	217	-	-	111	770	0.642	1.70	486	19.9	10.3
Preservatives	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**	**S11**	**S12**	**S13**	**S14**	**S15**	**S16**	**S17**	**S18**
PhEtOH	14.2	-	15.3	1.30	2009	1395	2455	3609	4017	1.45	15530	-	0.383	-	17.3	1993	1877	1849
MeP[c]	-	4.65	3.22	-	284	1244	654	789	887	-	1484	-	-	-	2.74	540	-	1350
BHA	-	-	-	-	-	2.78	-	-	-	-	-	-	-	-	-	-	-	-
BHT	0.544	1.98	-	0.105	0.0430	12.1	186	-	-	2996	-	20.3	9.93	5.01	625	0.237	25.2	

Table 7. *Cont.*

Preservatives	Rinse-off Samples [b]					Leave-on Samples [b]												
	S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**	**S11**	**S12**	**S13**	**S14**	**S15**	**S16**	**S17**	**S18**
EtP [c]	-	-	-	-	89.7	135	202	203	-		-	-	-	-	5.19	119	-	15.46
iPrP [c]	-	-	-	-	144	-	-	-	-	-	-	-	-	-	-	-	-	-
PrP [c]	-	1.61	0.374	-	60.1	470	1.45	364	262	1146	7660	-	-	-	1.76	62.4	-	588
IPBC	-	-	0.504	40.2	-	-	-	-	-	-	-	5.94	-	-	-	-	-	-
iBuP [c]	-	-	0.258	-	46.7	57.3	-	-	-	-	-	-	-	-	-	64.5	-	-
BuP [c]	-	-	1.17	-	91.0	146	-	-	-	-	-	-	-	-	0.280	122	-	-
Triclosan	-	-	-	-	-	-	-	-	-	-	-	-	2794	1.21	-	-	-	-
Plasticizers	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**	**S11**	**S12**	**S13**	**S14**	**S15**	**S16**	**S17**	**S18**
DEP	432	153	0.888	0.190	0.316	109	39.4	46.0	0.118	0.378	20.4	0.737	1.88	1539	0.254	40.5	303	0.300
DIBP	-	0.138	-	-	-	-	-	-	0.337	0.420	26.4	-	0.292	0.546	-	-	-	-
DBP	0.409	0.0722	0.0511	-	-	0.509	0.194	0.340	0.299	0.549	1434	-	2.24	0.575	1.37	-	-	1.24
DEHA	-	10.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	16387	-
DEHP	0.640	0.731	0.168	0.553	0.800	-	0.986	-	-	-	4.78	1.24	1.02	0.818	-	1.78	-	-
DCHP	-	-	-	-	-	-	-	-	-	-	-	-	0.196	-	-	-	-	-
DPhP	-	-	-	-	-	-	-	-	-	8.48	-	-	-	-	-	-	-	-
DNOP	-	-	-	-	-	-	-	-	-	-	-	-	0.444	0.0932	-	-	-	-
Musks	**S1**	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S10**	**S11**	**S12**	**S13**	**S14**	**S15**	**S16**	**S17**	**S18**
Celestolide	1.23	-	-	-	-	-	0.598	0.110	-	-	-	-	-	-	-	-	-	-
Phantolide	0.320	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Galaxolide	625	0.379	-	0.0820	-	114	93.2	128	-	0.119	3.90	199	0.120	0.844	-	86.8	211	-
Xylene	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3.14	-	-
Tonalide	244	-	-	-	-	-	-	20.8	-	-	3.54	-	-	0.153	-	26.3	-	-
Ambrettolide	-	-	16.0	34.7	-	-	-	-	-	-	10.8	-	-	-	-	-	-	-
Ketone	-	-	-	-	-	-	33.4	-	-	-	-	-	-	-	-	1368	-	-

[a] Equivalent to $\mu g \cdot g^{-1}$. [b] S1: Shower gel; S2, S3: Shampoos, S4, S5: Babies liquid soap; S6: Sunblock; S7: Aftersun; S8, S9: Body milk; S10: Lipstick; S11: Hands cream; S12, S13, S14: Deodorants; S15, S16: Baby moisturising lotions; S17: Makeup; S18: Moisturising milk. [c] Parabens concentration expressed as acid (% w/w × 10^4).

3.3.2. Preservatives

Phenoxyethanol was the most frequent found preservative (83% of the samples) at concentration values higher than 0.1% (1000 $\mu g \cdot g^{-1}$) in nine samples. In sample S11, phenoxyethanol concentration (1.5%) surpassed the maximum concentration permitted by European regulation (see Table 1). In the case of parabens, six of the seven targets were found in the analyzed samples. The most common was PrP (67%) at 0.1% in two leave-on samples (S9 and S10). Other parabens, MeP, EtP, BuP, iBuP, and iPrP, were found in 11, seven, five, four and one samples, respectively. Triclosan was detected in two samples, at very high concentration in a deodorant (S13), reaching the limit established by the European legislation (0.3%). BHT, IPBC, and BHA were detected in 13, three and one sample, respectively. The highest number of preservatives was found in S5 and S6, with eight targets. It should be noted that S5 is a care cream intended for babies. A hand cream (S11) does not comply with European restrictions regarding PhEtOH (>1%) and total paraben concentration (> 0.8%).

3.3.3. Plasticizers

DEP was found in all analyzed samples at concentration levels below 432 $\mu g \cdot g^{-1}$, except in the deodorant S14 (1539 $\mu g \cdot g^{-1}$). Two banned phthalates (DBP and DEHP) were detected in 13 and 11 samples, respectively, at concentrations between 0.05 and 4.8 $\mu g \cdot g^{-1}$. It should be noted that sample S11 (a hand cream) contained a DBP concentration >0.1%. In the other personal care products, the number of plasticizers was 1–6, highlighting the presence of DEHA at very high concentration (1.6%) in make-up (leave-on sample, S17).

3.3.4. Musks

Galaxolide was found in 72% of the samples at concentrations below 625 $\mu g \cdot g^{-1}$. Celestolide and ambrettolide were found in 17% of the samples at concentration levels between 0.11 and 35 $\mu g \cdot g^{-1}$. The restricted musks tonalide, ketone, xylene and phantolide were detected in at least one sample (tonalide in five samples); at concentrations fulfilling the EU limits, with the exception of musk ketone, found at >0.042% in sample S16, a baby moisturizing lotion.

4. Conclusions

A micro-MSPD-GC-MS method has been proposed for the determination of four families of compounds extensively used in cosmetics and personal care product formulations: fragrance allergens, preservatives, plasticizers, and synthetic musks. This study included 66 chemicals subjected to restrictions according European legislation. We compared the performance of two micro-MSPD procedures for the extraction of the targets, performing the sample disruption in mortar and in vial. The proposed in-vial method allows analytes extraction in less than 5 min, providing a quick and low cost extraction procedure with lower losses of the more volatile compounds. The method was validated showing satisfactory linearity, sensitivity, accuracy, and precision, with recoveries higher than 90% and RSD values below 10%. Finally, the method was applied to real cosmetic samples including different matrices to demonstrate the method performance. Forty-eight of the 66 targets were detected in the analyzed samples. Several compounds were present at concentrations higher than 0.1%, and two of the samples did not comply with

European requirements. The analyzed products intended for baby care contained similar or even higher numbers and concentrations of regulated compounds, highlighting the high number of preservatives, and the presence of musk ketone above the legal limit in one of these kinds of products.

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Author Contributions

All authors contributed equally to this work. Research design and supervision was mainly done by Maria Llompart and Carmen Garcia-Jares, and experimental by Maria Celeiro and Juan Pablo Lamas.

Conflicts of Interest

The authors declare no conflict of interest.

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