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Analysis of Fragrance Allergens in Personal Care Products, Toys, and Water Samples: A

Review

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Abstract

Fragrance allergens (FAs) refer to these volatile or semi-volatile fragrance compounds that can cause irritation and negative reactions. A large number of emerging FAs are widely used in household goods, and cause contact allergy or allergic contact dermatitis in eczema population and the general population. It shows an increasing prevalence and is regarded as a concern to public health. Recently, more and more studies have focused on the analytical methods of FAs in a variety of samples with different matrices. Therefore, a systematic and comprehensive overview of recent progress of analysis of FAs in various samples is needed. In this review, the physical and chemical properties, applications, hazards, and the recent advances of sample preparation and determination methods of common FAs in personal care products, toys, and water samples are systematically and comprehensively summarized. Meanwhile, this review also discusses the advantages and limitations of different sample pretreatment and detection methods, thus offering a deep-going discussion of the development and future trends in this area.

Keywords: Fragrance allergens; Sample pretreatment; Personal care products; Toys; Water samples

Introduction

Fragrance compounds refer to these compounds with unique smell extracted from plants and animals or the synthesized in the laboratory (1). From ancient times to modern times, fragrance compounds are ubiquitous in natural environment. Furthermore, they can exist in industrial products, such as personal-care products, health commodities or medicines. In order to cover up the unpleasant smell, to improve the antibacterial property or to increase the attractiveness of these products, manufacturers often add some fragrance compounds to the products. Although widely used, they are rarely mentioned in the product label of ingredient information. In reality, some fragrance compounds have certain degree of irritation to the skin, eyes, respiratory tract, etc., and can cause lung disease, dermatitis, migraine and even endocrine diseases (2, 3). What's more, they may also cause environmental pollution (4). These allergenic volatile or semi-volatile fragrance compounds are called fragrance allergens (FAs).

The sensitivity of different people varies greatly. For infants and women, the skin and mucous membranes are very sensitive, so the concentration of FAs that can cause negative reactions may be very low. Therefore, the composition and concentration of common FAs in personal care products (especially infants' products) and toys, have gradually attracted public attention. Many countries and organizations have issued standards for types and limits of fragrance compounds allowed for use. In Japan, where the allergens are strictly regulated, the use of nitro-musks has been banned since the 1980s. The European Union (EU) has stipulated the limits for dozens of FAs that may exist in children's toys and cosmetics in Directive 2009/48/EC of European Parliament on the Safety of Toy and EN71-13:2014 (5, 6). The current standard for daily essence products in China is GB/T 22731-2017 Daily Essence Limit (7). Among 11 kinds of common personal care products, the maximum limits of 99 fragrance compounds and the prohibition of 82 fragrance compounds were stipulated for goods such as toys, baby wipes, baby creams, etc. For lip products and toys (Category 1), the limits of FAs are the most stringent. In the fragrance industry, the most famous supervision organizations are the Research Institute for Fragrance Materials (RIFM) and International Fragrance Association (IFRA). RIFM is responsible for testing and collecting data on scented materials, and publishing them in the journal *Food and Chemical Toxicology*. More than 1,000 materials have been evaluated so far. According to the evaluation results, IFRA proposed the scope of daily essence prohibitions and restrictions in IFRA Code of Practice(8).

In the past few years, a few authors have published many reviews on FAs, but many of them emphasized the epidemiological characteristics, sensitization hazards and related legislations of FAs (1, 4, 9, 10). Several authors have reviewed the analytical methods of musk FAs in environmental samples and personal care products in human samples (11, 12). In addition, Debonneville et al. (13) summarized quantitative analysis of suspected FAs with GC or two-dimensional GC combined with quadrupole MS and some improvement of the data treatment, but they only focus on the literatures before 2004. Recently, with the deep research of exposure

1 hazards of FAs and the release of relevant national standards, the analysis of FAs in personal care products
2 including skin care products, cosmetics, hair care products, shower gel and women's health products, toys as
3 well as water samples, has gradually increased. In this review, we will briefly describe the physical and
4 chemical properties, application scope and hazard of common FAs, then summarize the reported sample
5 pretreatment and determination methods in recent years, with the emphasis on the advantages and
6 disadvantages of various methods, thus providing references for future related research.
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14 **Physical and Chemical Properties of FAs**

15 Most of the FAs are volatile and semi-volatile alcohols, aldehydes, esters, phenols, ketones, and alkenes
16 with boiling points below 350°C. Among them, aldehydes, esters and phenols are the most common FAs.
17 Most of the FAs have low water solubility except benzyl alcohol (33 g/L) and furfuryl alcohol (miscible with
18 water). These FAs are soluble in organic solvents such as acetonitrile, acetone, carbon tetrachloride. Table 1
19 shows the physical and chemical properties of common FAs.
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25 **Usages and Toxicity of FAs**

26 FAs can be from both natural and artificial sources. They are compounds with unique smell, and widely
27 used in personal care products such as shampoo, skin care products, cosmetics and other products including
28 wipes, paper towels and sanitary napkins, as well as toys. Almost all of the fragrance compounds have
29 transoral toxicity and negative effects on the nervous system temporarily or chronically. They can cause skin
30 and mucous membrane contact sensitization, endocrine disorder, dermatitis, asthma, and other diseases. The
31 basic information of the common FAs is presented in Table 1.
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37 The naturally extracted FAs include botanical and animal sources. There are various kinds of botanical
38 fragrance components extracted from flowers, fruits or leaves. Limonene, citral, linalool, citronellol, geraniol,
39 cinnamyl alcohol, etc. are often added in personal care products. Both limonene and citral have strong lemon
40 scent and are mainly used to prepare citrus essence, so they are often used as fragrant agents in detergents,
41 shampoo, and hair care products as well as cosmetics. D-limonene is reported to have a variety of
42 physiological and pharmacological effects. However, studies also showed that limonene in office environment
43 could increase the concentration of submicron particles in the air by ten times, thereby irritating respiratory
44 tract and lung (14). The EU stipulates that the contents of d-limonene in children's toys, if exceeding 100 ppm,
45 needs to be labeled(5). Citral is an estrogen that can cause skin irritation (15, 16). According to China's national
46 standard, the maximum limit of FAs for all types of lip products and toys is 0.04%, and the maximum limit
47 for all categories of personal care products is less than 5%(7). And the Directive 2009/48/EC prohibits the
48 addition of citral to toys(5). Linalool has sweet and fresh fragrance, and is widely used in various perfumes,
49 with the consumption of more than 1000 metric tons worldwide annually. However, linalool has anesthetic
50 effect, and may also cause swelling and pain of eyes, and skin of animals and human (17). According to EU
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regulations, when the content of linalool in children's toys exceeds 100 ppm, it needs to be labeled(5). Geraniol and citronellol have strong smell of fresh rose, so they are the main raw materials of rose essence which are often added in personal care products. However, both of them showed oral and skin toxicity in animal experiments (18, 19). According to the Directive 2009/48/EC, geraniol is banned in the production of toys, and it should be labeled if the content of citronellol exceeds 100 mg/kg(5). China has set the maximum limits of citronellol and geraniol in lip products and toys to be 0.8 and 0.3%, respectively(7). Cinnamyl alcohol has a long-lasting spicy and sweet cinnamon flavor. As its boiling point is higher than other organic compounds with similar molecular weight, cinnamyl alcohol is often used as a flavor fixing agent. Meanwhile, it is also used to prepare the essence of narcissus, gardenia, lily of the valley, rose, etc., and is widely used in soap, washing powder and shampoo. Cinnamaldehyde had bactericidal and disinfectant effects and strong fungal inhibition activity (20, 21). However, cinnamaldehyde exhibited skin irritation, and may cause oral ulcer and gingival swelling through oral contact (22). The maximum limit of cinnamaldehyde in other personal care products is less than 0.05% except mouthwash and toothpaste.(7) Animal fragrance compounds, mainly including natural musk, ambergris, and other animal secretions, are less toxic but expensive.

Compared with the fragrance compounds from natural source, the artificial fragrance compounds are much cheaper and easily available, and therefore have been added in personal care products extensively. However, their negative effects on human health and the environment have attracted increasing attention. The most widely used synthetic FAs include benzyl alcohol, furfuryl alcohol, benzaldehyde, phenylacetaldehyde, benzyl acetate, benzyl salicylate, benzyl acrylate, benzalacetone, coumarins, and synthetic musk. Benzyl alcohol, one of the simplest aromatic alcohols, has weak aromatic smell. During storage, it can be oxidized to benzaldehyde with a slightly bitter almond flavor. Benzyl alcohol is a very useful fragrance fixing agent in the preparation of jasmine, tuberose and other essences, and is commonly added in soaps and cosmetics. Benzyl alcohol has certain anesthetic effect and irritation effects on eyes, upper respiratory tract, and skin. Animal experiments showed that excessive intake of benzyl alcohol might cause vomiting, coma, ataxia, and even death (23). The IFRA Code of Practice has stipulated that the maximum limit of benzyl alcohol for products for body use is 0.34%(8). Furthermore, benzyl alcohol is not allowed in toys in EU(5). Benzaldehyde, possessing the smell of almond, is mainly used for the synthesis of food flavors. Phenylacetaldehyde has strong aroma of hyacinth and is an important kind of raw material for flower essence. However, benzaldehyde and phenylacetaldehyde are harmful if ingested orally or through the respiratory tract. Benzaldehyde shows a moderate irritative effect on human skin. The IFRA has stipulated that the maximum limits for both benzaldehyde and phenylacetaldehyde in lip products are 0.045%, and the limits are stricter in China (0.02%)(7, 8). In China, the maximum limits of benzaldehyde and phenylacetaldehyde in lip products and toys is 0.02%(7). Benzyl acetate, benzyl benzoate, eugenol and isoeugenol have obvious floral scent. They are intermediates for the synthesis of jasmine, cloves and other essences. Benzyl cinnamate, benzyl salicylate, benzyl acrylate and benzalacetone have the fragrance of honey or fruit and are often used to make the essence of nuts and fruits. 6-Methylcoumarin and 7-methylcoumarin are mainly used for coconut, vanilla, and caramel

essences. These fragrance compounds are not only used as fixing agents, but also widely used as resin materials or paint coatings in industrial production. However, animal experiments indicated that coumarin was a kind of carcinogen, and may be related to the increase of liver cancer and lung cancer (24). Synthetic musk is easier to prepare and cheaper than natural musk, but it can bioaccumulate in human tissues and exist in the environment (25, 26). At present, dozens of FAs with higher risk, including furfuryl alcohol, benzalacetone, benzyl acrylate, 6-methylcoumarin, 7-methylcoumarin and synthetic musk, are banned in many kinds of personal care products in China, EU and IFRA(5, 7, 8).

Sample Pretreatment Methods for FAs Analysis

In the analysis of FAs, the matrices are complex and also the FAs contents are at trace level. The purpose of sample pretreatment is to eliminate the interference of matrix and to concentrate the analytes, so as to improve the sensitivity of the method. Thus, sample pretreatment is one of the key steps to guarantee the accuracy and precision of the analysis. For liquid samples such as water, perfume and skin care products, the common pretreatment methods include dilution, liquid-liquid extraction (LLE), solid-phase micro-extraction (SPME), solid-phase extraction (SPE), headspace (HS) and pressurized liquid extraction (PLE). For solid samples such as toys and scented stationery, the most applied pretreatment methods include solid-liquid extraction (SLE), SPME and HS method. The sample pretreatment methods for FAs analysis are summarized in Figure 1.

Direct injection or dilution. The direct injection or dilution method means that the liquid sample is directly injected without pretreatment or only with dilution. This method is rapid and simple. At the early stage, most analysis of FAs focused on liquid samples with simple matrices, such as perfume and essential oil, so direct injection or dilution with suitable organic solvents was usually adopted. Mondello et al. (27) reported a gas chromatography (GC)-full-scan quadrupole mass spectrometry (qMS) for rapid determination of 25 FAs in perfume samples with direct injection. In their study, the LODs were 0.8-8.8 mg/kg and relative standard deviations (RSDs) were 0.1-5.0%. For thick liquid samples such as vegetable oils, dilution with a proper organic solvent before injection are employed to reduce the sample viscosity and avoid the column overload, thus improving the separation efficiency, prolonging the lifetime of columns, and protecting the analytical instrument. The commonly used dilution solvents include isooctane, fluorotoluene, hexane, acetone, acetonitrile, and ethyl acetate (28-33). The direct injection or dilution method is simple, time-saving, and suitable for rapid screening of FAs in simple liquid samples. Nevertheless, the sensitivity of the method is limited because the analytes are not concentrated (the LODs are usually at the mg/L level). For some samples with complex matrices, the interferents cannot be effectively removed, therefore affecting the accuracy and precision of FAs determination.

Solvent extraction. The solvent extraction is a classical method based on the principle of similar solubility,

using a suitable solvent to extract the analytes from the samples, so as to separate analytes from other matrix components. It is one of the commonly used separation and extraction methods, it is generally divided into two categories based on the nature of the sample, i.e., LLE and SLE.

LLE. LLE is one of the simplest and most extensively utilized sample preparation techniques, in which analytes are transferred from a liquid to another immiscible solvent according to the difference in distribution coefficients of solutes in two phases. It is typically applicable to aqueous samples, and an organic solvent generally serve as the extractant. In the analysis of FAs in cosmetics by gas chromatography - mass spectrometry (GC-MS) proposed by Rastogi et al. (34), the soap samples were dissolved with hot distilled water, and cooled and extracted by shaking directly with ethyl acetate. Then, the organic phase was taken for determination after centrifugation. During the extraction processes of LLE, agitation including ultrasound, vortex and oscillation is usually employed as auxiliary means, especially for thick samples such as lotions, creams and shampoos. This method can enhance interfacial contact, reduce boundary layer thickness and facilitates mass transfer between the two phases, thereby improving the extraction efficiency. Sánchez et al. (35) used vortex-assisted extraction after dissolving cream samples with ethyl acetate followed by headspace preparation for determining suspected allergens in cosmetic products, with the recoveries of 84-117%. Both Vill et al. (33) and David et al. (36) used ultrasound-assisted extraction (UAE) as a pretreatment method for the determination of FAs in personal care products by high performance liquid chromatography (HPLC) and GC-MS, respectively.

Although LLE is an economical, rapid and simple extraction technique, it requires manual operation and large amounts of organic solvents. So, it is unsuitable to routine high-throughput analysis due to its disadvantages of time-consuming procedure, large organic solvent consumption, and relatively poor extraction efficiency. Recently, miniaturized LLE approaches without the use of separatory funnels have attracted much interest. Liquid-liquid micro-extraction (LLME), with small amount of solvent consumption (microlitre quantities) is a popular choice for sample pretreatment. Combination of vortex and ultrasound methods can improve the extraction efficiency of LLME. Currently, various LLME techniques have been developed, such as dispersive LLME (DLLME), ultrasound emulsification LLME, vortex-assisted LLME and suspension drop micro-extraction. Compared with conventional LLE, LLME methods have the advantages of rapidity and efficiency. Considering that a large number of FAs in personal care products may continuously enter the aqueous environment through municipal sewage discharge, Bravo et al. (37) proposed a pretreatment method based on ultrasound-assisted emulsification-micro-extraction (USAEME) to detect FAs in water samples including tap water, baby bathwater, recreational place water, public washing place water, and sewage water. After removal of free chlorine from a 10-mL water sample by sodium thiosulfate, the oil-in-water (O/W) emulsion system was formed by adding 100 μ L of chloroform as the extractant solvent. And 2 g sodium chloride was added, followed by ultrasound water bath for 2 min. Then, the mixture was centrifuged and the chloroform layer was taken for analysis. The enrichment factor of this method was about 100, the method recoveries were 75-110%, and the LODs were at the sub-nanogram per millilitre level. LLME is suitable for

the pretreatment of trace lipophilic compounds because of its high extraction efficiency, good enrichment capacity and low risk for the environment and the operator. However, this method has some shortcomings such as low precisions and relatively complex operation.

SLE. SLE usually refers to the preparation technique of extracting solid and semi-solid samples with appropriate solvents. Vibration can boost the extraction efficiency and reduce the extraction time. This method is simple and can allow simultaneous treatment of several samples. In Masuck group's investigation on the emission of FAs from scented toys(38), the powdered sample was extracted with toluene-ethyl acetate (1:1, v/v) for 30 min. Then the supernatant was mixed with ethanol to separate polymers through precipitation, and the resulting supernatant was injected directly to GC-MS analysis. This assay obtained the RSDs of 1.17-8.65% and the LODs of 0.14-0.67 ng/cm³. However, in practice, in order to achieve better extraction efficiency, the shaking extraction progress often takes a long time. Accelerated solvent extraction (ASE) and UAE are common and efficient methods. ASE is also called pressurized liquid extraction (PLE), in which the analytes are extracted with a suitable solvent at an elevated temperature and high pressure. High temperature and pressure can realize quick extraction with small amount of solvent. Meanwhile, ASE is easy for automation and batch sample preparation. However, the method requires specific devices, which is costly and cumbersome when dealing with samples with high water content. What's more, the ASE may destroy the analytes as it is carried out at high temperature. In UAE, the sample is extracted with appropriate solvent with the aid of ultrasound. It is rapid (generally within 15-30 min), and the required equipment is simple and common. Lv et al. (39) used UAE for sample pretreatment in the determination of 21 FAs in toys by GC-MS. Samples were extracted by ultrasound with acetone for 20 min. The supernatant was filtered through a 0.45- μ m filter membrane and the filtrate was taken for analysis. The LOQ of the method were 0.02-40 mg/kg, with the recoveries of 82.2-110.8% and the RSDs of 0.6-10.5%. Similarly, Wei et al. (40) also adopted UAE with dichloromethane as the extraction solvent for analysis of FAs in toys by GC-MS. The method obtained the recoveries of 86.8-102.7% and the LOQs in the range of 0.25-1.25 mg/kg.

In addition, SLE can be combined with other sample preparation methods, thus achieving good extraction efficiency. Dang et al. (41) combined SLE with DLLME for the determination of five FAs in infant disposables by GC-MS. Samples were firstly extracted with acetonitrile, then dispersed with water, salted out with NaCl, concentrated with tetrachloromethane, and then centrifuged. Finally, the tetrachloromethane phase was used for analysis. In this assay, the vortex-assisted SLE allowed a fuller transfer of the analytes into the extractant (acetonitrile), and the DLLME process could achieve a 10-fold concentration, thereby improving the sensitivity of the assay. The recoveries of 78.7-106% were obtained for the five FAs, with the RSDs of 2.4-11.3% and the LODs of 0.01-0.1 mg/kg. However, for higher polar analytes such as benzyl alcohol, furfuryl alcohol, cinnamyl alcohol, etc., it is difficult to transfer them from the acetonitrile-water phase with high polarity to the tetrachloromethane phase with non-polarity, resulting in low recoveries. Therefore, the DLLME needs further improvement and optimization when applied to the extraction of multiple FAs with a wide range of polarity.

SPME. First presented in early 1990s, *SPME* is a solvent-free extraction technique. It uses a fiber with different coatings of polymeric sorbents for extraction and enrichment of target analytes. The trapped target compounds could be desorbed and determined by GC or LC. *SPME* integrates the sampling, separation and preconcentration of analytes into a single procedure. In addition, it is flexible, environmentally friendly, and suitable for different sample matrices.

The coating material of *SPME* fiber will affect the capacity and efficiency of extraction. At present, four commercial coatings, i.e., polydimethylsilane (PDMS), polyacrylate (PA), divinylbenzene (DVB) and carboxen (CAR) are commonly employed in *SPME*. Llompart and her team have published three articles on the extraction of FAs from water samples using *SPME* (42-44). They compared the adsorption efficiencies of five different commercial fiber coatings, namely PA, PDMS, PDMS/DVB, CAR/PDMS and DVB/CAR/PDMS, and studied the effects of *SPME* mode and the addition of NaCl on the extraction efficiency by experimental design. The optimal conditions consisted of 20% (w/v) NaCl, PDMS/DVB fiber and 20 min of extraction time at 100°C in headspace mode. Good linearity ($R^2 > 0.9925$), recoveries ($> 79\%$), and precision ($RSD < 15\%$) were achieved for 43 compounds. DIVIŠOVÁ et al. (45) and Cagliero et al. (46) chose *SPME* as well in the determination of FAs. However, they preferred a lower temperature (40-50°C) for the equilibration and extraction of FAs from skin care products and toiletries. The reason may be that the lower extraction temperature close to human body surface temperature could better simulate the actual use conditions.

Masuck et al. (38) investigated the emission of FAs from scented toys at 23°C and 40°C (consumer conditions). The study showed that when FAs were extracted by HS-*SPME* with 85 µm PA fibers, 24 h of incubation and 4 h of extraction were required at 23°C while 4 h of incubation and 3 h of extraction were required at 40°C to reach an equilibrium. Subsequently, they chose *SPME* conditions of 10 min incubation and 20 min extraction at 70°C for the pretreatment when comparing the extraction efficiencies of three HS techniques including static headspace (SHS), dynamic headspace (DHS) and full evaporation dynamic headspace (FE-DHS) (47). Lower temperatures required longer time to equilibrate and extract the analytes for sufficient sensitivity and precision. However, the water bath heating temperature above 90°C is difficult to maintain stable, and the evaporation of water will be faster, affecting the reproducibility of the extraction process. Therefore, the selection of the appropriate temperature and strict control of the extraction temperature and time are very important for the extraction performance of *SPME*. The deficiency of this method is that the variety of commercial extraction fibers is limited, and the fibers are easy to break and require skilled personnel operation.

HS. HS is a sample preparation technique for isolation of volatile analytes by directly injecting the headspace vapor above samples. In this method, the low or non-volatile matrix components will not be introduced to the analytical instrument, so the matrix effect can be effectively avoided. It has the features of simplicity,

environmental friendliness and fast speed. The HS sampling has unique significance in flavor and fragrance analysis, and is suitable for the determination of FAs. The method is usually employed in combination with GC. It is divided into SHS and DHS.

SHS. SHS has found extensive application in rapid analysis, in which the samples are placed in a sealed vial for equilibrium at specific temperature, and the headspace vapor is taken with a syringe and injected into GC for analysis. Researchers have reported its application in the determination of FAs in various samples. The extraction efficiency can be improved by optimization of SHS parameters. Li et al. (48) reported a SHS-GC-MS method to determine FAs in children's wooden products. In their study, sample (20 mg) was frozen and crushed, and acetone (40 μ L) was added for HS extraction. The factors including incubating temperature, equilibration time and pressing pressure, were optimized by response surface methodology. The LOQs of this method were 0.2-20 mg/kg, with the recoveries of 79.8-115.2% and RSDs of 0.6-9.9%. Despite of its simplicity, this method has insufficient sensitivity for trace analysis since the target analytes are not concentrated and the instrument limits the injection volume to no more than 5 μ L.

The HS operation temperature is usually lower than the boiling point of the extractant, which allows the analytes to reach gas-liquid equilibrium in the vial, and limits the sampling of semi-volatiles with higher boiling points at the same time. The full evaporation headspace (FEHS) technique can solve this problem. This method employs a HS operation temperature higher than 100°C, thus the trace amount of solvent (<100 μ L) and the analytes can evaporate instantly into the vapor phase in the HS vial and reach dynamic equilibrium (<10 min) quickly. Lv et al. (49) established a FEHS-GC-MS method for rapid determination of FAs in toys. The samples were crushed and extracted with acetone, and methanol was added to precipitate the polymer, then 40 μ L of supernatant was taken for FEHS pretreatment. Finally, the HS vapor was introduced into the GC-MS for analysis. The LOQs were 0.5-15 mg/kg, RSDs were 1.7-16.8%, and the spiked recoveries at three levels ranged from 81.0 to 135.7%. Desmedt et al. (50) also developed a FEHS-GC-MS method for the analysis of 24 volatile FAs in cosmetics with complex formulations including hydrophilic (O/W) and lipophilic (W/O) creams, lotions and gels. The sample was added with NaCl and 10 mL of hexane. The mixture was vortexed, sonicated, cooled and centrifuged for the collection of supernatants. Then, a total of 300 μ L supernatants were transferred for HS pretreatment at 135°C for 10 min with shaking, and 1 mL of HS vapor was taken for GC-MS analysis. The recoveries were 80-120% with RSDs of 1.93-12.45%. The FEHS method, combining an easy liquid extraction with SHS, is beneficial to improve the determination sensitivity and accuracy of semi-volatile FAs with high boiling points. However, it also compromises the simplicity of SHS.

The SHS is limited because not all the analytes in the samples can be volatilized. In addition, to achieve high sensitivity, this method requires a large volume of gas injection, resulting in the peak broadening of the analytes. Therefore, this method is disadvantageous for the chromatographic separation.

DHS. Known as purge and trap, DHS has been widely used in recent years. In the concentration process with DHS, a large volume of headspace vapor passes through a cryogenic trap or an adsorbent trap. The analytes are determined after thermal or solvent desorption. DHS has high sensitivity and ease of automation, and can

be used for the analysis of trace analytes with low boiling points, while its operation is more complex.

Masuck et al. (51) proposed a DHS-GC-MS method to analyze the migration of FAs in scented toys. The simulant sample was placed in a HS vial and NaCl was added, then the mixture was incubated at 30°C for 10 min. After purging with N₂, a Tenax TA glass tube was used to trap the analytes and then analytes were desorbed at 300°C for analysis. The recoveries of the method were 85-114%, and the LODs were 1.99-5.05 ng/mL. Masuck et al. (47) further investigated HS-SPME, DHS and FEHS methods for the determination of FAs in toys. The LODs of the three methods were 8800 ng/ mL (HS-SPME), 3710 ng/ mL (DHS) and 19.2 ng/ mL (FEHS), respectively. The results showed that DHS and FEHS methods could detect the FAs that HS-SPME could not detect.

SPE. SPE, which allows the isolation, clean-up, and concentration of the analytes in one procedure, is the most frequently utilized sample preparation technique based on the principle of chromatographic separation. Compared with LLE, SPE can achieve high extraction efficiency with simple operation and limited consumption of organic solvents, so it gains much attention in the extraction of a wide range of analytes. Besides, SPE is also easy for automation.

According to the analyte properties, SPE cartridges with different adsorbents can be selected. Silica SPE cartridge has strong retention ability for polar compounds. It has been widely used in the extraction of FAs in cosmetics. Rastogi et al. (34, 52) used SPE to treat cosmetic samples including shampoos, creams, lotions, lipstick and face powder. All the samples were extracted with methanol, purified with silica SPE cartridge and determined by GC-MS. The recoveries were 80-116%, and the RSDs were within 5%. Recently, ENVI-Carb, a nonporous graphitized carbon, has been widely used in SPE as an alternative sorbent (53). It has a dual retention mechanism of reversed phase and ion exchange, and exhibits a strong affinity for non-polar and polar compounds. Lv et al. (39) reported a GC-MS method for the determination of FAs in toys. In this method, the plastic toy samples of different materials were extracted by ultrasound with acetone, dichloromethane or tetrahydrofuran, and then purified with ENVI-Carb SPE cartridge. However, SPE is high-cost. With the development of material industry, new materials with better performance would be used in SPE.

Other pretreatment methods. In addition to the above-mentioned methods, researchers have been explored other sample preparation methods in order to achieve higher extraction efficiency and to improve the analytical performance of FAs determination. Lamas et al. (54) developed a solid phase dispersion-PLE method in combination with GC-MS for the analysis of 26 FAs in cosmetics with multi matrices. The samples were mixed with drying agent and dispersing sorbent at first, and then placed in a tightly closed PLE cell, followed by the extracted with hexane-acetone (1:1, v/v) as the solvent and florisil as the dispersion phase at 120°C for 15 min. The method showed good linearities ($r \geq 0.996$) and good precisions ($RSDs \leq 10\%$).

Size-exclusion chromatography (SEC), as its name implies, is a chromatographic technique that separates target molecules according to their sizes. It just requires simple operation and mild condition. Niederer et

al.(55) combined SEC with GC-MS to determine 24 FAs in cosmetics. The samples were extracted by ultrasound with acetone (containing the dye of internal marker for SEC), and the organic supernatant was filtered, purified by semi preparative SEC with the column of Phenogel and concentrated by rotary evaporator for GC-MS analysis. This method obtained good recoveries of 90-120% except hydroxycitronellal (66±5%). Besides the methods mentioned above, with the increase of the researches on FAs determination, other new sample preparation methods will be gradually applied to FAs analysis.

Determination Methods of FAs

GC and GC-MS. Dozens of common FAs have boiling points below 300°C, and GC has proved a rapid and effective analytical method without derivatization in the determination of FAs. In GC analysis of FAs, the inlet temperature is generally set at 250-300°C to ensure complete vaporization of the analytes. Capillary columns with different polarities can be selected from non-polar columns such as HP-1 and DB-1, low- and medium-polar columns such as HP-5 and DB-35, to strong polar columns such as HP-INNOWAX and DB-WAX, achieving good separation of FAs through a multi-stage ramp-up procedure. Due to the strong polarity of alcohol FAs such as furfuryl alcohol, cinnamyl alcohol, and amylcinnamyl alcohol, there is a more obvious peak tailing with the use of a low-polar column such as HP-5, while good peak shape could be obtained with the use of a strong polar column such as HP-INNOWAX. However, the strong polar column exhibits limited temperature tolerance, thus it is not suitable for rapid analysis of FAs with boiling point close to 300°C.

Flame ionization detector (FID) is the most widely used detector in FAs determination by GC. DIVIŠOVÁ et al.(45) established a SPME-GC-FID method for the determination of 24 FAs in cosmetics with a DB-WAX capillary column, achieving the LODs at ppb level and the recoveries higher than 80%. However, the peaks of eugenol and isoeugenol isomers, farnesol isomers and cinnamyl alcohol, citral isomers and methyl 2-octynoate were not completely separated by this method, which affected the determination accuracy. Moreover, the boiling points of coumarin, benzyl benzoate, benzyl salicylate and benzyl cinnamate were higher than 300°C, and the capillary column needed to be kept at high temperature (220°C) for a long time (28 min), and the program greatly prolonged the analysis time (65 min in total).

Some FAs have similar chemical structures, and a few of them have cis-trans isomers, so the excellent capability of separation and identification is required for accurate qualification and quantitation of complex sample matrices. More sensitive than GC-FID, GC-MS can also analyze the structure by the characteristic mass-to-charge ratio (m/z) and its abundance ratio. GC-MS has good qualitative ability and can identify the partially separated or even un-separated compounds with different characteristic ions. Electron impact (EI) ionization can produce reproducible and representative mass spectrograms, which are often used in GC-MS analysis of FAs. Internal standard curve method is an extensively employed quantitative method with good accuracy, using 1-fluoronaphthalene, benzyl alcohol-D7, 1,4-dibromobiphenyl as well as dibromobiphenyl as the internal standards (36, 38, 47, 50). Li et al. (48) developed a HS-GC-MS method for the determination of 48 FAs in wooden toys using response surface method with the recoveries ranging from 79.8 to 115.2% and

RSDs ranging from 0.6% to 9.9. It was applied to the determination of 30 toy samples, of which FAs including benzyl alcohol, trans-2-heptenal, eugenol, and isoeugenol were found to have high detection rate. The total ion chromatogram of a standard mixture of 48 FAs is presented in Figure 2.

Recently, Mazzucotelli et al. (32) established a GC-MS method for the determination of 29 FAs in perfumes and essential oils by using water-compatible columns with stationary phase based on ionic-liquids. This method could analyze aqueous samples directly by simple dilution and shorten the analysis time, at the same time it suffered a relatively low sensitivity due to the lack of concentration procedure. Compared with MS, tandem MS has better selectivity and can obtain more accurate results, especially for samples with complex matrices. Liu et al. (56) determined 58 FAs in acrylonitrile-butadiene-styrene (ABS) and polyvinyl chloride (PVC) plastic toys by dissolution precipitation combined with GC-MS/MS with recoveries of 70-130% and RSDs less than 11%. Besides, the combination of FID and MS has been reported in GC determination of FAs. Desmedt et al. (57) reported a method of HS coupled to GC to evaluate the presence of FAs in absorbent hygiene products. The identification was completed by MS and the simultaneous quantification was performed by FID. The method was validated using the total error approach with an acceptance value of $\pm 15\%$.

Multi-dimensional gas chromatography. Among various FAs, some aldehydes and alcohols have similar properties, the traditional GC-MS sometimes leads to over- or underestimations in the analysis when target compounds are coeluted. The occurrence of coelutions in GC-MS is inherent in the restricted peak capacity of chromatographic columns. Since traditional GC-MS may not achieve satisfactory separation and quantitation, comprehensive two-dimensional gas chromatography (GC $\times$ GC) with high resolution and large peak capacity has been applied to the analysis of these FAs, which may solve a few coelutions. Debonneville et al. (13) combined GC $\times$ GC-MS with a program called GC-Image for data treatment, which overcame the problem of coelution and dramatically simplified the data treatment. Then, their team (58) further evaluated the method based on the combination of GC $\times$ GC with a low-cost quadrupole MS. It showed good performances when applied to the analysis of FAs in fragrance concentrates. Mondello et al. (59) also evaluated the applicability of GC $\times$ GC combined with qMS for the determination of FAs, and proved that GC $\times$ GC could achieve better resolutions without prolonging the analysis time, and improved qualitative accuracy and quantitative sensitivity.

Besides the MS, the FID is common detector for GC $\times$ GC. Shellie et al. (60), evaluated suitability of GC $\times$ GC with FID for the analysis of FAs, however, the result showed that the analysis of few FAs was problematic.

On the basis of the results obtained in FAs analysis by other groups. Cordero et al. (61) established a GC $\times$ GC method for the determination of 24 FAs in perfumes. They utilized GC $\times$ GC-qMS in scan mode for identification and GC $\times$ GC-FID coupled with GC $\times$ GC-qMS in SIM mode for quantification. The method was

able to assess a good level of confidence of the results from its application, the RSDs of GC×GC-FID were 1.02-10.61%.

Besides the GC×GC method, the heart-cut gas chromatography (GC–GC) is another approach of multi-dimensional gas chromatography. Rey et al. (62) combined multiple heart-cut chromatography (GC–GC) with low thermal mass chromatography module (LTM) for the determination of 56 FAs and applied it to the determination of 62 commercialized perfumes. The performance of the method was evaluated by the accuracy profile approach to determine uncertainties around the regulation limit of 10 mg/kg. An acceptable result was obtained for most of the target analytes, which indicated that this method could be accurately defined under or above 10 mg/kg (the regulatory limit). Moreover, this method was time-saving, with total analysis time of less than 2 h. However, matrix effects may interfere with accurate identification of some analytes, especially for complicated matrix samples. Therefore, specific sample preparation procedures needed to be explored for these cases. Figure 3 shows the instrumental diagram for the GC-GC-FID-MS. When the valve is closed (a), the analytes pass through the 1st column to FID. When the valve is open (b), the analytes pass through the 1st column to the 2nd column, and then to MS.

Unlike the previous study in which one secondary-column (²D) was coupled to a dual detector (FID/MS), Sgorbini et al. (63) proposed a GC×2GC-MS/FID method. In this method, a primary column (¹D) was coupled to two parallel ²D columns with different selectivity then connected to MS and FID respectively. The design enables the system to operate closer-to-optimal ²D linear velocities and to double ²D loading capacity, providing higher resolution and peak capacity. The method overcame the problems in the quantitation of co-elutions with large concentration differences and the identification of chiral compounds without resorting to the MS dimension.

Although the new GC×GC technique can solve the qualitative problem of FAs in complex matrices, the instrument is expensive and the data processing is complex. Therefore, its application in routine monitoring still needs promoting. Besides, only the applications of GC×GC technique in ready-to-inject perfumes samples are developed. More validation studies of complex matrix samples are needed.

HPLC and HPLC-MS/MS. HPLC has been used sparingly since GC is able to meet the needs for the vast majority of FAs determination with simple instrumental conditions and short analysis time. Even so, due to the presence of chromophoric groups in most FAs, ultraviolet detection has been reported in the determination of FAs. Villa et al. (33) developed a method for simultaneous determination of 24 FAs in the scented products by reversed-phase HPLC coupled with a diode array detector (DAD), using p-anisaldehyde as the internal standard, with UV detection at 210, 254, and 280 nm. In their study, FA separation was achieved on a C18 column by using the mobile phase of acetonitrile-water and a simple gradient elution. The recoveries were 89.9-102.6% and the RSDs were 0.85-4.60%. The LODs were at the µg/mL level. Compared with HPLC, the HPLC MS/MS has less interference and higher sensitivity, and has been applied to the determination of FAs by some researchers. Wei et al. (64) used HPLC-MS/MS to detect five coumarin FAs in toys. Acetonitrile and

0.1% acetic acid were used as the mobile phases with gradient elution. The recoveries were 93.2-105.8%, the RSDs were 4.35-8.27%, and the analysis time of the five analytes was within 8 min. The analytical methods for FAs in different samples are summarized in Table 2.

Conclusion

Based on the extensive use of FAs in skin care products, cosmetics, wipes, stationery, toys and other household goods, and their hazard to human health, the relevant standards have been constantly improved. In recent years, important progresses have been made in the research of analytical methods for FAs in personal care products, toys, and water samples. The sample preparation methods such as LLE, SPME and HS, are commonly employed in analysis of FAs. However, it is quite necessary to improve the efficiency and stability of these methods for simultaneous extraction of a variety of FAs with large differences in boiling point and polarity in highly complex matrices, and to further explore the combination of novel materials with excellent adsorption ability with intelligent on-line extraction techniques based on traditional sample pretreatment methods. In addition, the integration of two or more extraction approaches is also a developing trend of rapid and high-efficiency sample preparation. The current detection methods for analysis of FAs mainly rely on GC-FID and GC-MS. In the latest years, new analytical instruments such as GC×GC with higher resolutions and peak capacity, have also been employed for the detection of FAs that only in simple matrix such as perfume samples. One of the main goals for future researches on FAs determination can be the development of instrumental methods with higher resolution (such as high-resolution MS) and sensitivity (such as tandem MS) for accurate qualification and quantitation analysis of FAs that vary greatly in contents in complex sample matrices. Besides GC based methods, other instrumental methods suitable for volatile compounds, such as proton transfer reaction mass spectrometry (PTR-MS), will also be attempted for rapid determination of FAs.

In general, the standard analytical methods for FAs in different complex matrices are still not perfect. It is quite necessary and important to explore rapid, efficient, green, economic, and automatic sample pretreatment techniques as well as high-sensitivity and high-throughput instrument methods for analysis of FAs. What's more, the effective combination of sample pretreatment technique and instrument method could be the development trend in the field of FAs determination. It is expected that more in-depth studies will be carried out to develop rapid, accurate, sensitive, simple and automatic methods for the routine determination of FAs.

Acknowledgments

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Conflict of Interest

The authors declare that we have no financial interests or personal relationships that could inappropriately influence the work reported in this paper.

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Figure Captions

Figure 1 The sample pretreatment methods for FAs analysis.

Figure 2 The total ion chromatogram of a standard mixture of 48 FAs (adapted from ref. [48] with permission).
Peak identification: 1. ethyl acrylate, 2. methyl trans-2-butenate, 3. methyl trans-2-butenate, 4. allylisothiocyanate, 5. trans-2-heptenal, 6. benzyl alcohol, 7. dimethyl citraconate, 8. citronellol, 9. diethyl maleate, 10. methyl heptene carbonate, 11. benzyl cyanide, 12. citral, 13. 4-methoxyphenol, 14. 4-tert-butylphenol, 15. hydroxy-citronellal, 16. 4-ethoxy-phenol, 17. cinnamal, 18. cinnamyl alcohol, 19. eugenol, 20. 4-phenyl-3-buten-2-one, 21. alpha-iso-methylionone, 22. 2-pentylidene-cyclohexanone, 23. isoeugenol, 24. dihydrocoumarin, 25. pseudoionone, 26. cyclamen alcohol, 27. 2,4-dihydroxy-3-methylbenzaldehyde, 28. lilial, 29. coumarin, 30. 6-isopropyl-2-decahydronaphthalenol, 31. 3,6,10-trimethyl-3,5,9-undecatrien-2-one, 32. 7,11-dimethyl-4,6,10-dodecatrien-3-one, 33. amyl cinnamal, 34. 7-methylcoumarin, 35. 6-methylcoumarin, 36. diphenylamine, 37. amyl cinnamyl alcohol, 38. 4-(p-methoxyphenyl)-3-buten-2-one, 39. hexyl cinnamaldehyde, 40. 1-(p-methoxyphenyl)-1-penten-3-one, 41. benzyl benzoate, 42. 4-tert-butyl-3-methoxy-2,6-dinitrotoluene, 43. 7-methoxycoumarin, 44. benzyl salicylate, 45. 4,6-dimethyl-8-tert-butylcoumarin, 46. 7-ethoxy-4-methylcoumarin, 47. benzyl cinnamate, 48. hydroabietyl alcohol.

Figure 3 The instrumental diagram for the GC-GC-FID-MS (adapted from ref. [62] with permission).

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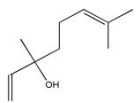
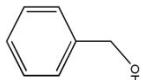
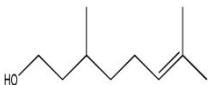
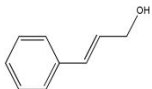
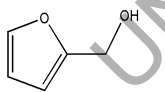
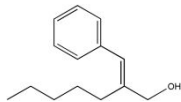
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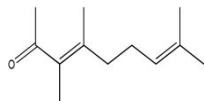
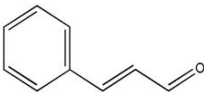
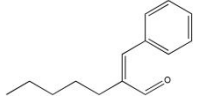
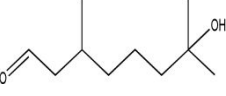
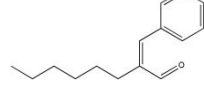
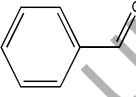
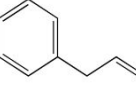
Table 1 The basic information of common FAs

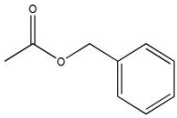
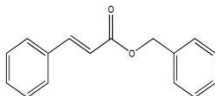
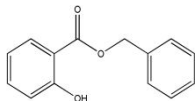
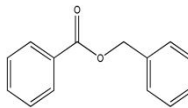
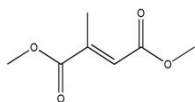
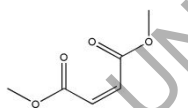
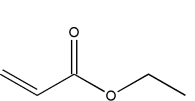
Table 2 The analytical methods for FAs in various samples

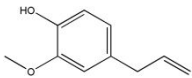
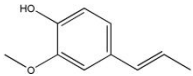
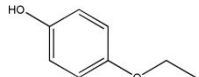
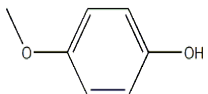
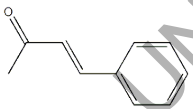
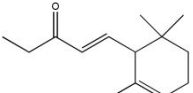
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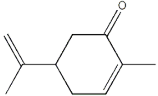
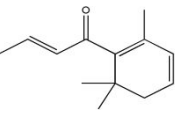
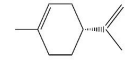
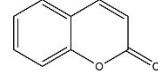
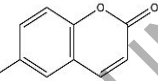
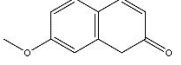
Table 1 The basic information of common FAs

FA	CAS No.	Chemical structure	Formula	Molecular weight (g/mol)	Physical properties	Toxicity	
						LD ₅₀ : Rats/Mice (peroral)	LD ₅₀ : Rabbits (skin contact)
Alcohol							
Linalool	78-70-6		C ₁₀ H ₁₈ O	154.25	b.p.198-199°C; water-solubility 1.45 g/L at 25°C; log P 2.68/2.97	2790 mg/kg (rats)	5610 mg/kg
Benzyl alcohol	100-51-6		C ₇ H ₈ O	108.14	b.p.205°C; water-solubility 33 g/L	1230 mg/kg (rats)	2000 mg/kg
Citronellol	106-22-9		C ₁₀ H ₂₀ O	156.26	b.p.225°C; slightly soluble in water	3450 mg/kg (rats)	2650 mg/kg
Geraniol	106-24-1		C ₁₀ H ₁₈ O	154.25	b.p.229-230°C; water-solubility 0.1 g/L at 25°C	3600 mg/kg (rats)	
Cinnamyl alcohol	104-54-1		C ₉ H ₁₀ O	134.18	b.p.250°C; water-solubility 1.8 g/L at 25°C	2000 mg/kg (rats)	> 5000 mg/kg
Furfuryl alcohol	98-00-0		C ₅ H ₆ O ₂	98.1	b.p.170°C; miscible with water	177 mg/kg (rats)	400 mg/kg
Amyl cinnamyl alcohol	101-85-9		C ₁₄ H ₂₀ O	204.31	b.p.141-143°C	4000 mg/kg (rats)	> 5000 mg/kg

FA	CAS No.	Chemical structure	Formula	Molecular weight (g/mol)	Physical properties	Toxicity	
						LD ₅₀ : Rats/Mice (peroral)	LD ₅₀ : Rabbits (skin contact)
Aldehyde							
Citral	5392-40-5		C ₁₀ H ₁₆ O	152.23	b.p.120°C and 229°C; water-solubility 0.4 g/L; log P 3.37/2.66	4960 mg/kg (rats)	
Cinnamaldehyde	104-55-2		C ₉ H ₈ O	132.16	b.p.250-252°C; water-solubility 1.42 g/L at 25°C; log P 2/1.98	2220 mg/kg (rats)	
Amyl cinnamaldehyde	122-40-7		C ₁₄ H ₁₈ O	202.29	b.p.284°C; insoluble in water; log P 4.330	3730 mg/kg (rats)	
Hydroxy citronellal	107-75-5		C ₁₀ H ₂₀ O ₂	172.26	b.p.257°C	5000 mg/kg (rats)	
α-Hexyl cinnamic aldehyde	101-86-0		C ₁₅ H ₂₀ O	216.32	b.p.174-176°C; water-solubility 0.005 g/L	2300 mg/kg (mice) 3100 mg/kg (rats)	
Benzaldehyde	100-52-7		C ₇ H ₆ O	106.12	b.p.179°C; water-solubility <0.1 g/L	1300 mg/kg (mice)	
Phenylacetaldehyde	122-78-1		C ₈ H ₈ O	120.15	b.p.195°C; water-solubility 3.03 g/L; log P 1.78	3890 mg/kg (mice)	

FA	CAS No.	Chemical structure	Formula	Molecular weight (g/mol)	Physical properties	Toxicity	
						LD ₅₀ : Rats/Mice (peroral)	LD ₅₀ : Rabbits (skin contact)
Ester							
Benzyl acetate	140-11-4		C ₉ H ₁₀ O ₂	150.17	b.p.206°C; water-solubility 3.1 g/L at 25°C; log P 2.07/1.65	2490 mg/kg (rats)	
Benzyl cinnamate	103-41-3		C ₁₆ H ₁₄ O ₂	238.28	b.p.195-200°C; insoluble in water	5530 mg/kg (rats)	
Benzyl salicylate	118-58-1		C ₁₄ H ₁₂ O ₃	228.24	b.p.320°C; water-solubility 8.8 mg/L; log P 4.31	2227 mg/kg (rats)	
Benzyl benzoate	120-51-4		C ₁₄ H ₁₂ O ₂	212.24	b.p.323-324°C; water-solubility 15.4 mg/L; log P 3.97	500 mg/kg (rats)	4000 mg/kg
Dimethyl citraconate	617-54-9		C ₇ H ₁₀ O ₄	158.15	b.p.211°C; water-solubility 28.6 g/L; log P 0.6	>5000 mg/kg (rats)	>5000 mg/kg
Diethyl maleate	141-05-9		C ₈ H ₁₂ O ₄	172.18	b.p.218.5°C; slightly soluble in water; log P 2.2	3200 mg/kg (rats)	5000 mg/kg
Ethyl acrylate	140-88-5		C ₅ H ₈ O ₂	100.12	b.p.99.4°C; water-solubility 15 g/L at 25°C; log P 1.3	800 mg/kg (rats)	1834 mg/kg

FA	CAS No.	Chemical structure	Formula	Molecular weight (g/mol)	Physical properties	Toxicity	
						LD ₅₀ : Rats/Mice (peroral)	LD ₅₀ : Rabbits (skin contact)
Phenol							
Eugenol	97-53-0		C ₁₀ H ₁₂ O ₂	164.2	b.p.253.2°C; water-solubility 2.46 g/L; log P 2.27	1930 mg/kg (rats)	
Isoeugenol	97-54-1		C ₁₀ H ₁₂ O ₂	164.2	b.p.260-262°C(cis);266°C(trans); water-solubility 356 g/L; log P 3.04	1560 mg/kg (rats)	
4-Ethoxyphenol	622-62-8		C ₈ H ₁₀ O ₂	138.16	b.p.246.5°C; water-solubility 9.22 g/L; log P 1.8		
4-Methoxyphenol	150-76-5		C ₇ H ₈ O	124.14	b.p.243°C; water-solubility 40 g/L; log P 1.58	1600 mg/kg (rats)	
Ketone							
Benzylideneacetone	122-57-6		C ₁₀ H ₁₀ O	146.19	b.p.261°C; water-solubility 1.350 g/L; log P 4.17	2031mg/kg (rats)	
6-Methylionone	1335-46-2		C ₁₄ H ₂₂ O	206.32	b.p.305.2°C; water-solubility 20 mg/L	5000 mg/kg (rats)	

FA	CAS No.	Chemical structure	Formula	Molecular weight (g/mol)	Physical properties	Toxicity	
						LD ₅₀ : Rats/Mice (peroral)	LD ₅₀ : Rabbits (skin contact)
Carvone	99-49-0		C ₁₀ H ₁₄ O	150.22	b.p.232°C; water-solubility 1300 mg/L; log P 3.070	1640 mg/kg (rats)	
Damascenone	23696-85-7		C ₁₃ H ₁₈ O	190.28	b.p.275.6°C		
Alkenes							
Limonene	5989-27-5		C ₁₀ H ₁₆	136.23	b.p.176-177°C; water-solubility 7.48 mg/L at 25°C; log P 4.5/3.22	4400 mg/kg (rats)	2000 mg/kg
Others							
Coumarin	91-64-5		C ₉ H ₆ O ₂	146.14	b.p.298°C; water-solubility 1.7 g/L; log P 1.39	293 mg/kg (rats)	
6-Methylcoumarin	92-48-8		C ₁₀ H ₈ O ₂	160.17	b.p.303°C; log P 2.060	1680 mg/kg (rats)	>5000 mg/kg
7-Methoxycoumarin	531-59-9		C ₁₀ H ₈ O ₃	176.17	b.p.247.77°C; water-solubility 0.133 g/L; log P 1.9	4300 mg/kg (rats)	

From: <https://pubchem.ncbi.nlm.nih.gov/>; <https://chem.nlm.nih.gov/chemidplus/>; <https://comptox.epa.gov/dashboard/>

Table 2 The analytical methods for FAs in various samples

No. of target FAs	Sample	Sample pretreatment	Analytical method	Method performance	Reference
25	Perfume	Direct injection	GC-MS; Column: SLB-5 (10 m×0.10 mm, 0.10 μm)	R ² ≥0.9990 Linear range: 1-1000 mg/kg; RSDs: 0.1-5.0%; LODs: 0.8-8.8 mg/kg; LOQs: 0.9-7.1 mg/kg	[27]
24	Perfume	Dilution with isooctane or fluortoluene	GC-MS; Column: column1, DB-1 (60 m×0.25 mm, 0.25 μm); column2, DB-1 (20 m×0.18 mm, 0.18 μm); column3, DB-5 (60 m×0.25 mm, 0.25 μm); column4, DB-17 (30 m×0.25 mm, 0.25 μm); column5, DB-17 (20 m×0.18 mm, 0.18 μm); column6, Delta-3 (30 m×0.25 mm, 0.25 μm)	R ² ≥0.9908; Linear range: 2-100 mg/L; Recovery: 100.5%	[29]

No. of target FAs	Sample	Sample pretreatment	Analytical method	Method performance	Reference
26	Fragrance raw materials and perfume oils	Dilution with acetone	GC-MS; Column: Varian CpSil-5 CB (50 m×0.25 mm, 0.25 µm); SGE Solgel-1 (60 m×0.25 mm, 0.25 µm)	$r > 0.999$; Linear range: 2-60 mg/kg	[31]
26	Plant oils meant to cosmetics	Dilution with alcohol or hexane	GC-MS; Column: DB-5 (30 m×0.32 mm, 1 µm)	$R^2 \geq 0.9903$; Linear range: 10-200 mg/L; RSDs: 0.016-0.42%; LODs: 2.1-50 mg/L; LOQs: 11-100 mg/L	[30]
24	Insect repellent, massage oil, moisturizing cream and hair conditioner	Insect repellent and massage oil samples: dilution with acetonitrile; Moisturizing cream and hair conditioner samples: ultrasound with acetonitrile and filter with a nylon membrane	HPLC-DVD; Column: RP18-e (250 mm×4.6 mm, 5 µm); Mobile phase: acetonitrile and water	$R^2 \geq 0.99$; Linear range: 0.1-500 µg/mL; RSDs: 0.85-4.60%; LODs: 0.01-0.74 µg/mL	[33]

No. of target FAs	Sample	Sample pretreatment	Analytical method	Method performance	Reference
29	Perfume and essential oils	Dilution with EtOH/H ₂ O solution	GC-MS; Column: Watercol 1460 (10 m×0.10 mm, 0.08 μm); Watercol 1910 (15 m×0.10 mm, 0.08 μm)	R ² ≥0.9917 (1460)/≥0.9969 (1910); Linear range: 5-1000 mg/L; Recoveries: >65%; RSDs: 1.0-7.5% (1460)/1.0-7.3% (1910); LODs: 1.1-2.8 mg/L (1460)/1.1-2.5 mg/L (1910); LOQs: 3.1-7.3 mg/L (1460)/3.2-7.2 mg/L (1460)	[32]
11	Cosmetics	Aftershave and deodorant spray samples: dilution with methanol; Shampoos, creams, lotions, lipstick and face powder: shake with methanol and filter with silica gel; Soap bar: dissolution in water with acetate, shake and centrifugation	GC-FID/MS; Column: CP-Sil 5 CB (50 m×0.32 mm, 1.2μm)	R ² ≥0.9950; Linear range: 50-5000 mg/L; Recoveries: 80-116%; RSDs: ≤11%; LODs: 1 mg/L	[52]
24	Perfume and cosmetics	Liquid sample: dilution with propyl acetate; Cream sample: dissolution in propyl acetate and	GC-MS; Column: DB-VRX (20 m×0.18 mm, 1 μm)	R ² >0.99; RSDs: ≤ 12% (solvent-vent injection)/ 10%	[35]

No. of target FAs	Sample	Sample pretreatment	Analytical method	Method performance	Reference
		shake		(hot-split injection); LODs: 0.0011-0.094 mg/L (solvent-vent injection)/0.0064-0.35 mg/L (hot-split injection); LOQs: 0.0033-0.29 mg/L (solvent-vent injection)/ 0.019-1.1 mg/L (hot-split injection); Recoveries: 84-117%	
28	Plant extracts, detergents and shampoos	Extraction with dichloromethane and centrifugation	GC-MS; Column: HP-1 (60 m×0.25 mm, 0.25 µm)	R ² ≥0.990; Linear range: 5-200 mg/kg; Recoveries: 80-120%; RSDs: 1.4-15%	[36]
25	Tap water, baby bathwater, recreational place water, public washing place water, and sewage water	Ultrasound-assisted emulsification-micro-extraction	GC-MS; Column: HP-5 (30 m×0.25 mm, 0.25 µm)	R ² ≥0.9974; Linear range: 0.020-20 µg/ml; Recoveries: 75-110%; RSDs: 0.1-23%; LODs: 0.006-1.15 ng/ml	[37]

No. of target FAs	Sample	Sample pretreatment	Analytical method	Method performance	Reference
26	Scented toys	Extraction with toluene ethyl acetate/Incubation and headspace	GC-MS; Column: DB-17 (30 m×0.25 mm, 0.25 µm)	R ² ≥ 0.990 (SLE-GC-MS)/ ≥ 0.896 (HS-SPME-GC-MS, 23°C)/ ≥ 0.939 (HS-SPME-GC-MS, 40°C); RSDs: 1.17-8.63% (23°C)/1.48-15.08 (40°C); LODs: 4.19-127 ng/cm ³ (GC-MS)/0.04-0.94 ng/cm ³ (HS-SPME-GC-MS, 23°C)/0.05-1.27 ng/cm ³ (HS-SPME-GC-MS, 40°C); LOQs: 4.48-168 ng/cm ³ (GC-MS, 23°C)/0.05-1.7 ng/cm ³ (HS-SPME-GC-MS, 23°C)/0.06-2.73 ng/cm ³ (HS-SPME-GC-MS, 40°C)	[38]
21	Toys	Velvet toys: extraction with acetone and filter. Plastic toys: ultrasound, centrifugation, and elution with methanol	GC-MS; Column: HP-1 (50 m×0.2 mm, 0.5 µm)	r > 0.9968; Linear range: 0.002-50 mg/L; Recoveries: 82.2-110.8%; RSDs: 0.6-10.5%; LOQ: 0.04-40 mg/kg (plush toys)/0.02-10 mg/kg (plastic toys)	[39]
43	Toys	Extraction with dichloromethane, ultrasound and filter with membrane	GC-MS; Column: DB-1 (30 m×0.25 mm, 0.25 µm);	r ≥ 0.9957; Linear range: 0.1-10.0 mg/L; Recoveries: 86.8-102.7%; RSDs: 3.85-11.49%; LOQs: 0.25-1.25 mg/kg	[40]

No. of target FAs	Sample	Sample pretreatment	Analytical method	Method performance	Reference
58	Plastic toys	Sonication with tetrahydrofuran, blending with methanol and filter	GC-MS/MS; Column: DB-17 (30 m×0.25 mm, 0.25 µm)	$R^2 \geq 0.9926$; Linear range: 0.1-600 mg/kg (ABS)/0.2-600 mg/kg (PVC); Recoveries: 76.9-129.6%(ABS)/70.3-126.5%(PVC); RSDs: 0.9-10.2%(ABS)/1.1%- 9.6%(PVC); LOQs: 0.1-10 mg/kg (ABS)/0.2-10 mg/kg (PVC)	[56]
5	Toys	Extraction by ultrasound with tetrahydrofuran, centrifugation with methanol, concentration and filter	HPLC-MS/MS; Column: XDB-C18 (100 mm×3.0 mm, 1.8 µm); HPLC mobile phase: acetonitrile and 0.1% acetic acid	$R^2 > 0.999$; Linear range: 10-1000 µg/L; Recoveries: 93.2-105.8%; RSDs: 3.65-8.27%; LOQs: 2.0-5.0 µg/L	[64]
5	Infant disposable products	Dispersive liquid-liquid micro-extraction	GC-MS; Column: HP-INNOWAX (30 m×0.25 mm, 0.25 µm)	$r \geq 0.99$; Linear range: 0.01-10 mg/kg; Recoveries: 78.7-106%; RSDs: 2.4-11.3%; LODs: 0.01-0.1 mg/kg; LOQs: 0.03-0.3 mg/kg	[41]

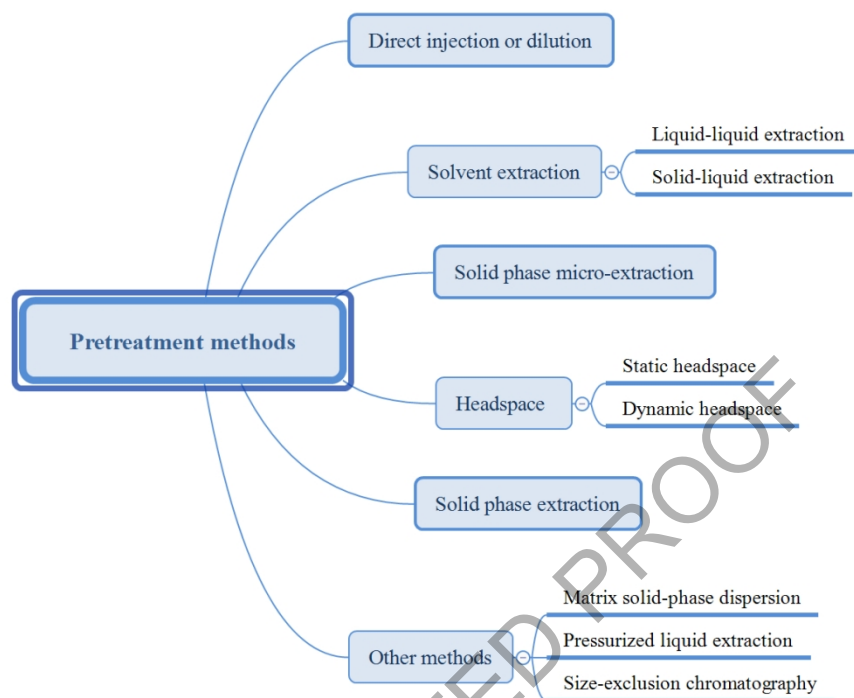
No. of target FAs	Sample	Sample pretreatment	Analytical method	Method performance	Reference
15	Baby bathwater	Headspace solid-phase micro- extraction	GC-MS; Column: DB-WAX (50 m×0.20 mm, 0.20µm)	$r \geq 0.993$; Linear range: 0.1-50 ng/mL; Recoveries: >80%; RSDs $\leq$ 10%; LODs: 0.001-0.300 ng/mL; LOQs: 0.004-1.000 ng/mL	[44]
26	Baby bathwaters, swimming pool waters and wastewaters	Headspace solid-phase micro- extraction	GC-MS; Column: HP-5(30 m×0.32 mm, 0.25 µm)	$r \geq 0.994$; Linear range: 1-20 ng/mL; Recoveries: 80-120%; RSDs $\leq$ 10%; LODs: 0.001-1.1 ng/mL; LOQs: 0.003-3.6 ng/mL	[42]
22	Continental waters	Headspace solid-phase micro- extraction	GC-MS/MS; Column: ZB-Semivolatiles (30 m×0.25 mm, 0.25 µm)	$R^2 \geq 0.9925$; Linear range: 0.1-1000 ng/L; Recoveries: 90-106%; RSDs < 15%; LODs: 0.023-14 ng/L; LOQs: 0.078-46 ng/L	[43]
24	Cosmetics	Headspace solid-phase micro- extraction	GC-FID; Column: DB-WAX (30 m×0.32 mm,0.5 µm)	$R^2 \geq 0.999$; Linear range: 0.1-1000 µg/mL; Recoveries $\geq$ 80%; RSDs: 0.5-5.8%; LODs: 0.007-2.7 µg/mL; LOQs: 0.023-8.9 µg/mL	[45]

No. of target FAs	Sample	Sample pretreatment	Analytical method	Method performance	Reference
29	Perfume and essential oils	Headspace solid-phase micro- extraction	GC-TCD/FID/MS; Column: Watercol 1460(30 m×0.25 mm, 0.20 µm); Watercol 1910(30 m×0.25 mm, 0.20 µm)	R ² ≥0.991 (1910)/≥0.997 (1460); Linear range: 50-5000 mg/L; Recoveries: 80.2-564.5% (1460)/64.7-115.8% (1910); RSDs: 0.78-5.38% (1460)/0.34-3.27% (1910); LODs: 2-3 mg/L (1460)/3-5 mg/L (1910); LOQs: 5-7 mg/L (1460)/7-9 mg/L (1910)	[46]
24	Scented toys	Headspace solid-phase micro- extraction/Dynamic headspace/Full evaporation headspace	GC-MS; Column: DB-17(30 m×0.25mm, 0.25 µm)	R ² >0.990; Recoveries: ≤6.0%; LODs: 8800 ng/mL (HS-SPME)/3710 ng/mL (DHS)/19.2 ng/mL (FE-DHS); LOQs: 29000 ng/mL (HS-SPME)/5500 ng/mL (DHS)/64 ng/mL (FE-DHS)	[47]

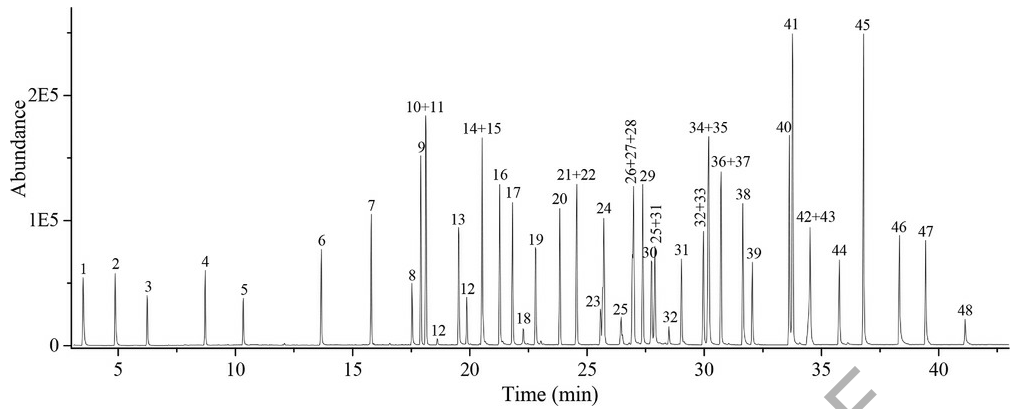
No. of target FAs	Sample	Sample pretreatment	Analytical method	Method performance	Reference
24	Toys	Dynamic headspace	GC-MS; Column: DB-17 (30 m×0.25 mm, 0.25 µm)	$R^2 \geq 0.991$; Recoveries: 66.3–128.2%; RSDs: 0.7–3.3%; LODs: 0.5–196.0 ng/mL; LOQs: 2.7–13.1 ng/mL (hydrophobic compounds)/270.0–632.0 ng/mL (hydrophilic compounds)	[51]
54	Plastic toys	Full evaporation headspace	GC-MS; Column: DB-35 (30 m×0.25 mm, 0.25 µm)	$r \geq 0.9987$; Linear range: 0.5–750 mg/kg; Recoveries: 81.0–135.7%; RSDs: 1.7–16.8%; LOQs: 0.5–15 mg/kg	[49]
48	Wooden toys	Headspace	GC-MS; Column: DB-35 (30 m×0.25 mm, 0.25 µm)	$R^2 \geq 0.9919$; Linear range: 0.2–1000 mg/kg; Recoveries: 79.8–115.2%; RSDs: 0.6–9.9%; LOQs: 0.2–20 mg/kg	[48]

No. of target FAs	Sample	Sample pretreatment	Analytical method	Method performance	Reference
24	Cosmetics	Full evaporation headspace	GC-MS; Column: VF-5 (40 m×0.25 mm, 0.25 µm)	$R^2 \geq 0.9963$; Linear range: 8-15 µg/ml; Recoveries: 80-120%; RSDs: 1.93-12.45%	[50]
19	Children's cosmetics and cosmetic-toys	Extraction with methanol and purification with solid phase extraction.	GC-MS; Column: CP-Sil 5 CB (50 m×0.32 mm, 1.2µm)	RSDs: $\leq 10\%$; LODs: 1 ppm	[34]
26	Cosmetics	Pressurized liquid extraction with hexane/acetone (1: 1, v/v) or ethyl acetate	GC-MS; Column: HP-5 (30 m×0.25 mm, 0.25 µm)	$r \geq 0.996$; Linear range: 0.02-10 µg/mL; Recoveries: 85-114%; RSDs: 0.2-9.5%; LODs: 0.0000012-0.00043 (% w/w); LOQs: 0.0000040-0.00060 (% w/w)	[54]

No. of target FAs	Sample	Sample pretreatment	Analytical method	Method performance	Reference
24	Cosmetics	Size-exclusion chromatography with acetone	GC-MS; Column: DB-35(60 m×0.32 mm, 0.25 µm)	R ² ≥0.995; Linear range: 0.06-1.00 mg/L; Recoveries: 90-120%; LOQ: 2-5 mg/kg	[55]

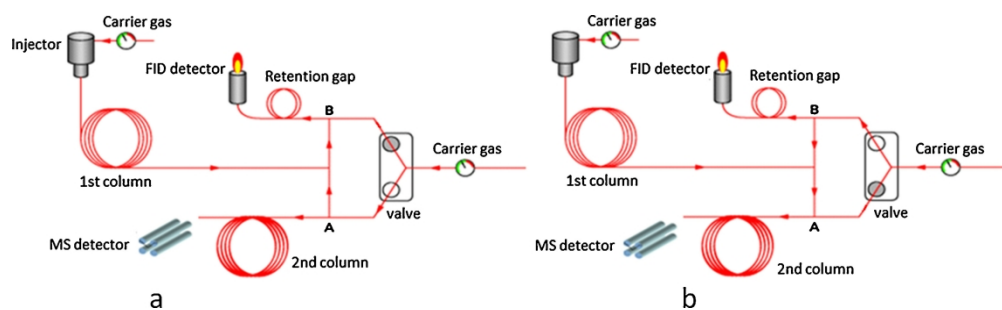


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42x16mm (599 x 599 DPI)

UNCORRECTED PROOF



160x47mm (500 x 500 DPI)