Doctoral Dissertation

博士論文

Dermal exposure to fragrance allergens in aromatherapy essential oils (EOs)

精油中の香料に含まれるアレルゲン経皮曝露評価に関する研究

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March, 2023

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1. Introduction

1.1. Background & Objectives

1.1.1. Prevalence of aromatherapy

Aromatherapy is a type of treatment/therapy of offering the psychological and physical benefits to humans through oral ingestion, massage, topical application, or inhalation of essential oils (EOs) extracted from flowers, bark, stems, leaves, roots or other parts of plants. [1, 2]. According to Babar et al. Aromatherapy is classified into cosmetic aromatherapy, massage aromatherapy, medical aromatherapy, olfactory aromatherapy, and psycho-aromatherapy [3]. Among them, on a consumer level, cosmetic aromatherapy which utilizes certain EOs on skin of body or face, and olfactory aromatherapy, which is inhalation of EO, are simple and effective ways to benefit from EOs.

These years, such two types of aromatherapy make aromatherapy widespread in several countries. For example, in the United States, the aromatherapy retail sales were more than 31 million dollars in 2012 [4]. In China, research from a domestic personal care manufacturer AFU in China stated that the sales of the aromatherapy products increase from 0.0743 million to 19.318 million USD between 2010 and 2017 [5]. In France, a survey conducted on general population found that 34% of the total respondents declared using EOs [6]. A study focusing on the nationally representative sample of Australian females aged 31–36 found that aromatherapy EOs were used by 15.2% pregnant women [7]. In Japan, there were 345 out of 1,096 Japanese university students used aromatherapy [8]. The reason for fast growing in sales and high prevalence of aromatherapy is that these consumers, from a health perspective, are looking for natural and holistic alternatives to household and personal care products.

1.1.2. Fragrance allergens in EOs

However, “natural” does not mean that there is no risk. Since EOs contain natural components which can be allergic, carcinogenic or toxic [9, 10], direct risks of aromatherapy might be allergic reactions, photo-toxicity, interactions with drugs, carcinogenicity, and toxicity after oral ingestion [11]. Among them, due to the naturally presenting fragrance allergenic compounds in EOs, such as limonene, citral or linalool [12, 13], the commonest adverse effect caused by using of EO was contact allergy [3, 11]. These fragrance allergens are included in the list of 26 most-known allergenic substances which have been stated in the seventh amendment of the European Union (EU) Cosmetic Directive [14]. This directive required that any of 26 fragrance allergens contained in cosmetic products exceeding certain acceptable levels must be declared on the label. Table 1 shows 16 fragrance allergens found as natural composition in EOs in accordance with EU Directive. Some of them are also included in the list of 54 established allergens in humans by Scientific Committee [12] shown in Table 2.

Table 1 List of fragrance allergens in EOs based on EU Directive

Allergens	**CAS Registry Number**
Anisyl alcohol	105-13-5
	1331-81-3
Benzyl alcohol	100-51-6
Benzyl benzoate	120-51-4
Benzyl salicylate	118-58-1
Cinnamyl alcohol	104-54-1
Cinnamal	104-55-2
Citral	5392-40-5

	141-27-5
	106-26-3
Citronellol	106-22-9
	1117-61-9
	26489-01-0
	6812-78-8
	141-25-3
	7540-51-4
Coumarin	91-64-5
Eugenol	97-53-0
Farnesol	4602-84-0
Geraniol	106-24-1
Hydroxy citronellal	107-75-5
Isoeugenol	97-54-1
	5932-68-3
Limonene	138-86-3
	7705-14-8
	5989-27-5
Linalool	78-70-6
	126-90-9
	126-91-0

[†] CAS Registry No. provided by the author.

Table 2 54 Established contact allergens in humans (Individual chemicals)

(Source: SCCS, pages 106–109 [12])

INCI name (or, if none exists, perfuming name according to CosIng)	**CAS Registry Number**
Acetylcedrene	32388-55-9
Amyl cinnamal	122-40-7
Amyl cinnamyl alcohol	101-85-9
Amyl salicylate	2050-08-0
trans-Anethole	4180-23-8
Anise alcohol	105-13-5
Benzaldehyde	100-52-7
Benzyl alcohol	100-51-6
Benzyl benzoate	120-51-4
Benzyl cinnamate	103-41-3
Benzyl salicylate	118-58-1
Butylphenyl methylpropional	80-54-6
Camphor	76-22-2
	464-49-3
beta-Caryophyllenen	87-44-5
Carvone	99-49-0
	6485-40-1
	2244-16-8
Cinnamal	104-55-2
Cinnamyl alcohol	104-54-1
Citral	5392-40-5
Citronellol	106-22-9

	1117-61-9
	7540-51-4
Coumarin	91-64-5
(Damascenone) Rose ketone 4	23696-85-7
alpha-Damascone	43052-87-5
	23726-94-5
cis-beta-Damascone	23726-92-3
delta-Damascone	57378-68-4
Dimethylbenzyl carbinyl acetate	151-05-3
Eugenol	97-53-0
Farnesol	4602-84-0
Geraniol	106-24-1
Hexadecanolactone	109-29-5
Hexamethylindanopyran	1222-05-5
Hexyl cinnamal	101-86-0
Hydroxyisohexyl 3-cyclohexene	31906-04-4
carboxaldehyde (HICC)	51414-25-6
Hydroxycitronellal	107-75-5
Isoeugenol	97-54-1
alpha-Isomethyl ionone	127-51-5
(dl)-Limonene	138-86-3
Linalool	78-70-6
Linalyl acetate	115-95-7
Menthol	1490-04-6
	89-78-1

	2216-51-5
6-Menthyl coumarin	92-48-8
Methyl 2-octynoate	111-12-6
Methyl salicylate	119-36-8
3-Methyl-5-(2,2,3-trimethryl-3-cyclopentenyl)pent-4-en-2-ol	67801-20-1
alpha-Pinene and beta-Pinene	80-56-8 and 127-91-3
Propylidene phthalide	17369-59-4
Salicylaldehyde	90-02-8
alpha-Santalol and beta-Santalol	15-71-9 and 77-42-9
Sclareol	515-03-7
Terpineol (mixture of isomers)	8000-41-7
alpha-terpineol	10482-56-1
	98-55-5
Terpinolene	586-62-9
Tetramethyl	54464-57-2
acetyloctahydronaphthalenes	54464-59-4
	68155-66-8
	68155-67-9
Trimethyl-benzenepropanol	103694-68-4
Vanillin	121-33-5

INCI: International Nomenclature of Cosmetic Ingredients

CosIng: Cosmetic ingredient database

Some EOs contain these fragrance allergens at high concentrations. For example, Coriander oil (*Coriandrum sativum*) contains an average of 68%

linalool, Dill oil (*Anethum graveolens*) distilled from leaf and seed contain average limonene at 31% and 37%, respectively [9]. There is max. 45% linalool and max. 47% linalyl acetate in Lavanda oil [15]. 33–55% of menthol is contained in Mentha oil as the main ingredient [16]. And 9.5% of camphor was in Rosemary oil [17].

1.1.3. Contact allergy reported in publications related to using of EOs

80 EOs are reported to cause contact allergy and the allergenic compositions in them have been extensively reviewed [18]. The relevance of positive patch test reactions also has been known through studies. The German Information Network of Departments of Dermatology (IVDK) investigated the frequency of contact allergy to EOs by patch test between 2000 and 2008 in 84,716 patients. 15,682 patients of them during this period had been tested with at least one EO, and 637 had positive reactions to at least one of the EOs. The most frequent allergenic EO was Ylang ylang (3.1% as mean of positive tests), Lemongrass (1.3%), Jasmine (1.6%), Sandalwood and clove oil (both 1.5%) [19]. Studies shows that some essential oils are important contact sensitizers. In Japan, the positive rate of Lavanda oil was 3.7% (0–13.9%) during the 9-year period from 1990 to 1998, and the patch test with Lavanda oil was found to be positive in increased numbers [20]. Contact allergy among aromatherapists and consumers due to tropical use of EOs has been reported in several case reports and case series [11, 21].

1.1.4. Crucial information for exposure assessment to fragrance allergens in EOs

Although fragrance allergens have the potential to cause skin sensitization, they can be formulated into cosmetics or detergents at safe levels by complying with specific regulations [12, 22]. However, there are no specific regulations to

limit fragrance allergens in aromatherapy EOs. Consequently, skin sensitization may result after dermal exposure to EOs especially when EOs are inappropriately used, for example, using undiluted EOs on the slightly sensitive skin [10]. From a quantitative perspective, dermal exposure to fragrance allergens in EOs has been demonstrated as a key risk factor in the induction of skin sensitization [23, 24]. The general toxicological principles of quantitative risk assessments can be applied to the induction of skin sensitization, thus, this exposure should be determined to assess the risk and better protect the consumer.

Generally, there are two approaches to assess the exposure: direct measurement or indirect estimation. However, since direct measurement is not practical in large epidemiological study due to the expense and effort, indirect estimation has been extensively used in exposure studies. Nowadays, to estimate consumer exposure to fragrance ingredients in personal care and cosmetic products, data are always needed as following [25, 26, 27]:

• use frequency of product

• skin sites of application of the products

• amount per use of each product

• chemical concentration of fragrance ingredient in the product

• retention factor[1]

• penetration factor[2]

• subject body weight and height

• surface area of exposed body sites

Contributed to large-scale consumer habits and ingredient survey, these

[1] Explained in Chapter 8, Glossary section.

[2]

necessary data, especially the use frequency and use amount, as well as the chemical ingredients, are available for personal care and cosmetic products in a variety of publications [25, 28, 29, 30]. However, for aromatherapy EOs, since there is no comprehensive habits data, nor penetration and retention data available, it was unable to estimate consumer exposure for fragrance allergens in EOs.

Fortunately, in 2014, in order to collect consumer habits data on aromatherapy, Dornic and his co-works conducted a web survey among 1,507 French general population to determine the use frequency, the number of drops per application (use amount) for 12 types of EOs (Lavanda, Eucalyptus, Mentha, Ylang ylang, Tea tree, Citrus, Vanilla, Ravintsara, Rosmarinus, Niaouli, Pinus, and Helichrysum), as well as the skin sites of application [6]. However, there were some limitations in this study. Firstly, this study did not cover some types of EO which may be popular in other countries. For example, through a pilot-survey conducted in China, we found that the most-used 11 types of EOs were Rose, Lavanda, Tea tree, Ginger, Mentha, Lemon, Sandalwood, Frankincense, Ylang ylang, Eucalyptus, and Jasmine. And in Japan, a survey conducted among 1,088 individuals aged 20–70 revealed that among females the top ten favorite EOs were Lavanda, Neroli, Bergamot, Geranium, Orange sweet, Frankincense, Rose, Sandalwood, Jasmine, and Ylang ylang [31]. Secondly, even if the most popular types of EO were the same, since consumer habits and practices could be strongly influenced by the demographics (e.g., age, gender, and region) which would generate different exposure factors (in particular, frequency of use and amount of use) for different populations [32]. Thirdly, the application body sites did not specified to each type of EOs, thus, data could not be used for estimating dermal exposure for skin sensitization risk

assessment. Consequently, although in 2016, Dornic et al. investigated the allergic composition of EOs, some types were not covered as well [33], and the concentration of fragrance allergens was not consumer-exposed concentration. Generally, these data are inadequate for generating exposure factors for assessing dermal exposure to fragrance allergens in EOs, especially for the other population in the world.

1.1.5. Aims of this study

This study was undertaken to help to fill that data gap existing in the French study as mentioned above, for example, consumer habits data could not be representative for the other populations. The study was designed to collect crucial information for estimating dermal exposure to fragrance allergens in EOs. Since the estimate of exposure will be used for assessing the skin sensitization risk related to use of EOs, dermal exposure is defined as the amount of fragrance allergen per skin surface area (e.g., $\mu g/cm^2$) for different body sites. Therefore, determining total body surface area based on subject body weight and height was included in my study. However, determining dermal retention factor and penetration factor were not included in this study.

The key objectives of the study are to collect and record the following information:

- use frequency of each type of EO (consumer habits)
- exposed body area for each type of EO (consumer habits)
- use amount per application for each type of EO (consumer habits)
- consumer-exposed inclusion level of fragrance allergens in each type of EO
- body surface area (calculated from the body weight and height data)
- surface area of exposed body sites

Such information could be used for an effective estimate of dermal exposure to

fragrance allergens in EOs. To highlight, information was based on the real Chinese consumers habits and practice survey, which would cover the most-used types of EO in China, and the exposed body sites would specify to each type of EO. Accordingly, the body surface area would be calculated from the Chinese consumer body weight and height data. Besides, the inclusion level of fragrance allergens would be the consumer-exposed level.

Finally, with the collected information, a dermal exposure assessment is aimed to be conducted incorporating a dermal exposure model.

1.2. Outline of Thesis

Chapter 1 presents the background and research objectives of the study Aromatherapy is known as the use of essential oils (EOs) to benefit the health of body, mind, and spirit. Nowadays, using of EOs are widespread among consumers, especially among females. However, EOs are composed of naturally presenting fragrance allergenic compounds, such as limonene, citral or oxidized linalool. Contact allergy due to tropical use of EOs has been reported in publications. From a quantitative perspective, dermal exposure to fragrance allergens has been demonstrated as a key risk factor in the induction of contact allergy. Therefore, this exposure should be determined to assess the risk and better protect the consumer. However, since there is no comprehensive habits data, nor body height and weigh and fragrance allergens data available, an effective estimate of dermal exposure can not be successfully conducted. Thus, in this thesis, necessary information for exposure assessment to fragrance allergens was collected, and dermal exposure to fragrance allergens was assessed.

Chapter 2 aims to provided consumer habits and practices data on frequency of use for each type of EO, and the skin sites of application for each

type of EO, as well as which types of EO should be for furthermore investigation, dilution rates of use for each type of EO by assessing the real usage patterns of aromatherapy EOs among Chinese consumers through a web-survey in April 2020 among 1,518 potential Chinese EO consumers.

Since only consumers using products containing a certain fragrance allergen will be exposed, integrating market share data, Chapter 3 aims to investigate the consumer-exposed inclusion level of fragrance allergens mainly based on the literature database. Besides, which kind of fragrance allergens in the investigated EOs is also discussed. These investigated EO were determined in chapter 2.

In chapter 3, the consumer-exposed inclusion level of allergens in EOs were determined. Thus, data on use amount of EOs per application is valuable to determine the use amount of fragrance allergens per application. For the case of EOs, use amount always means the number of drops per application and the weighting of each drop for each type of EO. Thus, chapter 4 aims to determine the number of drops per application and the weighting of each drop for each type of EO. The number of drops per application was calculated from the data on dilution rates of use which was determined in Chapter 2. The weighting of each drop was determined through a small weighting experiment.

Skin sensitization is a local effect, the exposure on different body sites should be separately assessed [24]. Thus, it is necessary to incorporate data on the surface area of exposed sites. Combining information on skin sites of application determined in chapter 2, chapter 5 aims to determine the body surface area for each individual and the surface area of exposed sites. Body surface area was calculated from data on the body weight and height which were collected from usage-pattern web survey. The data on surface area of

exposed body sites were directly sought from public literature.

Consumers may be exposed to one certain fragrance allergens from several types of EOs. Skin sensitization has been shown to be caused by the migration of allergens to the local lymph nodes where the product and allergens were applied, thus, dermal exposure should be assessed on separate body site. Chapter 6 aims to assess the dermal exposure to certain fragrance allergens contained in studied 11 types EOs on a certain body site through a dermal exposure model by combining data on the use of EOs with consumer-exposed inclusion level of fragrance allergens which were collected from chapter 2 to chapter 5.

Chapter 7 summaries the results obtained in this thesis and discusses how these data could be used for probabilistic exposure assessment by other studies. It also indicates the remaining data gaps needing further determination.

2. Frequency of use, Skin sites of application

Publication based on this chapter:

Xiao J, Nakai S. Usage Patterns of Aromatherapy Essential Oil Among Chinese Consumers. PLoS ONE. 2022; 17 (8): e0272031. DOI: 10.1371/journal.pone.0272031.

2.1. Background & Objectives

Information on the usage patterns of EOs is necessary for calculation of frequency of use and amount of use, as well as for determining skin sties of application and other additional necessary data (e.g., types of EO).

In recent years, studies have investigated the usage patterns of many cosmetic products among various populations in different regions, providing valuable information for exposure and risk assessment for substance contained in cosmetics [34, 35, 36, 37]. But for aromatherapy products, studies conducted on Australian pregnant women [7] and Japanese university students [8] gave data on the prevalence of aromatherapy among restricted sub-population. Until 2016, a survey of usage patterns of aromatherapy conducted among the French general population [6] provided important information regarding dermal exposure to fragrance allergenic molecules in EOs.

However, there is a lack of published usage-pattern/exposure data 1) on Chinese consumers whose consumption of EOs may be different from that of French consumers and 2) on specific application body sites according to each type of EO. Most importantly, because consumers buy EOs and dilute them in bases (e.g., vegetable oils or skin care products) to make a blend at varied dilution rates, data on dilution rates of use should be more accurate for

calculating the amount of use (i.e., the number of drops of EO). Thus, the dilution rates of use rather than the use amount of blend should be included in the survey on usage patterns of aromatherapy. The objectives of this chapter were to describe the usage patterns of EOs among Chinese consumers to provide important information on percentage of users with regard to types of EOs, skin sites of application, and dilution rates of use, as well as frequency of use per EO for generating exposure factors for dermal exposure estimating.

2.2. Materials & Methods

2.2.1. Study population

Chinese Aromatic & Aromatherapy WeChat groups are chatting groups established by the Chinese Aromatic & Aromatherapy Association. In this platform, there are approximately 1,500 EO consumers registered to share information on EOs, including safety precautions in aromatherapy practice, the receipt of EOs, the methods of EO storage, and the quality problems of EOs. However, the socio-demographic data on these consumers is unavailable. Approximately 1,500 consumers registered in Aromatic & Aromatherapy WeChat groups were invited to participate in our survey. Considering that EOs are used independent of age, for children (0–14) using EOs daily, but not registered in WeChat groups, their registering adults were asked an agreement to complete the survey on behalf of the children. Thus, the study population consisted of several age groups, which allowed us to examine the variability of use patterns across age.

2.2.2. Data collection

In late March 2020, all registered EO consumers in Chinese Aromatic & Aromatherapy WeChat groups were informed of the overall objectives of this survey. In April 2020, upon releasing the direct link to the website hosting the

questionnaire, an invitation was sent to everyone. To ensure the response rate, the links and invitations were sent to WeChat groups once a day and every day during the two-week period of the survey.

We developed a web-based questionnaire to determine the use patterns of EOs, specifically through the dermal route. This questionnaire contained general questions regarding demographics, body characteristics, and EO consumption data. The detailed usage patterns of EOs were assessed using questions concerning the types of EOs, body sites of application, frequency of use, and dilution rates of use for each EO. With respect to the types of EOs, 11 types of EOs (Rose, Lavanda, Tea tree, Ginger, Mentha, Lemon, Sandalwood, Frankincense, Ylang ylang, Eucalyptus, and Jasmine) were given as choices. These EOs were selected because they were the most popular EO among the panel of respondents in our pre-research survey. Skin sensitization has been shown to be caused by the migration of allergens to the local lymph nodes where the product and allergens were applied [23]. Therefore, the body sites the EOs were applied to should be determined to calculate the dermal exposure to fragrance allergens. Thus, we include different parts of the body as multiple choices to determine the body sites that each EO will be applied. Given that EOs are suggested to be diluted in bases to make a blend, we developed questions and multiple choices to describe the dilution rates in blend, that is, less than 1% (less than 1 drop in 5 mL base oil), 1% (1 drop in 5 mL base oil), 2% (2 drops in 5 mL base oil), 3% (3 drops in 5 mL base oil), 4% (4 drops in 5 mL base oil), 5% (5 drops in 5 mL base oil), more than 5% (more than 5 drops in 5 mL base oil), adding EO to cosmetic products, and undiluted (respondent was asked to give the number of drops in the latter two choices). The use amount of blend per use was not included in our survey, consequently, these

data were obtained from additional sources.

Such multiple choices were determined by closely observing safety precautions and recommendations provided on aromatherapy websites and widely consulting professional aromatherapists. Additional detailed information about the questionnaire is provided in Supplementary Information, S1. The study was approved by the Ethics Committee of Yokohama National University (No. non-medical-2019-17) in February 2020. All methods were performed in accordance with relevant guidelines and regulations. All subjects involved in the study have been properly instructed and they have indicated that they give their consent for information about themselves. The adults have been asked an agreement to give their consent on behalf of their children.

2.2.3. Data treatment

To summarize the demographic characteristics of the total consumers, basic descriptive statistics were used. With respect to the geographical data, the results of the living city were divided into four economic regions based on per capita gross regional product and indices by the National Bureau of Statistics of the People's Republic of China in 2013 (Supplementary Information, Figure S1): east, central, northeast, and west [38].

The same data analysis was conducted for the percentage of dermal users sorted by sex and age groups (0–14, 15–24, 25–39, 40–59, and 60–70).

To provide a better overview of the use patterns of EOs among Chinese consumers, we chose to describe the proportions of respondents on the type of EOs, exposed body sites, dilution rates of use across age groups, and frequency of use for each EO. Data on the type of EOs, exposed body areas,

dilution rates of use are treated as non-parametric. And data on frequency of use for each EO is treated as parametric. The chi-squared or Fisher's test was conducted to compare the differences in percentages of users on the type of EOs, exposed body area, and dilution rates of use across age groups.

To calculate the frequency for each EO used, responses were replaced by frequencies per day (daily replaced by 1, weekly by 1/7, monthly by 1/30). The response "yearly" was considered null and replaced by 0. Some of the respondents provided the number of times the EO was used; then, the frequency was multiplied by the value of times. The values for the number of times were assigned using the following criteria: For answers such as "X-Y times," the value was replaced by the average value; that is, (X + Y)/2. Then, for answers such as "more than Z," the value was replaced by Z. The Kruskall-Wallis test was conducted to compare difference in frequencies of use per age and per type of EO among females. When no statistical differences were observed, the sample was pooled per type of EO. The pooled samples of responses were used to calculate the mean, standard deviations (SD), 25th percentile (P25), 50th percentile (P50), 75th percentile (P75), 95th percentile (P95), and 99th percentile (P99) values per type of EO.

2.3. Results

2.3.1. General demographics

In total, 534 out of 1,518 potential participants (after exclusion of 44 invalid respondents) completed the web survey, which correspondents to a response rate of 35.2%. The sex distribution was compared among age (0–14, 15–24, 25–39, 40–59, 60–70), pregnancy status, profession, and economic region

(northeast, center, east, and west) groups. In our population sample, female consumers were overrepresented (N = 481; 90.1%). In addition, the age groups (0–14, 15–24, 25–39, 40–59, 60–70) represented 15.09%, 9.43%, 30.19%, 39.62%, and 5.66% of the male consumers, respectively, and the age groups for females were 2.08%, 4.57%, 63.41%, 28.69%, and 1.25%, respectively. The proportion of salaried males and females were the highest (33.96% and 30.77%, respectively) in socio-professional status. The majority of the consumers were from the east of China for male (67.92%) and female (87.94%) consumers (Supplementary Information, Table S1).

2.3.2. Prevalence of dermal use

The prevalence of dermal use was defined as the percentage of users exposed through the dermal route calculated based on the total number of consumers. Table 3 shows the percentages for male and female dermal users related to the total number of consumers per age group. Generally, 70% of male respondents (N = 37 on 53) and 95% of female respondents (N = 457 on 481) were exposed through dermal route.

Table 3. Percentage of users through dermal route per age group.

	Males (N = 53)		**Females (N = 481)**	
Age groups	**Number of users**	**Frequency of dermal users N(%)**	**Number of users**	**Frequency of dermal users N(%)**
0–14 years	8	7 (87.5%)	10	7 (70%)
15–24 years	5	4 (80.0%)	22	15 (68.1%)

25–39 years	16	9 (56.2%)	305	294 (96.3%)
40–59 years	21	16 (76.1%)	138	135 (97.8%)
60–70 years	3	1 (33.3%)	6	6 (100%)

2.3.3. Usage patterns among female dermal users

As the female dermal users were overrepresented (N = 457; 92.5% of total dermal users), usage patterns were described on female dermal users only. The percentages of females on the types of EOs, exposed body sites, and dilution rates were calculated based on 457 female dermal users.

2.3.4. Types of EOs applied on the skin among females

Figure 1 shows the percentage of female dermal users by age groups for 11 types of EOs. The sum of percentages is over 100% because of the multiple answers allowed per consumer. For females aged 0–14, they used only two types of EOs: Lavanda (42.9%) and Tea tree (57.1%) oils. Among the senior age groups (15–70), Lavanda oil was the most used EO with 46.7%, 51%, 68.1%, and 50% for females aged 15–24, 25–39, 40–59 and 60–70, respectively. Then, Rose oil was used by 33.3% (15–24), 41.5% (25–39), 52.6% (40–59), and 50% (60–70) of female users. The percentage of females aged 40–59 who used Lavanda oil was higher compared with other age groups ($p < 0.05$). However, for the other 10 types of EOs, no significant difference was observed among different age groups. Although for some EOs (i.e., Tea tree and Sandalwood oil), the percentages of females aged 0–14 or 60–70 were evidently higher than other age groups. Because of small sample size of such groups (only seven aged 0–14 and six aged 60–70), no significance was observed.

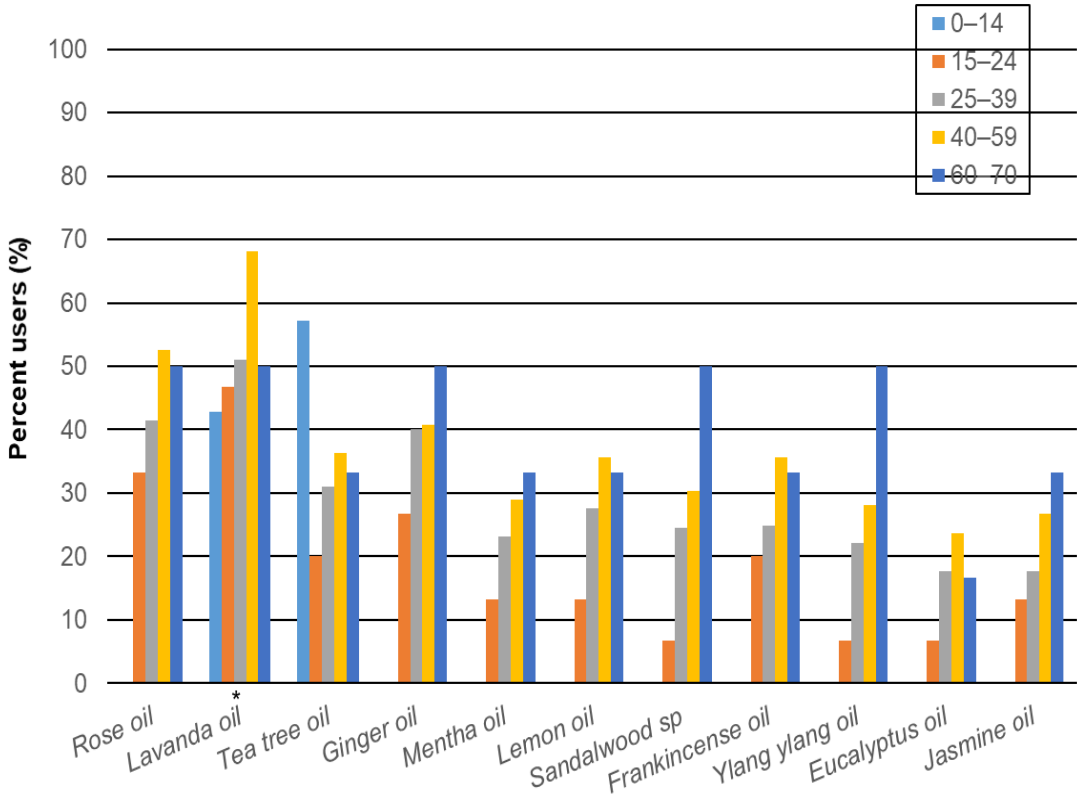


Figure 1. Percentage of female dermal users by age groups for 11 types of essential oils. Significant statistical differences ($p < 0.05$) marked with *.

2.3.5. Skin sites of application

Figure 2 shows a heat map providing the percentage of users who applied 11 different EOs on 15 body sites classified by age groups. According to our survey, female consumers aged 0–14 used Lavanda and Tea tree oils only, and 43% of them applied these two EOs on the breast/chest and back. Consumers aged 25–39 and 40–59 used EOs on almost all listed parts of the body. However, the majority of them applied Rose, Lavanda, Sandalwood, Frankincense, and Jasmine on the whole face. Compared with the diversities in body sites exposed by such age groups, the body sites of application of females aged 15–24, and 60–70 were relatively restricted. For example, women aged 60-70 tended to apply EOs on their face and lower limbs (thighs, calves/shins, and feet). Except for the philtrum, wrists, breast/chest, and back, significant differences were

found among different age groups when they used Lavanda oil. Significant differences were also observed when they used Rose oil on the face, Ginger oil on the feet, and Sandalwood oil on the face ($p < 0.05$).

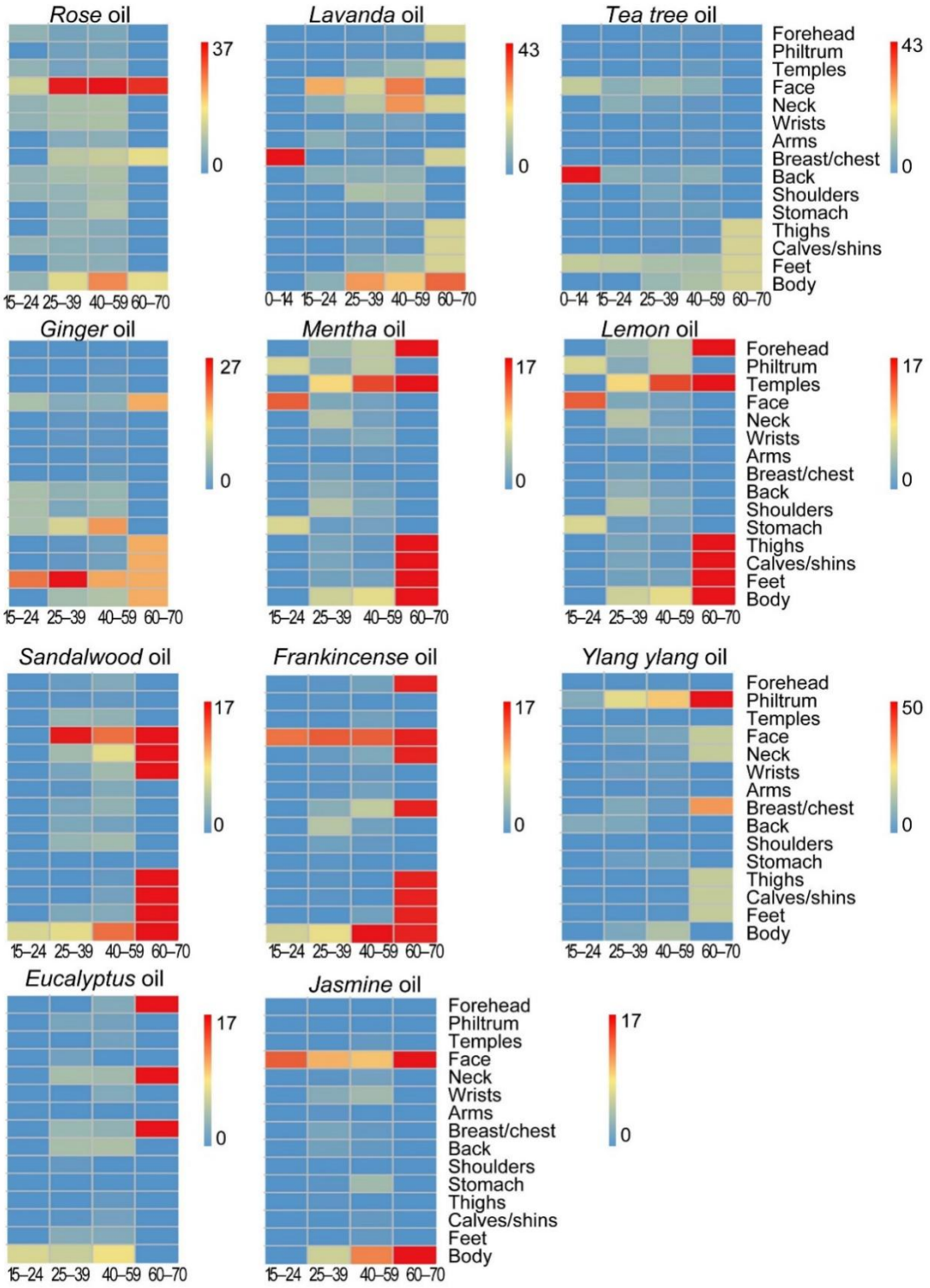


Figure 2. A heat map is used to show the percentage of users who used each essential oil

(EO) on different parts of the body (y-axis) from different age groups (x-axis). The redder cells indicate that the higher (highest) percentages of users applied EOs on sites of the body across age groups. For example, the majority of females (27%) aged 25–39 applied Ginger oil on their feet.

The following should be noted:

1. Females aged 0–14 used Lavanda and Tea tree oils only;

2. Scales are not unified. Ununified scales gave the reddest cells per each EO, which the extreme values on the most exposed body sites for each EO across age groups were easily found.

2.3.6. Frequencies of use

Table 4 shows the mean, SD, and selected percentile (P25–P99) values for the frequency of use for each type of EO. N is the number of female dermal users per EO. All values are represented on day^{-1}. For example, on average, female users applied Lavanda 0.68 times per day, with a P50 and P95 twice a week (0.28) and twice a day (2.00), respectively. Rose oil was used at a mean frequency of 1.06 times per day as the highest frequency. Lavanda, Tea tree, Sandalwood, Frankincense, and Eucalyptus were the EOs with similar mean values of 0.57–0.68 representing four to five times a week. Moreover, according to the mean value of the use frequency, females used Mentha, Lemon, Ylang ylang, and Jasmine less frequently compared with other EOs. Notably, that for Eucalyptus and Jasmine oil P99 values are not given.

Table 4. Frequency of use (per day) for each essential oil (EO).

Types of EO	Mean	SD	P25	P50	P75	P90	P95	P99
Rose oil (N = 201)	1.06	0.91	0.14	1.00	2.00	2.00	2.00	4.97
Lavanda oil (N = 255)	0.68	0.76	0.14	0.28	1.00	2.00	2.00	4.00

Tea tree oil (N = 150)	0.73	0.95	0.14	0.28	1.00	2.45	2.50	4.49
Mentha oil (N = 111)	0.38	0.67	0.00	0.14	0.28	1.00	2.00	3.00
Lemon oil (N = 133)	0.32	0.46	0.06	0.14	0.35	1.00	1.00	2.66
Sandalwood oil (N =117)	0.68	0.65	0.14	0.28	1.00	2.00	2.00	2.91
Frankincense oil (N = 126)	0.62	0.65	0.14	0.28	1.00	1.65	2.00	2.50
Ylang ylang oil (N = 107)	0.36	0.49	0.03	0.14	0.56	1.00	1.00	2.00
Eucalyptus oil (N = 86)	0.57	1.13	0.00	0.14	1.00	1.00	4.00	-
Jasmine oil (N = 92)	0.45	0.52	0.03	0.14	1.00	1.00	1.00	-

The differences in the frequency of use of all 11 types of EOs were analyzed by age groups. When no significant difference was observed, the samples were then pooled per the type of EO to determine the mean, standard deviation (SD), and selected percentiles (P25–P99). For example, among female consumers, the median frequency of use of Lavanda oil is 0.28, corresponding to twice a week. N is the number of female dermal users per EO. The Kruskall-Wallis test was conducted to compare difference in frequencies per age and per type of EO among females. When no statistical differences were observed, the sample was pooled per type of EO. For example, Ginger oil was excluded because of the difference in the frequency of use among age groups.

2.3.7. Dilution rates of use

In this study, we provided the distribution of the prevalence of use and dilution rates of EOs in blend for all 11 types of EOs per age group in Figure 3.

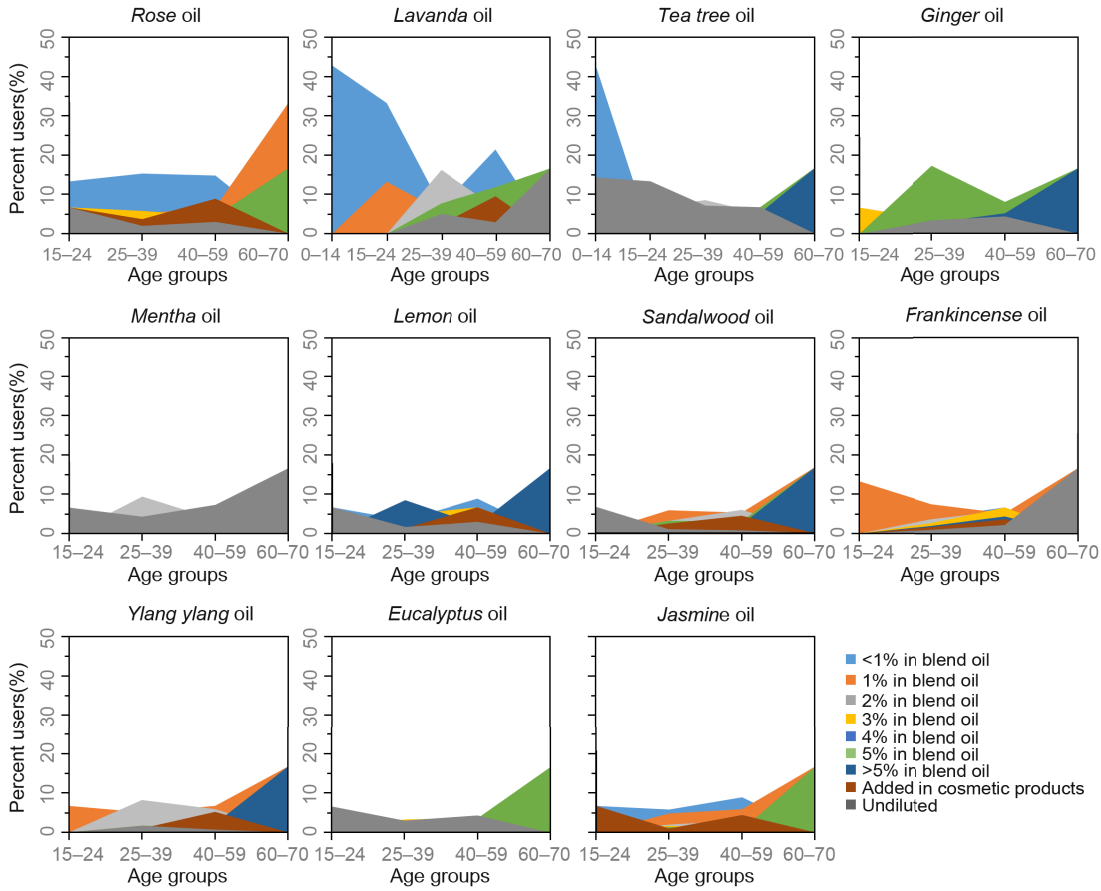


Figure 3. Distribution of the prevalence of use and dilution rates of use in blend for the 11 types of essential oils across age groups. For example, 9.5% of females added two drops of Mentha oil in 5 mL bases to make a 2% dilution rate of blend oil. Notably, females aged 0–14 consumed Lavanda and Tea tree oil only.

The percentage (42.9%) of Lavanda oil users at <1% dilution rates was higher in aged 0–14 compared with that of the senior age groups ($p < 0.05$). However, no significant difference was observed in the percentages of users for the other 10 EOs across age groups. Then, 42.9% of children (0–14) used <1% dilution of Tea tree oil. Moreover, for the senior age groups (25–59), generally, the dilution rates differed within the types of EOs, especially for Rose, Lavanda, Lemon, Sandalwood, Frankincense, Ylang ylang, and Jasmine oil. Such EOs were also frequently applied on the whole face or parts of face. For

example, as for Lavanda oil, 6.8%, 5.8%, 16.3%, 3.1%, 1%, 7.8%, 2.7%, 2.4%, and 5.1% of females aged 15–24 used at <1%, 1%, 2%, 3%, 4%, 5%, and >5% dilution; adding EO in cosmetic products; and undiluted, respectively. From another perspective, for the other EOs, a higher percentage of consumers aged 15–59 used undiluted Tea tree oil, whereas females aged 60–70 used 5% and > 5% in blend oil (16.7%, 16.7%); 17.3% and 8.1% of females aged 25–39 and 40–59, respectively, used 5% of Ginger oil in blend oil, whereas females aged 60–70 used 5% and >5% in blend oil (16.7%, 16.7%). Moreover, for Mentha oil, except for females aged 25–39 (9.5%) who used EO at 2% dilution, other age groups tended to use undiluted ones. Finally, most users aged 15–59 used undiluted Eucalyptus, whereas users aged 60–70 used 5% of it in blend oil.

2.4. Discussion

In this study, we provided a database on the usage patterns of 11 types of EOs. This database includes the general demographical data, prevalence of dermal use, percentages of users for the types of EOs used, exposed body sites, dilution rates of use, and frequency of use. To the best of our knowledge, this comprehensive study is the first to provide data on EO usage patterns.

2.4.1. Response Rate

Generally, the response rates in web questionnaire surveys are lower than traditional ones [39]. The response rate of this study was 35.6%, which is higher compared with some European studies that also used web-based questionnaires [37, 40].

Different from the French study conducted on a representative panel of the general French population, our survey was conducted on aromatherapy consumers [6]. Although our results are not representative of the Chinese general population, the data obtained were valuable to generate the dermal

exposure factor. Similar to the French study, a very low proportion of males (53 out of 534, approximately 9.9%) was observed, showing that men are less attracted to aromatherapy than women. In the French study, 60% (74 out of 123) of the female dermal user aged 25–59, whereas, in our study, the majority of female dermal users are aged 25–59 about 97% (443 out of 457, approximately 97%). The lower response in children can be explained by the lack of time of parents to answer the questionnaire, which could take 10 min.

2.4.2. Usage Patterns of Aromatherapy Products

The usage patterns of aromatherapy varied by age groups among female dermal users. For example, for the types of EO, a higher percentage of females aged 40–59 used Lavanda on the skin. Another example is the frequency use of Ginger oil. Females aged 60–70 used Ginger oil more frequently than other age groups; thus, Ginger oil was not included in Table 4 (Supplementary Information, Figure S2).

Notably, consumers always practice their aromatherapy at home by diluting EO in bases (i.e., vegetable oil or cosmetics) to make a blend for use, which is the major difference in usage pattern between formulated cosmetic products and aromatherapy products. Thus, our study included questions regarding the dilution rates of use, which is more accurate to determine the number of drops of EO in blend. This case also makes our study different from the French study in 2016 [6]. Use of highly concentrated and undiluted EOs bears a risk of skin sensitization [41]. Due to lack of recommendations applied to aromatherapy EOs, females (15–70) tented to use undiluted Tea tree and Mentha oil. High percentages of females aged 60–70 used each EO at ≧5% dilution rates. This leaves further exposure and risk assessment to fragrance allergens in EOs highly necessary.

Through market promotion and recommendation from the aromatherapy websites, Lavanda oil has been known as one of the safest oils and helpful for skin disorders and anxiety [42, 43]. Thus, among the 11 types of EOs we studied, Lavanda oil was used by 55.8% of female dermal users as the most popular EO. In the French study, the highest percentage of females (60%) used Lavanda on skin [6]. That is also the reason why parents chose Lavanda oil for their children (0–14). Tea tree oil was another EO used by children. Contributing to their antiviral and antimicrobial activity, these two EOs were recommended to be applied on breast/chest or back to relieve respiratory infection [44, 45, 46]. However, cases of contact dermatitis due to the tropical application of Tea tree oil or Lavanda oil or the combination of Tea tree and Lavanda oil were also reported [47, 48, 49, 50]. Hence, further investigation is needed to determine which kind of fragrance allergens and the concentration of them to assess the contact allergy risk of Lavanda and Tea tree oils.

In this study, we report the application areas of 11 types of EOs. The results showed that higher percentages of females aged 25–59 used Rose, Lavanda, Sandalwood, Frankincense, and Jasmine oils on the whole face compared with other parts of body. This information is particularly important to assess sensitization risk because in use tests, the neck and face are more sensitive than other parts of the body [12]. The face is a highly exposed body area, where the French study also described that 71% of adult females apply EOs on their face [6]. Research found that adult females aged 15–70, use on average nine different products on their face daily, with a 95th percentile exposed to 18 products [34]. The results in other studies indicated that gender (female) and age are risk factors for skin sensitization caused by fragrance allergens [51, 52]. Combining the mean values of use frequency per EO, we hypothesize that the

majority of females aged 25–59 used Rose, Lavanda, Sandalwood, Frankincense, and Jasmine oil as kinds of facial care products (i.e., day/night cream) at home. Moreover, they tended to dilute EOs according to their preference which caused the diversity of dilution rates. In consideration of such usage pattern of EO, co-exposure to fragrance allergens contained in EOs and cosmetics could be one of the reasons why females above a certain age are more vulnerable to fragrance allergy.

2.4.3 Limitations and Uncertainties

We assumed that some consumers added EOs in cosmetic products, that is, night cream or body lotion. However, the question related to this topic was not specially formulated in the questionnaire. Moreover, the questionnaire referred to the general frequency and dilution rates of use for each EO, but the questionnaire should have been divided into specific parts of the body. For example, in one individual, Rose oil might be used on the face twice a day with 1% blend oil while it also being used on back once a week with 5% blend oil.

In addition, in our population sample, female consumers were overrepresented (N = 481; 90.1%) compared with males. Although we only used the data of female consumers to determine the factors for exposure assessment, females aged 0–14 and 60–70 were underrepresented. Therefore, some comparative analysis may be biased. A complementary study specific to children and the elderly would be necessary to define their exposure more precisely.

2.5. Conclusion

This chapter describes the individual usage patterns of aromatherapy products among Chinese female consumers. In consideration of usage pattern of females aged 25-59, co-exposure to fragrance allergens contained in EOs

and cosmetics makes them vulnerable to fragrance allergy. The information on use frequency for each type of EO and the recorded application sites for each type of EO, making it possible to more accurately estimate dermal exposure as dose per unit area of skin. In addition, information on the types of EOs could be used for further safety studies (e.g., which types of EO should be under investigation for determining the inclusion level of fragrance allergens), and data on dilution rates of use could be used for calculation of use amount per application (e.g., the number of drops).

3. Consumer-exposed inclusion level of fragrance allergens in EOs

3.1. Background & Objectives

Determining which kind of fragrance allergens and the inclusion level of fragrance allergens is essential for calculating and assessing the dermal exposure to allergens, thus, for quantitative risk assessment of contact allergy.

Each type of EO may contain several natural products [33]. The allergen will not be in included in these products at the same level, and some products will not include the allergen at all. Since only consumers using products containing a certain allergen will be exposed, for realistic exposure estimates, it is necessary to have the data on the inclusion level of allergens the consumers exposed to rather than the inclusion level of allergens in products.

Market share data could give the consumption for different products. Thus, when incorporating data on the inclusion level of fragrance allergens with the market share, the consumer-exposed inclusion level of allergens could be obtained.

Thus, by incorporating qualitative and quantitative data collected mainly from literature database, together with market share data, this chapter aimed to determine information on which kind of allergens and the consumer-exposed inclusion level of allergens in each type of EO.

3.2. Materials & Methods

3.2.1. EOs' inventory in study and market share

In chapter 2, 11 types of EOs with their common names were determined. In this study, we studied 6 types of EOs: Rose, Ginger, Lemon, Frankincense, Sandalwood, and Jasmine oils. The other 5 types of EOs, such as Lavanda, Eucalyptus, Mentha, Tea tree, and Ylang ylang were excluded since they were already included in the French study [33].

Although it has been reported that EOs have therapeutic benefits, due to a lack of particular regulation applicable, EOs (including blend oils) directly go to the consumers fall under the category of cosmetics referring to GB/T 26516-2011 [53]. According to GB 5296.3-2008 (Introduction for use of cosmetic products - General labelling for cosmetics), EOs should be labelled with their INCI names on the containers [54].

Combining observing the labelling on the aromatherapy products on Chinese market, we used the published Chinese INCI name list version 2010 and 2015 to make an EOs' inventory. Each type of EO was shown with a common name. Different products included in the same type of EO were given with their INCI names where the Latin names of plant, extraction methods, and parts of the plant (e.g., flower, resin, and peel) were also documented (Table 5). There were 14 different products within 6 types of EOs to be included in this study (Table 5).

Table 5 Essential oils' (EOs') inventory

Types of EO with common name	Different natural products with INCI name
Rose oil	*Rosa centifolia* flower oil
	Rosa centifolia flower extract
	Rosa damascena flower oil
	Rosa damascena flower extract
	Rosa gallica flower oil
	Rosa gallica flower extract
	Rosa hybrid flower extract
Ginger oil	*Zingiber officinale* (ginger) root oil
Lemon oil	*Citrus medica* limonum (lemon) peel oil

Sandalwood oil	*Santalum album* (sandalwood) oil
Frankincense oil	*Boswellia carterii* resin extract
	Boswellia serrate resin extract
Jasmine oil	*Jasminum officinale (jasmine)* flower extract
	Jasminum sambac (jasmine) flower extract
N = 6	N = 14

† INCI: International Nomenclature of Cosmetic Ingredients

There is no available data on market share for different products within each type of EO in China. Through the usage-pattern web survey (mentioned in chapter 2), we found that 76.97% and 14.42% of the respondents (N = 534) purchased EOs from Aromatherapy organization & beauty salon and Distributors & suppliers of raw materials for personal care products (PCPs) respectively (Supplementary information, Table S2). Hence, we conducted a survey among these two types of suppliers to collect the market share data. Suppliers who were registering members of Chinese Aromatic & Aromatherapy, Aromatherapy organization & beauty salon who has more than 100 registered consumers and Distributors & suppliers of raw materials for PCPs whose annual sales of EOs going to aromatherapy industry is more than 500 kg 2018–2020 were the target suppliers in our survey. In late September 2020, we asked Chinese Aromatic & Aromatherapy Association to send email to 26 qualified suppliers. The mailing included a letter on the request for an online call, details of our study, a guarantee to treat the conversation confidentially. In early October 2020, after obtaining respondents and agreements from 6 Aromatherapy organization & beauty salon and 5 Distributors & suppliers of raw materials for PCPs, we started an online call with respect to the market share

of different products 2018–2020, according to the EOs' inventory (Table 5) among these 11 suppliers. To obtain sufficient data from commercial EOs, we also asked suppliers to provide us the GC-MS analysis of EOs if possible.

3.2.2. Fragrance allergens of interest and data collection on fragrance allergens

Since each product is natural complex mixtures of chemicals, a selection of the compositions as target allergens was conducted. 26 most-known allergenic substances have been stated in the seventh amendment of the European Union (EU) Cosmetic Directive [14]. This directive required that any of 26 allergens contained in cosmetic products exceeding certain acceptable levels must be declared on the label. 16 of them can be found as natural compositions in EOs which have been aforementioned in Table 1. Thus, these 16 fragrance allergens were selected as target allergens in our study. For further comparing the concentration of allergens in other five types of EOs reported by Dornic et al. in 2016 [33], we also included pinenes in the allergens list (Table 6). Pinenes were the sum of α and β forms, which was described as "established contact allergens in humans" by SCCS in Table 2.

Table 6 List of fragrance allergens of interest

Allergens	**CAS Registry Number**
Anisyl alcohol	105-13-5
	1331-81-3
Benzyl alcohol	100-51-6
Benzyl benzoate	120-51-4
Benzyl salicylate	118-58-1
Cinnamyl alcohol	104-54-1

Cinnamal	104-55-2
Citral	5392-40-5
	141-27-5
	106-26-3
Citronellol	106-22-9
	1117-61-9
	26489-01-0
	6812-78-8
	141-25-3
	7540-51-4
Coumarin	91-64-5
Eugenol	97-53-0
Farnesol	4602-84-0
Geraniol	106-24-1
Hydroxy citronellal	107-75-5
Isoeugenol	97-54-1
	5932-68-3
Limonene	138-86-3
	7705-14-8
	5989-27-5
Linalool	78-70-6
	126-90-9
	126-91-0
α-Pinene	80-56-8
β-Pinene	127-91-3

† CAS Registry No. provided by the author.

Beside of asking GC-MS analysis from suppliers, to obtain as much data on allergens contained in EOs as possible, searches and selection of scientific articles were performed in the PUBMED SCIENCEDIRECT and ZHIWANG databases.

For each product, the searches of articles were conducted by searched for the INCI names, e.g., "*Rosa damascene* flower oil" "*Rosa damascene* flower extract", followed by the word: "analysis" and/or "composition". Here, extraction methods were limited to (hydro)distillation and solvents extraction, but for Lemon oil, extraction methods were limited to mechanical press.

For some products, the exclusion criteria were applied for the period of publication. For example, "*Rosa damascene* flower oil", due to the huge volume of data, the date of publication was limited to after 2000 to obtain the latest data. On the other hand, no limitation of period was given since there was relatively smaller amount of available data. The inclusion level of allergenic compounds in percentages (%) was used.

3.2.3. Calculation of consumer-exposed inclusion level of fragrance allergens integrating market share

Tozer et al. calculated the "effective inclusion level" of ZnPt by multiplying the inclusion level of ZnPt in antidandruff shampoo by the market share [55]. Similarly, in our study, consumer-exposed inclusion level of a certain kind of allergen contained in each type of EO was calculated by using the following generic formula:

$$C = \sum_{i=1}^{n} C_i M_i \qquad (1)$$

Where C is the inclusion level of a certain kind allergen contained in each type of EO (%), C_i is the inclusion level of a certain kind of allergen in the i product obtained from database, M_i is the market share for i products. A triangular distribution for the inclusion level of fragrance ingredient in the cosmetic product was used for calculating of the dermal exposure [25]. It was assumed that such distribution was applicable for the inclusion level of fragrance allergen in EOs. Thus, the inclusion level of a certain kind allergen was adjusted to triangular distribution in Crystal Ball software with the Chi-squared goodness of fit test (Decisioneering Inc., Denver, Co., USA). Due to insufficient market share data, the median value was applied in the calculation. During calculation in the formula, C_i and M_i are probabilistically combined with Monte Carlo simulation analysis in Crystal Ball software.

3.3. Results

3.3.1. Different products and their market share

Trough the supplier survey, the products within each type of EO and their market share are obtained and given in Table 7. There were 14 different products with their INCI names or Latin names included in 6 types of EOs. For example, Rose contains 6 different products which come from different subspecies (*Rosa centifolia*, *Rosa damascene*, *Rosa gallica* and *Rosa setate* x *Rosa rugosa*) and different extraction methods (e.g., distillation, solvents extraction). Through supplier survey, differences between Table 5 and Table 7 were shown. For example, although do not appear in the INCI list, "*Rosa setate* x *Rosa. rugosa* flower oil" and "*Santalum spicatum* wood oil" could be purchased by Chinese consumers.

Table 7 Different products included in the database with their market share

Types of EO	INCI name/Latin scientific name	Market share (min-med- max)
Rose	*Rosa centifolia* flower extract	0-0.2-0.9
	Rosa damascena flower oil	0-0.2-1
	Rosa damascena flower extract	0-0.1-0.75
	Rosa gallica flower oil	0-0-0.5
	Rosa gallica flower extract	0-0-0.2
	Rosa setate x Rosa. rugosa flower oil^{+}	0-0-0.2
Ginger	*Zingiber officinale* (ginger) root oil	1
Lemon	*Citrus medica* limonum (lemon) peel oil	1
Sandalwood	*Santalum album* (sandalwood) oil	0.05-0.2-0.8
	Santalum spicatum wood oil^{+}	0.2-0.8-0.95
Frankincense	*Boswellia carterii* resin extract	0.5
	Boswellia serrate resin extract	0.5
Jasmine	*Jasminum officinale* (jasmine) flower extract	0.05-0.4-1
	Jasminum sambac (jasmine) flower extract	0-0.6-0.95
N = 6	N = 14	

Be noted, 5 types of EOs such as Lavanda, Eucalyptus, Mentha, Tea tree, and Ylang ylang which were already included in the French study [33] were excluded.

Since on China market, there is only one product included in Ginger and Lemon, the market share is 1 for both. For Frankincense oil, because all 11 suppliers had no idea of the subspecies, we chose to assume that two subspecies had the same rates of consumption. And for the other types of EO,

the market shares for different products are shown with the minimum, median and maximum values. For example, the maximum value of market share for "*Rosa damascena* flower oil" was 1, that means the maximum rate of occurrence of such product was 1.

3.3.2. Frequency of occurrence of fragrance allergens in studied EOs

In the collected 100 literatures from different databases and 13 GC-MS analysis reports from suppliers, 420 assays were collected as useful datasets. Among them, 13 kinds of allergens were found in these 6 types of EOs. Specifically, Linalool (89%), pinenes (88%), citronellol (81%) and geraniol (80%) were present more than 80% in total collected datasets (Figure 4, n = 420). Cinnamyl alcohol and isoeugenol were found in Jasmine oil only. And eugenol was contained in Rose oil only.

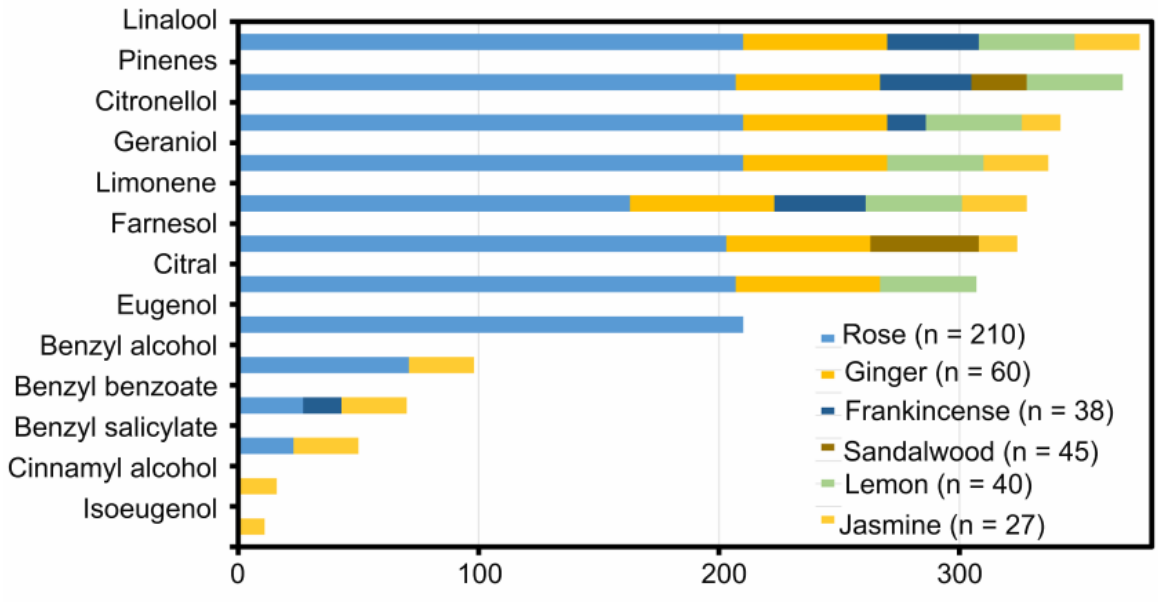


Figure 4. Occurrence of allergens in the 6 types of EOs: the appearance of each kind of allergen found in different types of EOs based on the collected data (n = 420). For example, linalool was found in 375 products out of 420 collected datasets (89%).

3.3.3. Consumer-exposed inclusion level of fragrance allergens

Integrating market share data, the consumer-exposed inclusion level of allergens contained in 6 types of EOs are shown in Table 8. Clearly, Rose and Jasmine contained a total of 11 different kinds of allergens, which was the maximum number. Then was followed by Ginger (7), Lemon (6), Frankincense (5) and Sandalwood (2) which contains the least kinds of allergens. When come to the inclusion level of allergens, the 3 highest inclusion level of fragrance allergens contained in each type of EO are presented in Table 4 as well. For example, when comparing the mean consumer-exposed inclusion level of 11 kinds of fragrance allergens contained in Rose, Citronellol, Geraniol and Farnesol were the 3 allergens with the highest inclusion level. Pinenes were present in four types of EOs, such as Ginger, Lemon, Sandalwood, and Frankincense with mean consumer-exposed inclusion level of 2.7%, 12.8%, 0.1%, and 18%, respectively.

Table 8 Three highest inclusion level of allergens for each type of EO.

Types of EO	Number of different allergens	3 allergens with the highest inclusion level (mean value in percentage)
Rose	11	Citronellol (13.6%) Geraniol (5.8%) Farnesol (1.1%)
Ginger	7	Citral (14.7%) Geraniol (4.3%) Pinenes (2.7%)
Lemon	6	Limonene (67.0%)

		Pinenes (12.8%)
		Linalool (0.1%)
Sandalwood	2	Farnesol (16.1%)
		Pinenes (0.1%)
Frankincense	5	Pinenes (18.0%)
		Limonene (12.5%)
		Linalool (0.9%)
Jasmine	11	Linalool (15.0%)
		Citronellol (11.2%)
		Benzyl alcohol (5.4%)

Be noted, 5 types of EOs such as Lavanda, Eucalyptus, Mentha, Tea tree, and Ylang ylang which were already included in the French study [33] were excluded.

3.4. Discussion

3.4.1. INCI list and supplier survey on market share

INCI list gives more information about the natural product (Latin name of the plant, extraction method and part of the plant used) compared to the Latin name. Thus, before the suppliers' survey and searching in database, utilizing the INCI list to make a EOs' inventory increased the effectiveness of supplier survey and data collection in literature database.

Through supplier survey, it is confirmed that two new subspecies: "*Rosa setate x Rosa. rugosa*" and "*Santalum spicatum*" are appearing in today's Chinese retail market during these two years. Because of its high price, "*Rosa damascene*" is gradually replaced by "*Rosa setate x Rosa. rugosa*", a typical hybrid Chinese rose. And "*Santalum spicatum*" is used to replace "*Santalum album*" which is in the International Union for Conservation (IUCN) of nature

Red list of threatened species [56]. Since 2018, the market share of these two new products has been keeping growing, which was confirmed by survey but not shown here.

3.4.2. Database

Botanical ingredients contained in different natural products show great natural variabilities due to lots of parameters, such as, origins, subspecies, parts of extractions and so on [57]. Thus, the use of database is successful to identify the qualitative and quantitative information of allergens. By using the scientific database, 420 dosages of data were created for 6 types of EOs, which is relatively larger volume of collected data compared to French study in 2016 [33]. The same as Dornic et al. did, we decided to share raw data from database (Supplementary information, S2, S3), hence, other can use it for risk assessment, or amendment and completion.

3.4.3. Fragrance allergens in EOs

The formula illustrated in this paper provides a simple framework for calculating the consumer-exposed inclusion level of a certain kind of allergen in each type of EO with incorporation of market share data. More realistic results are generated by using a probabilistic approach, enabling a more accurate estimate of consumer exposure.

Linalool and limonene, which were most frequently indicated fragrance allergens in other studies, belong to the established fragrance contact allergens of special concern in their oxidized form [58, 59, 60, 61]. In our study, linalool was the most often appearing allergen while limonene was ranked the fifth.

During observing the highest consumer-exposed inclusion level of allergens in each type of EO in more detail, study shows that the allergens and their inclusion level vary over different types of EO. It appears that floral EOs

such as Rose and Jasmine, as well as Ylang ylang reported by Dornic contain the most kinds of allergens, while woody EOs, like sandalwood contains relatively the least. Lemon contains 67% limonene, which is in good agreement with Dornic's results where citrus contain 68.3% limonene (both in mean values). As for pinenes, which was the second often occurring allergens in our study, the mean exposure concentrations of pinenes are also determined in Eucalyptus (5.5%), Tea tree (2.6%) by Dornic and his coworkers in 2016 [33]. Generally, EOs as natural products could contain even higher inclusion level of fragrance allergens than purely synthetic products just like Klaschka reported in 2016 [62].

3.4.4. Co-exposure and aggregate exposure to fragrance allergens

Because of the co-occurrence of fragrance allergens in each type of EO, the combination exposure (co-exposure) to a variety of allergens may result in great risk of contact allergy [63].

Limonene and linalool were also the most common natural fragrance chemicals in personal care and cleaning products [64, 65]. Results in our study demonstrate that application of EOs on skin could contribute to the dermal aggregate exposure to allergenic substances when consumers apply both personal care product and EOs on their skin. As an additional source of allergens, EO consumers could expose to relatively large amounts of fragrance allergens through dermal route. Further strategies should be considered, just like regulations on cosmetics, to protect the consumers from contact allergy.

3.4.5. Limitations

The names in INCI list are not always accurate and updated, thus, many names of natural substances do not appear in INCI list [66], which may make the EOs' inventory does not always correct. The GC-MS analysis data required

from suppliers are not large enough to supplement database collected from literature which may contains many data from laboratory-prepared EOs [41]. Supplier survey was too short which would underestimate or overestimate the proportion of different products within each type of EO.

3.5. Conclusion

Linalool was observed most frequently (89% of all assays) in these 6 types of EOs, which was also the most common fragrance chemical in personal care products (PCPs). The highest consumer-exposed inclusion level of allergens (mean value) in Rose, Ginger, Lemon, Sandalwood, Frankincense, and Jasmine oil were citronellol (13.6%), citral (14.7%), limonene (67.0%), farnesol (16.1%), pinenes (18.0%) and linalool (15.0%), respectively. Attention should be paid to EO consumers not only because of their co-exposure to fragrance allergens but also high inclusion level of allergens they may expose to. The data on consumer-exposed kind of and inclusion level of allergens in EOs can be used for estimation of dermal exposure to fragrance allergens in EOs.

4. Use amount per application

4.1. Background & Objectives

To calculate consumer dermal exposure to fragrance allergens in EOs, it is important to have information in the use amount of fragrance allergens per application. In chapter 3, we determined which kind of allergens and the consumer-exposed inclusion level of allergens (%) in EOs. Thus, data on use amount of EOs per application is valuable to determine the use amount of fragrance allergens per application. For EOs, use amount of EOs per application was calculated from the number of drops per application and the weighting of each drop per each type of EO [33]. Thus, this chapter aims to determine the number of drops per application for each type of EO and the weighting of drop per each type of EO.

4.2. Materials & Methods

4.2.1. The number of drops per application

Figure 5 shows how consumers perform their aromatherapy (dilute EOs in bases to make a blend, then use blend onto body sites). Thus, to calculate the number of drops per application, two parameters: 1. the dilution rate of use in blend; 2. the use amount of blend per application are necessary.

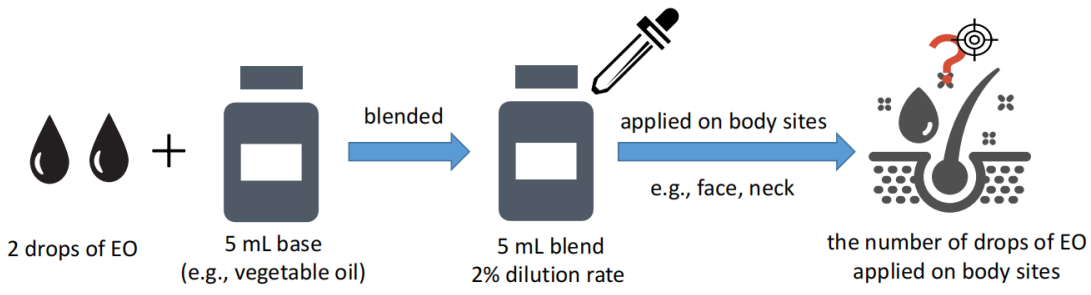


Figure 5. Description of consumers' real use of aromatherapy (dilute EOs in bases to make a blend, then use blend onto body sites, using 2% dilution rate as an example). Calculation: Number of drops per application applied on skin = dilution rate of use in blend × use amount

of blend per application (For example, if consumer added 2 drops of EO into 5 mL base to make a blend, when she/he used the blend onto face, the number of drops of EO per application is $\frac{2\ drops}{5\ mL} \times$ use amount of blend per application (mL)). Notably, the volume of EO added was considered negligible.

4.2.1.1. Data on the dilution rates of use in blend

Data on the dilution rates of use in blend for 11 types of EO were collected in the web-survey in April 2020 (chapter 2). Because of the small sample size of male, data on 457 females were used only.

4.2.1.2. Estimation of use amount of blend

Since the survey data did not contain information on the use amount of blend per application, and considering that the use amount of blend applied on different body sites should be different, questions regarding how much blend you usually used on your different parts of body were raised in the Chinese Aromatic & Aromatherapy We Chat groups. Photos which could help to make the consumers clearly answer the use amount of blend were also supplied as shown in Figure 6. The quantification of the original visualized response options for liquid products (in Figure 6) in metric gram measures was given in Table 9.

Figure 6. Photos used to support answering the amount normally used per application of EOs. (Source: Bernhard, 2017 [67])

Table 9 Use amount per application for liquid products.

Visualized unit	Unit amount (g)	Reference
drop	0.14	Bernhard, 2017 [67]
teaspoon	3.2	Bernhard, 2017 [67]
tablespoon	9.3	Bernhard, 2017 [67]

Combining Figure 6 and Table 9, an estimation of the use amount of blend per application on different body sites were shown in Table 10. However, although estimation of use amount of blend per application on different body sites was obtained, no further breakdown was performed to different body sites, because the resulting data sets would have been too small. Another reason is that in the survey (chapter 2), the questionnaire was designed to ask the general dilution rate for each type of EO rather than specific sites of body (in fact, it should be divided into specific body sites). Consequently, a mean value of use amount of blend for every body site was considered. According to Table 10, the mean value of use amount of blend was 3.9 g. Thus, a conservative mean value 4.0 g (≈ 4.0 mL) was used as the use amount of blend for every body site.

Table 10 Estimation of use amount of blend per application on different body sites (g).

Areas	Forehead	Philtrum	Temples	Face	Neck	Wrists	Breast /chest	Shoulders	Stomach	Thighs	Calves /shins	Feet
Estimate	0.28	0.14	0.14	3.2	1.6	0.28	9.3	4.7	4.7	9.3	9.3	4.7

The estimate above was derived from Chinese Aromatic & Aromatherapy WeChat groups. According to the questions how much blend you usually use on your different parts of body (e.g., face, neck) per application. Since a fewer of responses (N = 16) were collected, the mean values were given as the estimate of use amount of blend per application on different body sites.

Be noted that arms and back were not included in Table 10, since lower percentages of dermal users applied EOs on such areas which were described in Figure 2 of chapter 2. And for skin sensitization risk assessment, exposure assessment for whole body is less meaningful, whole body was also excluded

4.2.1.3. Quantification

According to the calculation described in Figure 5, responses were replaced by the number of drops per application. In this study, a conservative use amount of blend per application of 4 mL was used for the calculation of the number of drops per application. Table 11 shows how the responses replaced by “the number of drops per application”. For example, less than 1% (less than 1 drop in 5 mL base oil) was replaced by 0.50, and more than 5% was replaced by 6.00. For the response which the number of undiluted drops or added in cosmetic products was not provided, according to IFA’s safety guidelines for consumers (2% dilution rate is recommended), “2 drops” was considered and replaced by. Some of the respondents provided the number of drops undiluted or added in cosmetic products. The values for the number of drops was assigned using the following criteria: For answers such as “X–Y drops,” the value was replaced by the average value; that is, (X + Y)/2. Then, for answers such as “more than Z,” the value was replaced by Z.

Table 11 Quantification of the number of drops per application

Original response code	Number of drops
● less than 1% (less than 1 drop in 5 mL base oil)	0.4
● 1% (1 drop in 5 mL base oil)	0.8
● 2% (2 drops in 5 mL base oil)	1.6
● 3% (3 drops in 5 mL base oil)	2.4
● 4% (4 drops in 5 mL base oil)	3.2
● 5% (5 drops in 5 mL base oil)	4.0
● more than 5% (more than 5 drops in 5 mL base oil)	4.8
● Adding EO to cosmetic products, please specify	

● Undiluted, please specify	
Not specified	1.6
e.g., “X–Y drops”	(X + Y)/2
e.g., “more than Z”	Z

The number of drops per application was calculated from multiplying use amount of blend per application by dilution rates of use. For example, when females used 4 mL blend oil at a dilution rate of 2%, 1.6 drops of EO was applied on skin.

4.2.1.4. Data treatment

The number of drops per application was calculated based on 457 female dermal users. The Kruskall-Wallis test was conducted to compare the number of drops per age and per type of EO among females. When no statistical differences were observed, the sample was pooled per type of EO. The pooled samples of responses were used to calculate the mean, standard deviations (SD), 25th percentile (P25), 50th percentile (P50), 75th percentile (P75), 95th percentile (P95), and 99th percentile (P99) values per type of EO. Statistical data analyses were performed using IBM SPSS statistics 26.0.0.0 (IBM, Armonk, USA). Differences with a *p*-value of less than 0.05 were considered significant.

4.2.2. The weighting of each drop per each type of EO

Lavanda, Mentha, Tea tree, Eucalyptus, and Ylang ylang were excluded because in French studied, Donics et al. have measured the weighting of each drop [69]. The grams of each drop of Rose, Ginger, Lemon, Sandalwood, Frankincense, and Jasmine oils were measured by pre- and post-weighting. Different products belong to the 6 types of EOs were bought in Aromatherapy organization & salon to measure the grams of each drop by pre- and post-

weighting. For each product, 10 weightings were carried out with a different number of drops (from 3 to 5 drops depending on the case). The mean weights and standard deviations of each drop for each type of EO were determined. These data resulted in a normal distribution of weight taking into account the variability of the weight of the drops for the different product corresponding to each type of EO.

4.3. Results

4.3.1. The number of drops used per application for each type of EO

Table 12 shows the mean, SD, and selected percentile (P25–P99) values for the number of drops per application for each type of EO. N is the number of female dermal users per EO. For example, on average, female users applied Rose 1.62 drops per application, with a P50 (1.6 drops) and P95 (4.0 drops), respectively. Here, a P50 (1.6 drops) means that when the individual (P50) applied 4 mL bases for a single time, 1.60 drop of Rose was used. Ginger oil was used by females at a mean number of drops of 2.65 drops per application as the highest number. Followed by Eucalyptus oil, the mean number of drops per application is 2.45. Rose, Mentha, Sandalwood, Frankincense, Ylang ylang, and Jasmine were the EOs with similar mean values of 1.37–1.80 drops per application. Notably, that for Eucalyptus and Jasmine oil P99 values are not given.

Table 12 Number of drops used per application

Type of EO	Mean	SD	P25	P50	P75	P90	P95	P99
Rose oil (N = 201)	1.62	1.50	0.40	1.60	2.40	4.00	4.00	4.80
Ginger oil (N	2.65	1.51	1.60	2.40	4.00	4.45	4.80	4.80

= 180)								
Mentha oil (N = 111)	1.70	1.13	0.80	1.60	1.60	4.00	4.30	4.80
Sandalwood oil (N = 117)	1.80	1.39	0.80	1.60	2.40	4.00	4.80	4.80
Frankincense oil (N = 126)	1.74	1.41	0.80	1.60	2.40	4.24	4.80	6.41
Ylang ylang oil (N = 107)	1.75	1.21	0.80	1.60	1.60	4.00	4.80	4.80
Eucalyptus oil (N = 86)	2.45	1.38	1.60	1.60	4.00	4.80	4.80	
Jasmine oil (N = 92)	1.37	1.22	0.40	0.80	1.60	3.76	4.00	

The differences in the number of drops per application of all 11 types of EOs were analyzed by age groups. When no significant difference was observed, the samples were then pooled per the type of EO to determine the mean, standard deviation (SD), and selected percentiles (P25–P99). For example, the median number of drops of Rose oil used by females per application is 1.60, which means when the individual (P50) applied 4 mL blend for a single time, 1.60 drop of Rose was used. N is the number of female dermal users per EO. Lavanda, Tea tree, and Lemon oil were excluded because of the difference in number of drops per application among age groups.

4.3.2. The weighting of each drop per each type of EO

There were 25 EOs corresponding to the 6 types of investigated EOs were purchased from 3 Aromatherapy organization & salon in Shanghai (China) for weighing. As explained in Chapter 3, several natural products may have the

same common name on Chinese market. Rose for example may refer to *Rosa damascene* flower oil or *Rosa damascene* flower extract. Considering the potential variability between the weights of the drops, the different products of the same type of EO were thus sought during these purchases. For each type of oil, the mean weight of a drop associated with its respective standard deviation (in mg) is presented (Table 13). These data made it possible to define the normal distributions of the different weights that could be used in the exposure calculations.

Table 13 Mean weight and standard deviations (SD) of the different types of essential oils (EOs) weighted (in mg). 26 EOs, corresponding to 6 types of EOs and 11 different products, were studied. For example, the mean measured weight for 6 EOs bought from Aromatherapy organization & salon corresponding to 3 different Rose products was 30.934 mg (± 7.913 mg).

Type of EO	Number of EOs weighted	Studied products	Mean (mg)	SD (mg)
Rose	6	*Rosa damascena* flower oil *Rosa damascena* flower extract *Rosa setate x Rosa. rugosa* flower oil	30.934	7.913
Ginger	3	*Zingiber officinale* (ginger) root oil	28.910	3.545
Lemon	3	*Citrus medica*	23.447	0.732

		limonum (lemon) peel oil		
Sandalwood	6	*Santalum album* (sandalwood) oil *Santalum spicatum* wood oil	35.199	2.043
Frankincense	5	*Boswellia carterii* resin extract *Boswellia serrate* resin extract	26.091	3.771
Jasmine	3	*Jasminum officinale* (jasmine) flower extract *Jasminum sambac* (jasmine) flower extract	29.363	1.332

Be noted, 5 types of EOs such as Lavanda, Eucalyptus, Mentha, Tea tree, and Ylang ylang which were already included in the French study [69] were excluded.

4.4. Discussion & Conclusion

4.4.1. The number of drops per application

Different from finished consumer products, consumers always perform their aromatherapy at home, this practice includes dilute the essential oils into bases (vegetable oil or cosmetics) which makes the quantification of the number of drops per application very difficult. Bernhard also observed a large variability in the use of Tea tree oil when added in cosmetic products ranging

from 1 drop in 10g base to more than 4 drops in 10g base [67]. There were more respondents answered without clear amount of base [67].

In my study, the survey data did not contain information on the amount of EO per application. Instead, questions related to dilution rates of use for 11 types of EO in the web-survey which were more accurate to determine the use amount of EOs if we know the use amount of blend. However, although we have an estimation for the use amount of blend for different body sites, the use amount of EO could not be successfully divided into specific body sites, because of the questionnaire designing. A conservative assumption of 4 mL amount of blend for every exposed body site was used. Obviously, it will influence the exposure results and, in most cases, lead to overestimation. Nevertheless, since such conservation assumption was used, the number of drops was calculated and could be used for estimating dermal exposure.

In French study, data on the number of drops per application were directly collected from questionnaire survey [6]. Generally, females used average approximately 3 drops of Lavanda, Eucalyptus, Ylang ylang, Mentha, Tea tree and Citrus on their skin. While in this study, generally, females used average less than 2 drops for all types of EOs, except for Ginger and Eucalyptus oils. Females aged 25–39 used 10 drops of Lavanda oil as the highest number (supplementary information, Figure S3), which was the same in French study.

4.4.2. The weighting of each drop for each type of EO

There are several natural products share one common name of EO, and there are great variabilities in the weight of each drop between different products. Thus, different products were purchased for weighting. It is notable that in Table 7, through market survey, six Rose products were sold with the common name of Rose oil on Chinese market, while in Table 13, only three

Rose products were purchased for weighting. The reason why other three Rose products were not included is due to the high price and availability of Rose products. In fact, the weighting data on the other three Rose products should make the weighting of each drop for Rose more accurate. However, compared to using a deterministic value of 30 mg which determined by Tisserand and Young [70], the distribution of the weight of each drop in this part of study would make the assessment of dermal exposure more realistic.

5. Body Surface Area (BSA) and surface area of exposed sites

5.1. Background & Objectives

Skin sensitization is a local effect, the exposure on different body sites should be separately assessed [24]. Moreover, the dermal exposure is measured as the amount of substance per unit surface area (e.g., μg/cm^2). Thus, it is necessary to incorporate data on the surface area of exposed body sites. In chapter 2, exposed body sites were determined and shown (Figure 2). Consequently, relative percentage of body surface area value (P_{BSA}) were taken directly from published data (Table 14).

Table 14 Relative percentage of body surface area values (P_{BSA}) could be used in the calculation of dermal exposure per unit surface area. For each body site, the percentage related to the body surface area of the individual is given for females. For example, the entire face of a female individual, represents 3.10% of her total body surface area.

(Source: Dorinc et al., [69])

Body area	P_{BSA} (Females)	Reference
Forehead	1.03%	Prendergast, 2018
Philtrum	0.11%	Prendergast, 2012
Temples	0.21%	Prendergast, 2012
Entire face	3.10%	USEPA, 2011
Neck	2.00%	Boniol et al., 2008
Wrists	1.20%	USEPA, 2011
Breast/chest	14.30%	Boniol et al., 2008
Shoulders	1.80%	Boniol et al., 2008
Stomach	3.00%	Boniol et al., 2008

Thighs	17.40%	Boniol et al., 2008
Calves/shins	11.50%	Boniol et al., 2008
Feet	6.60%	USEPA, 2011

Male's data were not included in Table 14, since the data on exposed body sites were collected on females only which were described in Figure 2 of Chapter 2. Furthermore, arms and back were not included in Table 14, since lower percentages of dermal users applied EOs on such areas. And for skin sensitization risk assessment, exposure assessment for whole body is less meaningful, whole body was also excluded.

However, these data were the percentages related to the total body surface area. To determine the surface area of exposed body sites in cm^2 or m^2, it is crucial to have the data on the body surface area (BSA). In Europe, BSA data are included in the SCCS safety guidance for the testing of cosmetic ingredients and their safety evaluation [71]. And in 2017, Dornic et al. reported additional BSA data for French population [72]. However, there is little information on the BSA in China. Therefore, except the sorted data on the surface area of exposed sites (P_{BSA}) which has been shown in Table 14, another objective of this chapter is to determine the BSA of the Chinese consumers.

5.2. Materials & Methods

5.2.1. Determination of the Body Surface Area (BSA)

To calculate the BSA (m^2), the following formula was used:

$$BSA = 0.02350 \times Height\ (m)^{0.42246} \times Weight(kg)^{0.51456} \qquad (2)$$

This formula was proposed by Gehan and George in 1970 [73]. It was considered by the US EPA to be the best choice for estimating the total body surface area [74].

5.2.2. Origin of data

Data on weight and height of each respondent were collected in the web survey in April 2020 which was described in chapter 2. Because of the small sample size of male (0–70), data collected on 457 females aged 0–70 were used only.

5.2.3. Quantification

In our survey, the body weight and height were not measured. Instead, in body characteristics section of questionnaire, choices as shown in Table 15 were given to the respondents. Table 15 demonstrates how the responses replaced by value of body weight and height. For example, less than 45 kg was replaced by 45 kg, and more than 180 cm was replaced by 180 cm.

Table 15 Quantification of body weight and height

Original response code	Quantification
● < 45.0 kg	45.0 kg
● 45–49 kg	47.0 kg
● 50–54 kg	52.0 kg
● 55–59 kg	57.0 kg
● 60–64 kg	62.0 kg
● 65–69 kg	67.0 kg
● > 70.0 kg	70.0 kg
● < 155.0 cm	155.0 cm
● 155–159 cm	157.5 cm
● 160–165 cm	162.5 cm
● 165–170 cm	167.5 cm
● 170–175 cm	172.5 cm

● 175–180 cm	177.5 cm
● > 180 cm	180 cm

5.2.4. Data treatment

The mean, standard deviations (SD), 25th percentile (P25), 50th percentile (P50), 75th percentile (P75), 95th percentile (P95), and 99th percentile (P99) values were collected for the data on body weight and height, as well as the calculated values of BSA. Statistical data analyses were performed using IBM SPSS statistics 26.0.0.0 (IBM, Armonk, USA).

5.3. Results

In total, data on body weight and height for 497 females aged 0–70 were used to calculate the Body Surface Area (BSA). The mean, SD, P25, P50, P75, P90, P95 and P99 for body weight, height, and BSA were given in Table 16. In this study, the Chinese EO female consumers weighed on average 56.23 kg, with an average 161.77 cm, and average BSA of 1.61 m^2.

Table 16 Anthropometric data of the Chinese females aged 0–70.

Anthropometric Data	Mean	SD	P25	P50	P75	P90	P95	P99
Weight (kg)	56.23	5.13	52.50	57.50	57.50	62.50	62.50	70.00
Height (cm)	161.77	4.23	157.5	162.5	162.5	167.5	167.5	172.5
BSA (m^2)	1.61	0.80	1.55	1.60	1.64	1.69	1.76	1.82

For each female aged 0–70, data on body weight, body weight and Body surface Area (BSA) were provided in cm, kg and m^2, respectively. BSA was calculated using the

Gehan and George formula [72], based on body weight and height data for 457 females aged 0–70.

5.4. Discussion & Conclusions

Considering the sample size of children (0–14, N = 7), adolescents (15–24, N = 15), and elderly (60–70, N = 6), the data on body weight and height were not sorted by age groups. Consequently, the BSA were not calculated per age group. Anthropometric data reported in other studies, for example, the SCCS notes [71] and Dornic's [72] were of very high quality, since they are based on measurements or larger sample size. But data in this study came from quantification of responses in questionnaire, and the sample size was relatively smaller. However, our collected data for weight and height are consistent with data from Zhang et al. In their study, an average body weight of Chinese female university student was 54.7 kg, with an average body height of 161.5 cm [75].

Data obtained from European are representative of a relatively tall and heavy population which could not be used for the calculation of dermal exposure of Chinese consumers. When comparing such data obtained in Europe, for example, the average body weight and height of French women (63.53 kg, 163.63 cm) and Chinese women (56.23 kg, 161.77 cm) in this study, Chinese women seems "lighter and shorter" than French women. Dermal exposure is the dose per unit area (e.g., μg/cm^2). When the same amount of fragrance allergens applied, the larger BSA, the less amount of fragrance allergens human exposed to. Since BSA is the calculation of body weight and height, the European data seems under protective for "lighter and shorter" populations. This makes the work of collecting the anthropometric data on Chinese consumers through the usage-pattern survey very valuable for assessing the dermal exposure to fragrance allergens.

To conclude, considering the variability between different sub-populations, it is important to know the anthropometric (body weight, height, and surface area) data of the various sub-populations. In the future, more work should be conducted to determine the variability of anthropometric data in sub-populations. Incorporating the values of relative percentage of body surface area (P_{BSA}) from published data, this chapter provided the calculated BSA (combining the consumer data on body weight and height from usage-pattern survey) as useful anthropometric information for estimate of dermal exposure ($\mu g/cm^2$) on different body sites.

6. Dermal exposure to fragrance allergens in EOs

This chapter is being submitted as "title" on Food Chem Toxicol.

6.1. Backgrounds & Objectives

One type of EO main contain several kinds of fragrance allergens, while one kind of fragrance allergen can be contained in several types of EO. Consumers may expose to one certain kind of fragrance allergen from several types of EOs. Skin sensitization has been shown to be caused by the migration of allergens to the local lymph nodes where the product and allergens were applied [23]. Therefore, dermal exposure should be assessed on separate body site.

It is thus appropriate to assess the dermal exposure to certain kinds of fragrance allergen contained in studied 11 types EOs on a certain body site through a dermal exposure model by combining data on the use of EOs with consumer-exposed inclusion level of fragrance allergens which were collected from chapter 2 to chapter 5.

6.2. Materials & Methods

6.2.1. Studies population

Children (0–14), adolescents (15–24) and elderly (60–70) were not taken into account in the assessment of dermal exposure given the limited number of responses obtained. Thus, information collected from 429 female consumers aged 25–59 was used for the exposure calculation and assessment.

6.2.2. Fragrance allergen investigated

In chapter 3, 13 allergenic substances were found in Rose, Ginger, Lemon, Sandalwood, Frankincense, and Jasmine oils. Among them, linalool, pinenes,

citronellol, and geraniol were observed frequently (more than 80%) in total collected datasets. In Donic's study, limonene was found as the second most occurred allergens in studied EOs [33]. Additionally, it was were most frequently indicated fragrance allergens in previous studies, belong to the established fragrance contact allergens of special concern in their oxidized form [58, 60, 61]. Thus, limonene was also included in dermal exposure assessment beside of linalool, pinenes, citronellol, and geraniol.

6.2.3. Skin site of application investigated

Results from Chapter 2 showed that higher percentages of females aged 25–59 used Rose, Lavanda, Sandalwood, Frankincense, and Jasmine oils on the whole face compared with other parts of body. In use tests, the face is more sensitive than other parts of body [12]. Besides, the face is a highly exposed body area. Research found that adult females aged 15–70, use on average nine different products on their face daily, with a 95th percentile exposed to 18 products [34].

6.2.4. Calculation of dermal exposure

Daily exposure to a certain allergen was calculated per individual using the following formula:

$$E_{allergen/d} = \frac{\sum F \times C \times N \times W}{BSA \times P_{BSA}} \quad (3)$$

Where $E_{allergen/d}$ is the dermal exposure to a certain allergen per day from 11 types of EO on the face according to the individual's usage pattern (in μg/cm^2/d).

F is the frequency of use of the EO (in day^{-1}) (in chapter 2).

C is the triangular distribution of the consumer-exposed inclusion level of allergens in each type of EO (in Chapter 3, supplementary information S3).

W is the normal distribution of the weighting of each drop of EO (in μg) (in Table

13, chapter 4).

N is the number of drops per application (in number) (in chapter 4).

BSA is the total body surface areas of the individual (in cm^2) (in chapter 5).

P_{BSA} is the relative percentage of body surface area. The P_{BSA} for face is 3.10% (in Table 14, chapter 5).

The penetration factor and retention factor were considered to be 1.

It has to be noted that data on C and W for Lavanda, Eucalyptus, Mentha, Tea tree, and Ylang ylang, were obtained from the studies of Dornic and his co-works [33, 69].

Using the usage pattern data for the target population (e.g. frequency of use, number of drops, body surface area), and combing the probabilistic data on concentration of allergens and the weight of a drop of EO, it was practical to estimate the dermal exposure for each subject. For each individual, the exposure value at the 90th percentile (P90) was taken into account which was consistent with consumer exposure values used in the SCCS Notes of Guidance [71]. The process of calculation was repeated for each individual to build a distribution of exposure in the studied population. The distribution of population daily dermal exposure to an allergen was reported as summary statistics (e.g., mean, standard deviation (SD), as well as selected percentiles).

6.2.5. Simulation of exposure

During the dermal calculation in the formula, the concentration of an allergen (i.e., linalool) and the weighting of a drop were probabilistically combined with Monte Carlo simulation analysis in Crystal Ball software (Decisioneering Inc., Denver, Co., USA). Monte Carlo simulation rely on ranges of realistic possible inputs (e.g., concentration of allergens, weight of a drop) which are randomly selected to conduct enough calculations to produce a

distribution of exposure results. A triangular distribution for concentrations of fragrance ingredients in cosmetics was used for calculating of dermal exposure [25]. Thus, the probabilistic concentration data of allergens were adjusted to a triangular distribution in Crystal Ball software with the Chi-squared goodness of fit test (Decisioneering Inc., Denver, Co., USA) for calculating of dermal exposure. And the normal distribution of the weighting of a drop of EO was used. For simplicity, for each subject, randomly selecting a concentration and a weighting of a drop value from the distribution of concentration of allergen and weighting of a drop to conduct the calculation of dermal exposure. 10,000 iterations were performed according to recommendations of the US EPA [76]. Figure 7 gives a simple illustration of simulation.

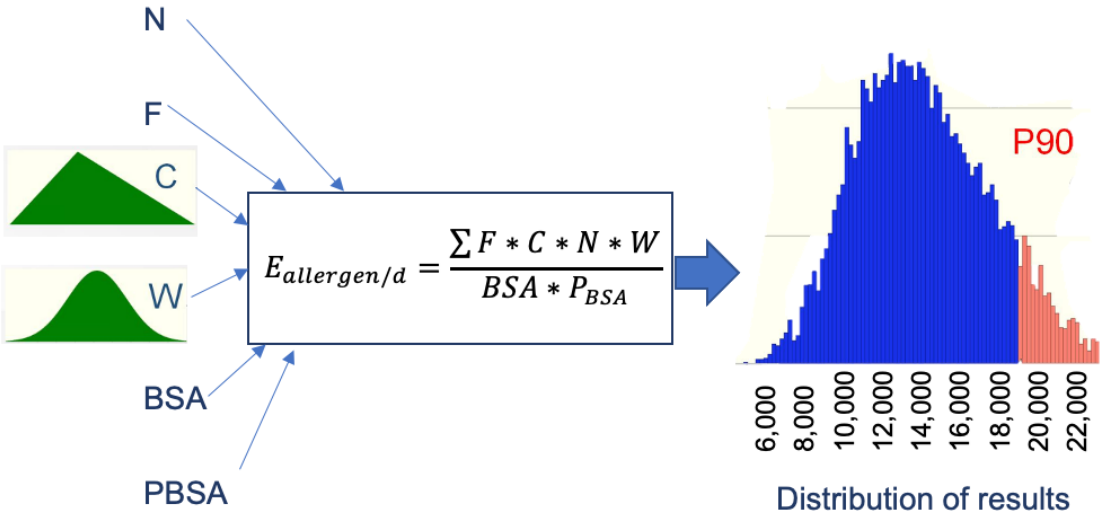
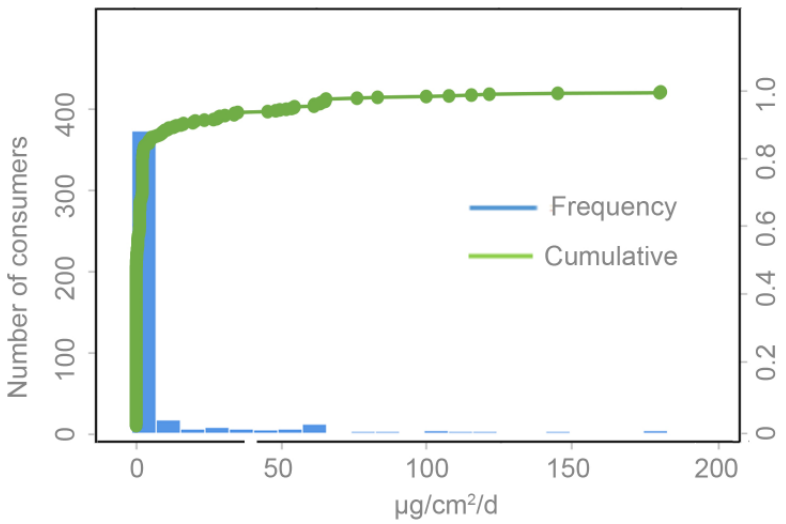


Figure 7. Simple illustration of simulation.

6.3. Results - Dermal exposure to fragrance allergens on face

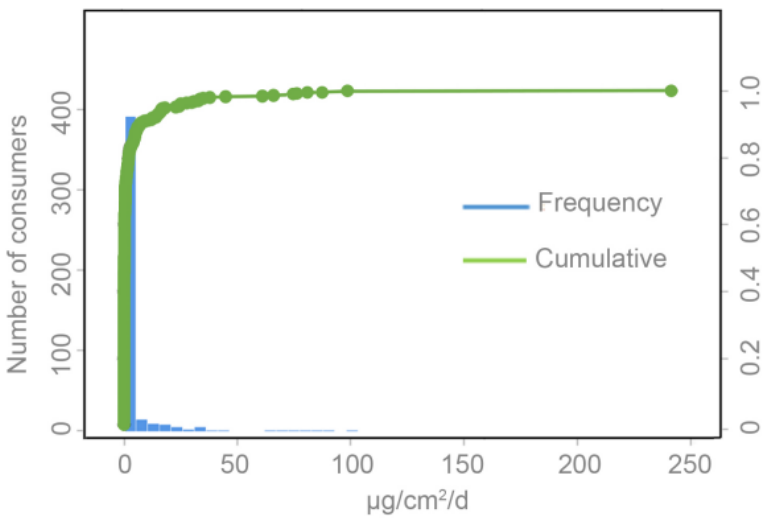
Results of dermal exposure are presented in the form of histograms relating amount of allergens used per unit surface area (in μg/cm^2/d) to the number of female consumers aged 25–59 in China. Figure 8–12 show the

population distribution (N = 429) of dermal exposure to investigated allergens from 11 types of EOs. The dermal exposure value (μg/cm^2/d) is shown across the x-axis. The height of the blue bars and the left side of y-axis represent the number of consumers who were observed to be exposed to that value of exposure. The green curve represents the cumulative distribution function (CDF) for the dermal exposure, with the percentile shown on the right side of y-axis. Summary statistics are also given in the figures, including the mean, standard deviation (SD), minimum (Min), maximum (Max) and selected percentiles (P5–P99.5).



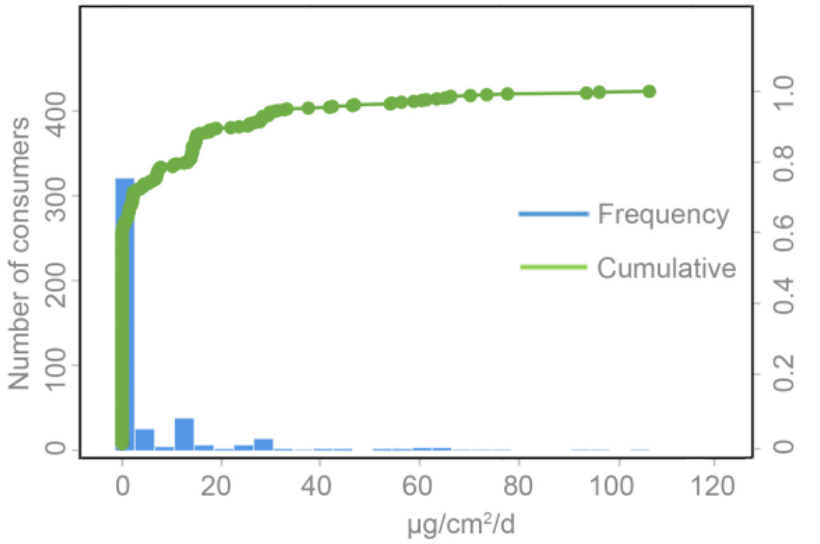
Mean	6.98
Std Dev	21.86
Minimum	0
Maximum	181.17
P5	0
P25	0
P40	0
P50	0.16
P60	1.15
P70	2.12
P80	2.19
P90	15.84
P95	54.26
P99	120.46
P99.5	176.38

Figure 8. Dermal exposure to linalool on face per unit surface area (μg/cm^2/d) in the target population (females aged 25–59, N = 429). Summary statistics are shown inset.



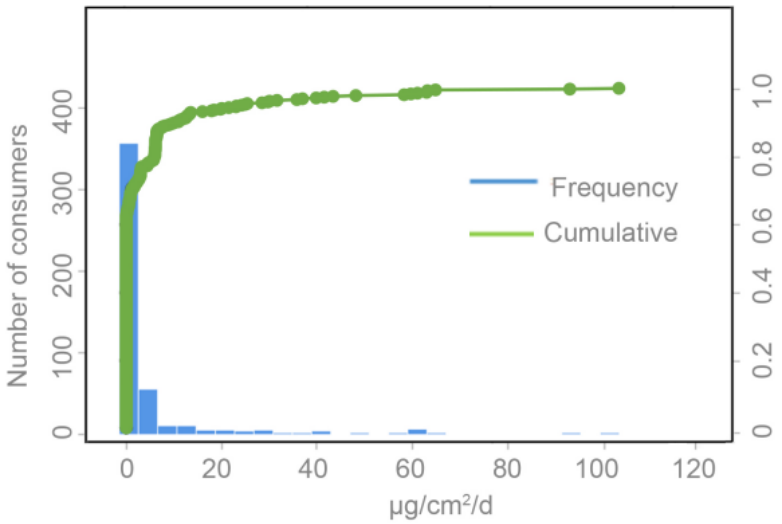
Mean	4.10
Std Dev	16.29
Minimum	0
Maximum	241.46
P5	0
P25	0
P40	0
P50	0.11
P60	0.22
P70	0.53
P80	2.04
P90	7.33
P95	23.81
P99	79.37
P99.5	96.99

Figure 9. Dermal exposure to pinenes on face per unit surface area (µg/cm^2/d) in the target population (females aged 25–59, N = 429). Summary statistics are shown inset.



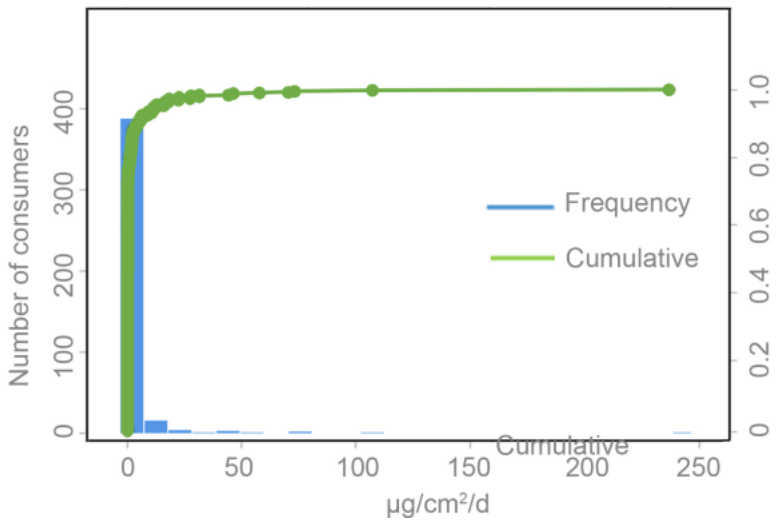
Mean	6.92
Std Dev	15.62
Minimum	0
Maximum	106.49
P5	0
P25	0
P40	0
P50	0
P60	0.071
P70	2.26
P80	13.32
P90	25.38
P95	37.86
P99	77.08
P99.5	96.18

Figure 10. Dermal exposure to citronellol on face per unit surface area (µg/cm^2/d) in the target population (females aged 25–59, N = 429). Summary statistics are shown inset.



Mean	4.33
Std Dev	12.13
Minimum	0
Maximum	103.93
P5	0
P25	0
P40	0
P50	0
P60	0
P70	1.2
P80	6.03
P90	11.00
P95	24.88
P99	63.56
P99.5	89.90

Figure 11. Dermal exposure to geraniol on face per unit surface area (µg/cm^2/d) in the target population (females aged 25–59, N = 429). Summary statistics are shown inset.



Mean	2.88
Std Dev	14.59
Minimum	0
Maximum	235.71
P5	0
P25	0
P40	0
P50	0.015
P60	0.056
P70	0.062
P80	1.02
P90	4.58
P95	12.59
P99	67.26
P99.5	102.00

Figure 12. Dermal exposure to limonene on face per unit surface area (µg/cm^2/d) in the target population (females aged 25–59, N = 429). Summary statistics are shown inset.

Linalool: The calculated mean dermal exposure to linalool was 6.98 µg/cm^2/d (assuming 100% dermal penetration and retention). Fig.1. shows that at least 40% of the population was not exposed to linalool on face daily by using these 11 types of EOs. The maximum of dermal exposure to linalool was 181.17

μg/cm^2/d, while the median exposure value was 0.16 μg/cm^2/d.

Pinenes: The calculated mean dermal exposure to pinenes was 4.10 μg/cm^2/d (assuming 100% dermal penetration and retention). Fig.2. shows that at least 40% of the population was not exposed to pinenes on face daily by using these 11 types of EOs. The maximum exposure value was 241.46 μg/cm^2/d, while the median value was 0.11 μg/cm^2/d.

Citronellol: The calculated mean dermal exposure to citronellol was 6.92 μg/cm^2/d (assuming 100% dermal penetration and retention). Fig.3. shows that at least 50% of the population was not exposed to citronellol on face daily by using these 11 types of EOs. The maximum exposure value was 106.49 μg/cm^2/d.

Geraniol: The calculated mean dermal exposure to geraniol was 4.33 μg/cm^2/d (assuming 100% dermal penetration and retention). Fig.4. shows that at least 60% of the population was not exposed to geraniol on face daily by using these 11 types of EOs. The maximum of dermal exposure to linalool was 103.93 μg/cm^2/d.

Limonene: The calculated mean dermal exposure to limonene was 2.88 μg/cm^2/d (assuming 100% dermal penetration and retention). Fig.5. shows that at least 40% of the population was not exposed to limonene on face daily by using these 11 types of EOs. The maximum of dermal exposure to limonene was 235.71 μg/cm^2/d, while the median value was 0.015 μg/cm^2/d.

6.4. Discussion

In this study, we combined the usage patterns data of 11 types of EOs on each individual which was obtained from a web-questionnaire survey, with concentration data of linalool, pinenes, citronellol, geraniol, and limonene obtained from our own study and literature [33], to estimate the dermal

exposure to such allergens to face.

The complexity of usage pattern of EO consumers was captured by the statistics, and the calculated population distribution of dermal exposure also supported this view. For example, the maximum of dermal exposure to linalool was 181.17 μg/cm^2/d, while at least 40% of the studied population was not exposed to it. However, the value 0 only means that individual may not be exposed to linalool on face through tropical use of such 11 types of EOs per day. Such population would be exposed to pinenes as an example, as well as other allergens which were not selected as investigated allergens (i.e., farnesol).

Due to varied usage patterns of aromatherapy, for example, some females uses Sandalwood oil which contains no linalool, thus, such females would not be exposed to linalool, while some females have a favorite on Rose oil which contains a large amount of linalool, thus, such females would be exposed to a higher level of linalool, the exposure to linalool would be varied large. That is also the reason why the maximum exposure value approximately 200 times the mean value in Figure 8.

6.4.1. Comparison of exposure values with SCCS general threshold

It is not clear that whether there exist thresholds for induction of skin sensitization in previous studies. However, the SCCS provides a general threshold in elicitation of 0.8 μg/cm^2 for common fragrance allergens as tolerable level for the majority of sensitized consumers [12]. According to SCCS opinion, limitation in exposure base on elicitation threshold will not only help the sensitized subjects, but also significantly reduce the risk of induction.

In order to determine how much of the studied population exposed to higher level of linalool, pinenes, citronellol, geraniol, and limonene, we compared the exposure values with the threshold value (Table 17). The

percentile values closest to the SCCS general threshold are presented in the 2nd column with their corresponding exposure value in the 3rd column (Table 17). Based on our results on daily exposure of 429 female individuals aged 25–59, more than 42%, 37%, 34%, 32%, and 21% of them were exposed to linalool, pinenes, citronellol, geraniol, and limonene, respectively, exceeding this general threshold in elicitation on a particular day.

A studied conducted to determine the aggregate dermal exposure to geraniol in personal care product and household cleaning agents revealed that 13% of the simulated population (20,000 individuals) exceeds SCCS general threshold for elicitation on a particular day (Nijkamp et al., 2015). In our study, there is at least 32% of studied population exposed to geraniol exceeding this general limit. From such comparison, higher percentage of EO consumers was exposed to geraniol exceeding general limit value.

Table 17 Comparison of dermal exposure to fragrance allergens with SCCS threshold value (0.8 μg/cm^2)

	Percentile value closest to SCCS general threshold	Exposure value (μg/cm^2/d)
Linalool	P58	1.06
Pinenes	P73	0.84
Citronellol	P63	1.11
Geraniol	P68	0.87
Limonene	P79	0.89

6.4.2. Limitations & uncertainties

A triangular concentration distribution of fragrance allergens was used in this study to perform a probabilistic exposure calculation, while in the studies of

Dornic et al. a uniform type of distribution was applied [33, 69]. Both of such two types of distributions may not precise since both of us do not know the actual concentration of allergens present in EOs. The data on concentration collected from the literature which may contain many data from laboratory-prepared EOs [41], and such data do not exactly reflect the facts of the qualitative and quantitative composition in EOs on consumer market. Besides, contributing to available data on actual use levels of fragrance ingredients in products from big fragrance houses and personal care product manufactures, distributions of concentration, such as disaggregated, triangular, uniform, as well as lognormal, have been constructed for fragrance ingredients in finished products (i.e., personal care products) [25, 77]. However, there is a lack of such data used to define a true distribution of concentration for fragrance allergens in EOs. Thus, an exhaustive study of the different EOs on the market would be necessary in order to refine the concentration distribution of fragrance allergens to provide more accurate estimates of exposure in the future.

Another uncertainty in this study is that all investigated fragrance allergens used for dermal exposure assessment were assumed in unoxidized form. Many fragrance allergens themselves are non-sensitizing, or low-sensitizing, but they are easily autoxidzied after air-exposure [78]. For example, studies show that linalool and limonene are not direct allergens, however, strong sensitizers are formed because of autoxidation when they are in contact with air [79, 80]. Air-exposed citronellol shows stronger sensitizing potency than pure citronellol [81]. Oxidation forms of geraniol are much more allergenic than their mother compound [82, 83]. It is impossible to detect the amount of oxidized allergens formed after EOs applied onto skin, however, the investigated allergens were selected because they are observed frequently in 11 types of EOs and also

better for comparison with other studies, i.e., geraniol contained in personal care and house cleaning products [77].

Additionally, in reality, only chemicals will penetrate, dependent on a number of factors including skin site, skin type, and chemical type, will induce skin sensitization [24]. And the retention factor is defined as the amount of the chemical will be remaining on the skin [24]. Since such data have not been generated, in this study, a default skin penetration and retention value of 100% was used. Thus, the results generated can be conservative. However, contributing to the probability data on the concentration of fragrance allergens, the results here could be realistic than using a deterministic value. However, incorporating of data on of consumer usage pattern and the probability data on the concentration of fragrance allergens makes the assessment of dermal exposure to fragrance allergens in EOs feasible and realistic.

6.4.3. Regulations and risk management

In connection of the results obtained in this study, and study of co-exposure to limonene on face which revealed that the contribution of EOs is much higher than that of cosmetics [69], the risks of induction and elicitation are apparent. However, to the authors' best knowledge, specific regulations for aromatherapy EOs have not been issued in the world. In China, aromatherapy EOs fall under the category of cosmetics referring to GB/T 26516-2011 [53], which gives no recommendations on how to perform aromatherapy safely at home by consumers themselves. Thus, to reduce such risks, risk management should be focused on reducing dermal exposure to fragrance allergens by the following ways, such as: reducing the dilution rates of use, avoiding to apply EOs which contain larger amount of allergens (i.e., Rose absolute) [84]. In future, specific regulations for aromatherapy EOs should be implemented to protect EO

consumers against skin sensitization. For those, who are not exposed to such 6 fragrance allergens, although they apply EOs on skin in their daily life, concerns should be paid as well since there are other naturally present allergens which are not listed in Chapter 3 and of course not considered for exposure assessment in this study. Studies should be performed onto them in the future to protect EO consumers.

6.5. Conclusion

To conclude, combining the consumer usage pattern data of 11 types of EOs and probabilistic data on concentration of fragrance allergens allowed us to assess daily dermal exposure to linalool, citronellol, geraniol, limonene, and pinenes on face. It appeared that more than 42%, 37%, 34%, 32%, and 21% of 429 female individuals aged 25–59 were exposed to linalool, pinenes, citronellol, geraniol, and limonene, respectively, exceeding this general threshold in elicitation on a particular day. Thus, recommendations should be given on which type of EOs should be relatively safe (contained lower concentration of fragrance allergens), on which frequency of use, as well as the use amount in terms of number of drops.

7. Summary

In Chapter 1 of this thesis, the background of the study reported in chapters 2 to 6 is presented and the research objectives are set out. Aromatherapy is known as the use of essential oils (EOs) to benefit the health of body, mind, and spirit. Nowadays, using of EOs are widespread among consumers, especially among females. However, EOs are composed of naturally presenting fragrance allergenic compounds, such as limonene, citral or oxidized linalool. Contact allergy due to tropical use of EOs has been reported in publications. From a quantitative perspective, dermal exposure to fragrance allergens has been demonstrated as a key risk factor in the induction of contact allergy. Therefore, this exposure should be determined to assess the risk and better protect the consumer. However, since there is no comprehensive habits data, nor anthropometric and fragrance allergens data available, an effective estimate of dermal exposure cannot be successfully conducted. Thus, in this thesis, information on frequency of use (Chapters 2), skin sites of application (Chapters 2), consumer-exposed inclusion level of fragrance allergens (Chapters 3), amount of use per application for each type of EO (Chapter 4), body surface area (chapter 5), surface area of exposed body sites (Chapter 5) were investigated. Finally, utilizing such information, dermal exposure to a certain fragrance allergen (linalool) on face was assessed (Chapter 6).

In Chapter 2 of this thesis, a web survey was conducted on 1,518 potential Chinese EO consumers to assess consumer usage patterns including types of EOs, use frequency for each type of EO, exposed body sites, and dilution rates of use for each type of EO. The usage patterns of 11 types of EOs were collected among female consumers (N = 457; ages 0–70). For females aged 0–14, they used Lavanda (42.9%) and Tea tree (57.1%) oils only. Among the

senior age groups (15–70), Lavanda oil was the most used EO with 46.7%, 51%, 68.1%, and 50% for females aged 15–24, 25–39, 40–59 and 60–70, respectively. The mean frequency of use (per day) for Rose, Lavanda, Tea tree, Mentha, Lemon, Sandalwood, Frankincense, Ylang ylang, Eucalyptus and Jasmine oil was 1.06, 0.68, 0.73, 0.38, 0.32, 0.68, 0.62, 0.36 0.57 and 0.45, respectively. Consumers aged 25–59 applied EOs on almost all listed parts of body. The dilution rates of use differed within the types of EOs. Generally, the majority of females aged 25–59 used Rose, Lavanda, Sandalwood, Frankincense and Jasmine oil on their whole face more than three times a week at diverse dilution rates. It was concluded that the information on use frequency for each type of EO and the recorded application sites for each type of EO, making it possible to more accurately calculate dermal exposure as dose per unit area of skin. In addition, information on the types of EOs could be used for further safety studies (e.g., which types of EO should be under investigation for determining the concentration of fragrance allergens), and data on dilution rates of use could be used for calculation of use amount per application.

In chapter 3 of this thesis, data on the presence and inclusion level of fragrance allergens in 6 types of EOs were collected based on ingredient list mainly from literature database. To investigate the consumer-exposed inclusion level of fragrance allergens, the market share data from a supplier survey was incorporated. Based on 420 assays which were collected from 100 literatures and 13 analysis of ingredient lists obtained from suppliers, 13 allergenic substances were found in these 6 types of EOs. Among them, linalool was observed most frequently (89% of all assays), which was also the most common fragrance chemical in personal care products (PCPs). The highest consumer-exposed inclusion level of allergens (mean value) in Rose, Ginger, Lemon,

Sandalwood, Frankincense, and Jasmine oil were citronellol (13.6%), citral (14.7%), limonene (67.0%), farnesol (16.1%), pinenes (18.0%) and linalool (15.0%), respectively. Attention should be paid to EO consumers not only because of their co-exposure to fragrance allergens but also high inclusion level of allergens they may expose to. The data on consumer-exposed kind of and inclusion level of allergens in EOs can be used for estimation of dermal exposure to fragrance allergens in EOs.

In chapter 4 of this thesis, the number of drops per application and the weighting of each drop for each type of EO exposure were investigated. The number of drops per application was calculated using the data on dilution rates of use which was descried in chapter 2. A small weighting experiment was conducted to determine the weighting of each drop for 6 types of EO. With a conservative assumption of use amount of bases as 4.0 mL, the mean number of drops for Rose, Ginger, Mentha, Sandalwood, Frankincense, Ylang ylang, Eucalyptus, and Jasmine oil were 1.62, 2.15, 1.70, 1.80,1.74, 1.75, 2.45 and 1.37, respectively. And the weighting of each drop with its mean and standard deviation values for these 6 types of EO were Rose (32.934, 7.913), Ginger (28.910, 3.545), Lemon (23.447, 0.732), Sandalwood (35.199, 2.043), Frankincense (26.291, 3.771), and Jasmine (29.363, 1.332). A conservative assumption of 4 mL amount of bases for every exposed body site was used. Obviously, it will influence the exposure results and, in most cases, lead to overestimation. Nevertheless, since such conservation assumption was used, the number of drops was calculated and could be used in the dermal exposure assessment. Moreover, considering the variability in the weight of each drop between different products, the mean values and corresponding standard deviations of the weighting of each drop per each type of EO were given for

more accurate exposure estimation.

In chapter 5 of this thesis, the body surface area (BSA) for each individual which was calculated from data on the body weight and height which were collected from the usage-pattern web survey. And data on exposed body surface area were directly sought from published data. For example, the entire face of a female individual, represents 3.10% of her total body surface area [74]. The Chinese EO female consumers weighed on average 56.23 kg, with an average 161.77 cm, and average BSA of 1.61 m^2. Incorporating the values of relative percentage of body surface area (P_{BSA}) from published data, this chapter provided the calculated BSA (combining the consumer data on body weight and height from usage-pattern survey) as useful anthropometric data to estimate of dermal exposure (μg/cm^2) on different body sites.

In chapter 6 of this thesis, dermal exposure to linalool, pinenes, citronellol, geraniol, and limonene on face were calculated and assessed on 429 female users aged 25–59. The mean dermal exposure to linalool, pinenes, citronellol, geraniol, and limonene were 6.98, 4.10, 6.92, 4.33, and 2.88 μg/cm^2/d, respectively. Based on our results more than 42%, 37%, 34%, 32%, and 21% of them were exposed to linalool, pinenes, citronellol, geraniol, and limonene, respectively, exceeding the SCCS general threshold in elicitation on a particular day. These original data will be useful for safety assessors and safety agencies in order to protect EO consumers. The lack of regulations on aromatherapy EOs remains problematic, and could represent a loophole for the protection of the consumers against contact allergy.

Summary statistics on use frequency for each type of EO, exposed body area, consumer-exposed inclusion-level of fragrance allergens, use amount per application for each type of EO, body surface area and surface area of exposed

site are provided for 457 female consumers aged 0–70. Altogether, it is concluded that this work provide important information for dermal exposure assessment to fragrance allergens in EOs.

However, whether such information can be used as exposure data by other studies, it is important to evaluate the quantity and relevance of available information. In particular, the population groups to which the data refer (representative or non-representative), and the overall amount and quality of the data should be considered [85]. Besides, just like estimating exposure to fragrance ingredients in personal care and cosmetic products, whether these data can be used as input variables for a probabilistic exposure assessment, the combination of consumer habits and ingredients data with probabilistic analysis is necessary in the future [86, 87, 88]. It is believed that efforts to provide information resources on consumer habits will make aromatherapy EOs possible to be assessed in the methodological scheme of Quantitative Risk Assessment (QRA) as a basis for setting concentration limits for fragrance allergens [89].

Additionally, despite these information, there remain a number of data gaps:

1. The sample sizes of children (0–14), adolescents (15–24), and elderly (60–70) are relatively small. Thus, data on such as frequency of use for each type of EO could not be break down to age groups. And dermal exposure cannot be assessed for such three age groups.
2. The conservative assumption of 4.0 mL amount of bases for each body site.
3. The retention factors and penetration factors of EO applied on skin.
4. Oxidized forms of fragrance allergens (e.g., linalool, limonene) and other allergens which also present in 11 types of EOs should be investigated as

well.

Therefore, future work should be conducted to fill these data gaps in order to provide more information for exposure assessment to fragrance allergens in EOs, and also considering of the distribution of dermal exposure to such allergens on face, specific regulations for aromatherapy EOs should be established in the future.

8. Glossary and abbreviations

In this thesis the definitions and abbreviations were applied for convenient use.

8.1. Glossary

Fragrance allergens: a fragrance chemical which possesses the intrinsic toxicological property (e.g., hazard) that with sufficient skin exposure in humans it can cause the induction of skin sensitization/contact allergy [22].

Contact allergy: the asymptomatic condition which an individual has when they are sensitized to a specific chemical, and which can be detected by a diagnostic patch test [22].

Diagnostic patch test: a clinic procedure designed to reveal whether an individual has contact allergy and who is then susceptible to the development of allergic contact dermatitis upon subsequent exposure to the allergen [22].

Frequency/prevalence: these and related terms endeavor to follow their standard usage in epidemiology [22].

Retention factor: how much a product remains on the skin after application [24].

Penetration factor: how much a substance through the skin barrier and into the skin [90].

8.2. Abbreviations

AEAJ: Aroma Environment Association of Japan

BSA: Body Surface Area

EU: European Union

EO: Essential Oil

GC-MS: Gas Chromatography-Mass Spectrometry

IFA: International Federation of Aromatherapy

INCI: International Nomenclature of Cosmetic Ingredients

IUCN: International Union for Conservation

OECD: Organization for Economic Co-operation and Development

PCPs: Personal Care Products

SCCS: Scientific Committee Consumer Safety

USEPA: United States Environmental Protection Agency

WHO: World Health Organization

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10. Supplementary information

10.1. S1: Questionnaire

Usage patterns of aromatherapy among the Chinese population who are using essential oils

A large survey questionnaire focusing on determining the conditions of essential oils (EOs) used by the Chinese population who are using EOs

* Questions are mandatory and must be completed before submitting.

Section 1 General data (7 questions)

1. What is your gender? *

○Male

○Female

○Prefer not to say

2. What is your age? *

○0-14

○15-24

○25-39

○40-59

○60-70

3. Are you pregnant? *

○Yes

○No

○Maybe

4. What is your occupation? *

○Student

○Self-employed

○Salaried

○Certified aromatherapist

○Housewife

○Retired

○Others

5. What is your body weight? *

○<45 kg

○45-49 kg

○50-54 kg

○55-59 kg

○60-64 kg

○65-69 kg

○≥70 kg

6. What is your body height? *

○<155 cm

○155-159 cm

○160-164 cm

○165-169 cm

○170-174 cm

○175-179 cm

○≥180 cm

7. Which city are you living in now? *

_____

Section 2 EOs' consumption (4 questions)

8. Do you use EOs? *

○Yes

○No (Please skip to the end of the questionnaire and submit your answer)

9. For which type of use? (Multiple selection) *

□Inhalation

□Ingestion

□Dermal

□Others

10. Where do you buy your oils? (Multiple selection) *

□Plantation

□Specialized store

□Web store

□Supermarket

□Aromatherapy organization & salon

□Distributors & Suppliers of raw materials for personal care products

□Others (gifts from friends, etc)

11. Who advised you to use EOs? *

○Friends

○Family

○At the point of sale

○Media (TV, Web, Personal media (Weibo, WeChat), etc))

○Aromatherapist

○Beautician

○Others (magazines, books, etc)

Section 3 dermal use (6 questions)

12. Do you use Rose oil? *

○Yes

○No

13. Where do you apply oils on your body? (Multiple selection) *

□Forehead

□Philtrum

□Temples

□Face

□Neck

□Wrists

□Arms

□Breast/chest

□Back

□Shoulders

□Stomach

□Thighs

□Calves/shins

□Feet

□Whole body

14. How often do you use it? *

○Daily _____

Please write the number of frequencies.

○Weekly _____

Please write the number of frequencies.

○Monthly _____

Please write the number of frequencies.

○Yearly _____

Please write the number of frequencies.

15. How much do you use oil per application? *

○Less than 1% (less than 1 drop in 5 mL base oil)

○1% (1 drop in 5 mL base oil)

○2% (2 drops in 5 mL base oil)

○3% (3 drops in 5 mL base oil)

○4% (4 drops in 5 mL base oil)

○5% (5 drops in 5 mL base oil)

○More than 5% (more than 5 drops in 5 mL base oil)

○Add in cosmetic products _____

Please write the number of drops.

○Undiluted _____

Please write the number of drops.

16. Do you use Lavender oil? *

○Yes

○No

17. Where do you apply oils on your body? (Multiple selection) *

□Forehead

□Philtrum

□Temples

□Face

□Neck

□Wrists

□Arms

□Breast/chest

□Back

□Shoulders

□Stomach

□Thighs

□Calves/shins

□Feet

□Whole body

18. How often do you use it? *

○Daily _____

Please write the number of frequencies.

○Weekly _____

Please write the number of frequencies.

○Monthly _____

Please write the number of frequencies.

○Yearly _____

Please write the number of frequencies.

19. How much do you use oil per application? *

○Less than 1% (less than 1 drop in 5 mL base oil)

○1% (1 drop in 5 mL base oil)

○2% (2 drops in 5 mL base oil)

○3% (3 drops in 5 mL base oil)

○4% (4 drops in 5 mL base oil)

○5% (5 drops in 5 mL base oil)

○More than 5% (more than 5 drops in 5 mL base oil)

○Add in cosmetic products _____

Please write the number of drops.

○Undiluted _____

Please write the number of drops.

20. Do you use Tea Tree oil? *

○Yes

○No

21. Where do you apply oils on your body? (Multiple selection) *

□Forehead

□Philtrum

□Temples

□Face

□Neck

□Wrists

□Arms

□Breast/chest

□Back

□Shoulders

□Stomach

□Thighs

□Calves/shins

□Feet

□Whole body

22. How often do you use it? *

○Daily _____

Please write the number of frequencies.

○Weekly _____

Please write the number of frequencies.

○Monthly _____

Please write the number of frequencies.

○Yearly _____

Please write the number of frequencies.

23. How much do you use oil per application? *

○Less than 1% (less than 1 drop in 5 mL base oil)

○1% (1 drop in 5 mL base oil)

○2% (2 drops in 5 mL base oil)

○3% (3 drops in 5 mL base oil)

○4% (4 drops in 5 mL base oil)

○5% (5 drops in 5 mL base oil)

○More than 5% (more than 5 drops in 5 mL base oil)

○Add in cosmetic products _____

Please write the number of drops.

○Undiluted _____

Please write the number of drops.

24. Do you use Ginger oil? *

○Yes

○No

25. Where do you apply oils on your body? *

□Forehead

□Philtrum

□Temples

□Face

□Neck

□Wrists

□Arms

□Breast/chest

□Back

□Shoulders

□Stomach

□Thighs

□Calves/shins

□Feet

□Whole body

26. How often do you use it? *

○Daily _____

Please write the number of frequencies.

○Weekly _____

Please write the number of frequencies.

○Monthly _____

Please write the number of frequencies.

○Yearly _____

Please write the number of frequencies.

27. How much do you use oil per application? *

○Less than 1% (less than 1 drop in 5 mL base oil)

○1% (1 drop in 5 mL base oil)

○2% (2 drops in 5 mL base oil)

○3% (3 drops in 5 mL base oil)

○4% (4 drops in 5 mL base oil)

○5% (5 drops in 5 mL base oil)

○More than 5% (more than 5 drops in 5 mL base oil)

○Add in cosmetic products _____

Please write the number of drops.

○Undiluted _____

Please write the number of drops.

28. Do you use Mint oil? *

○Yes

○No

29. Where do you apply oils on your body? (Multiple selection) *

□Forehead

□Philtrum

□Temples

□Face

□Neck

□Wrists

□Arms

□Breast/chest

□Back

□Shoulders

□Stomach

□Thighs

□Calves/shins

□Feet

□Whole body

30. How often do you use it? *

○Daily _____

Please write the number of frequencies.

○Weekly _____

Please write the number of frequencies.

○Monthly _____

Please write the number of frequencies.

○Yearly _____

Please write the number of frequencies.

31. How much do you use oil per application? *

○Less than 1% (less than 1 drop in 5 mL base oil)

○1% (1 drop in 5 mL base oil)

○2% (2 drops in 5 mL base oil)

○3% (3 drops in 5 mL base oil)

○4% (4 drops in 5 mL base oil)

○5% (5 drops in 5 mL base oil)

○More than 5% (more than 5 drops in 5 mL base oil)

○Add in cosmetic products _____

Please write the number of drops.

○Undiluted _____

Please write the number of drops.

32. Do you use Lemon oil? *

○Yes

○No

33. Where do you apply oils on your body? (Multiple selection) *

□Forehead

□Philtrum

□Temples

□Face

□Neck

□Wrists

□Arms

□Breast/chest

□Back

□Shoulders

□Stomach

□Thighs

□Calves/shins

□Feet

□Whole body

34. How often do you use it? *

○Daily _____

Please write the number of frequencies.

○Weekly _____

Please write the number of frequencies.

○Monthly _____

Please write the number of frequencies.

○Yearly _____

Please write the number of frequencies.

35. How much do you use oil per application? *

○Less than 1% (less than 1 drop in 5 mL base oil)

○1% (1 drop in 5 mL base oil)

○2% (2 drops in 5 mL base oil)

○3% (3 drops in 5 mL base oil)

○4% (4 drops in 5 mL base oil)

○5% (5 drops in 5 mL base oil)

○More than 5% (more than 5 drops in 5 mL base oil)

○Add in cosmetic products _____

Please write the number of drops.

○Undiluted _____

Please write the number of drops.

36. Do you use Sandalwood oil? *

○Yes

○No

37. Where do you apply oils on your body? (Multiple selection) *

□Forehead

□Philtrum

□Temples

□Face

□Neck

□Wrists

□Arms

□Breast/chest

□Back

□Shoulders

□Stomach

□Thighs

□Calves/shins

□Feet

□Whole body

38. How often do you use it? *

○Daily _____

Please write the number of frequencies.

○Weekly _____

Please write the number of frequencies.

○Monthly _____

Please write the number of frequencies.

○Yearly _____

Please write the number of frequencies.

39. How much do you use oil per application? *

○Less than 1% (less than 1 drop in 5 mL base oil)

○1% (1 drop in 5 mL base oil)

○2% (2 drops in 5 mL base oil)

○3% (3 drops in 5 mL base oil)

○4% (4 drops in 5 mL base oil)

○5% (5 drops in 5 mL base oil)

○More than 5% (more than 5 drops in 5 mL base oil)

○Add in cosmetic products _____

Please write the number of drops.

○Undiluted _____

Please write the number of drops.

40. Do you use Frankincense oil? *

○Yes

○No

41. Where do you apply oils on your body? (Multiple selection) *

□Forehead

□Philtrum

□Temples

□Face

□Neck

□Wrists

□Arms

□Breast/chest

□Back

□Shoulders

□Stomach

□Thighs

□Calves/shins

□Feet

□Whole body

42. How often do you use it? *

○Daily _____

Please write the number of frequencies.

○Weekly _____

Please write the number of frequencies.

○Monthly _____

Please write the number of frequencies.

○Yearly _____

Please write the number of frequencies.

43. How much do you use oil per application? *

○Less than 1% (less than 1 drop in 5 mL base oil)

○1% (1 drop in 5 mL base oil)

○2% (2 drops in 5 mL base oil)

○3% (3 drops in 5 mL base oil)

○4% (4 drops in 5 mL base oil)

○5% (5 drops in 5 mL base oil)

○More than 5% (more than 5 drops in 5 mL base oil)

○Add in cosmetic products _____

Please write the number of drops.

○Undiluted _____

Please write the number of drops.

44. Do you use Ylang ylang oil? *

○Yes

○No

45. Where do you apply oils on your body? (Multiple selection) *

□Forehead

□Philtrum

□Temples

□Face

□Neck

□Wrists

□Arms

□Breast/chest

□Back

□Shoulders

□Stomach

□Thighs

□Calves/shins

□Feet

□Whole body

46. How often do you use it? *

○Daily _____

Please write the number of frequencies.

○Weekly _____

Please write the number of frequencies.

○Monthly _____

Please write the number of frequencies.

○Yearly _____

Please write the number of frequencies.

47. How much do you use oil per application? *

○Less than 1% (less than 1 drop in 5 mL base oil)

○1% (1 drop in 5 mL base oil)

○2% (2 drops in 5 mL base oil)

○3% (3 drops in 5 mL base oil)

○4% (4 drops in 5 mL base oil)

○5% (5 drops in 5 mL base oil)

○More than 5% (more than 5 drops in 5 mL base oil)

○Add in cosmetic products _____

Please write the number of drops.

○Undiluted _____

Please write the number of drops.

48. Do you use Eucalyptus oil? *

○Yes

○No

49. Where do you apply oils on your body? (Multiple selection) *

□Forehead

□Philtrum

□Temples

□Face

□Neck

□Wrists

□Arms

□Breast/chest

□Back

□Shoulders

□Stomach

□Thighs

□Calves/shins

□Feet

□Whole body

50. How often do you use it? *

○Daily _____

Please write the number of frequencies.

○Weekly _____

Please write the number of frequencies.

○Monthly _____

Please write the number of frequencies.

○Yearly _____

Please write the number of frequencies.

51. How much do you use oil per application? *

○Less than 1% (less than 1 drop in 5 mL base oil)

○1% (1 drop in 5 mL base oil)

○2% (2 drops in 5 mL base oil)

○3% (3 drops in 5 mL base oil)

○4% (4 drops in 5 mL base oil)

○5% (5 drops in 5 mL base oil)

○More than 5% (more than 5 drops in 5 mL base oil)

○Add in cosmetic products _____

Please write the number of drops.

○Undiluted _____

Please write the number of drops.

52. Do you use Jasmine oil? *

○Yes

○No

53. Where do you apply oils on your body? (Multiple selection) *

□Forehead

□Philtrum

□Temples

□Face

□Neck

□Wrists

□Arms

□Breast/chest

□Back

□Shoulders

□Stomach

□Thighs

□Calves/shins

□Feet

□Whole body

54. How often do you use it? *

○Daily _____

Please write the number of frequencies.

○Weekly _____

Please write the number of frequencies.

○Monthly _____

Please write the number of frequencies.

○Yearly _____

Please write the number of frequencies.

55. How much do you use oil per application? *

○Less than 1% (less than 1 drop in 5 mL base oil)

○1% (1 drop in 5 mL base oil)

○2% (2 drops in 5 mL base oil)

○3% (3 drops in 5 mL base oil)

○4% (4 drops in 5 mL base oil)

○5% (5 drops in 5 mL base oil)

○More than 5% (more than 5 drops in 5 mL base oil)

○Add in cosmetic products _____

Please write the number of drops.

○Undiluted _____

Please write the number of drops.

56. Do you use other types of EO absent from above list?

Please write other types of EO absent from our list.

10.2. Figure S1: Geographical Units

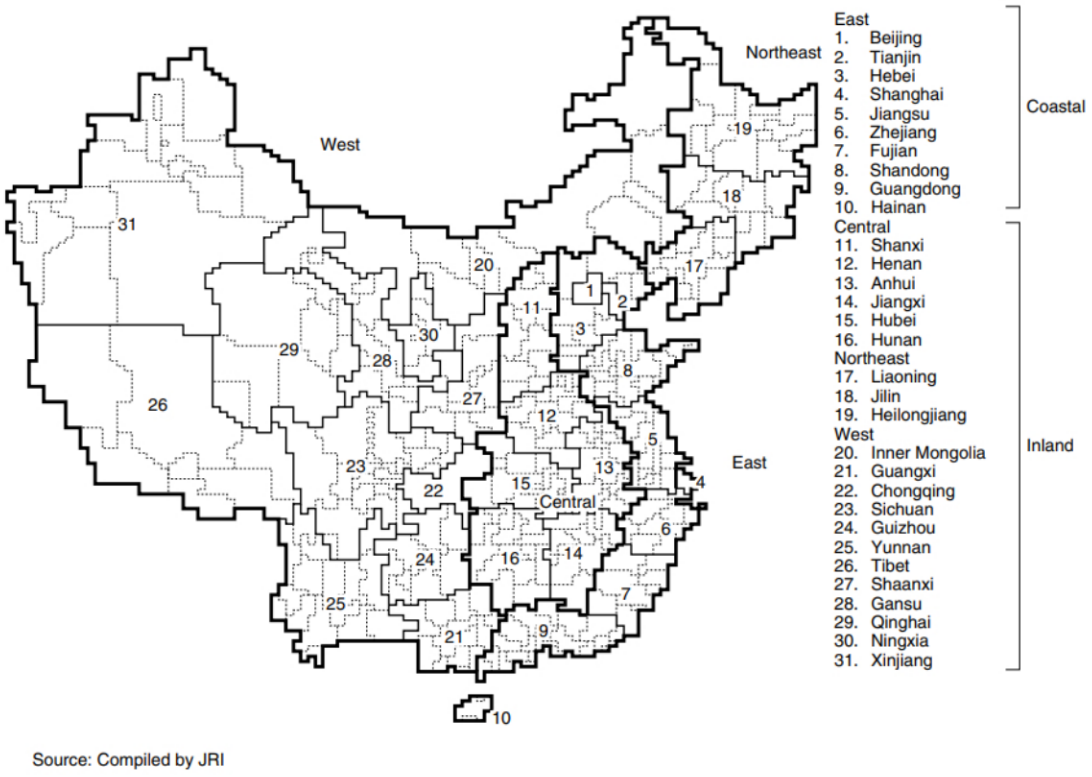

Figure S1. Geographical Units for Prefecture-level Cities

10.3. Figure S2: Use frequency of Ginger oil

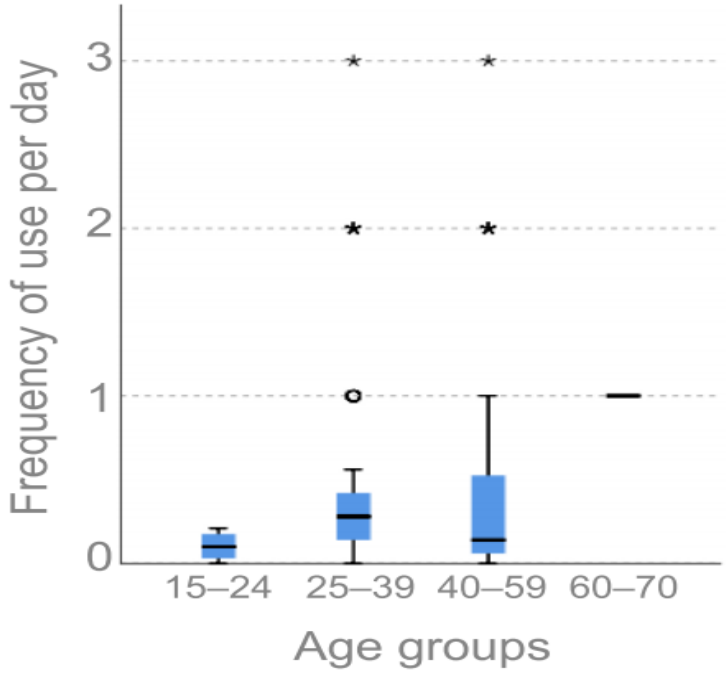

Figure S2. Result expressed in day-1: difference on use frequency of females using Ginger oil was determined for 4 age groups with a Kruskall-Wallis test. Notably, females aged 0-

14 do not use Ginger oil.

10.4. Table S1: Demographics of the total consumers

Table S1 Demographical characteristics of the total consumers.

Number of consumers related to the total consumers/Percentage	*Total*	*Male*	*Female*
	N = 534 (100%)	N = 53 (9.90%)	N = 481 (90.10%)
0–14	N = 18 (3.37%)	N = 8 (15.09%)	N = 10 (2.08%)
15–24	N = 27 (5.06%)	N = 5 (9.43%)	N = 22 (4.57%)
25–39	N = 321 (60.11%)	N = 16 (30.19%)	N = 305 (63.41%)
40–59	N = 159 (29.78%)	N = 21 (39.62%)	N = 138 (28.69%)
60–70	N = 9 (1.69%)	N = 3 (5.66%)	N = 6 (1.25%)
Pregnancy	N = 20 (3.74%)		N = 20 (4.16%)
None pregnancy	N = 514 (96.26%)	N = 53 (100%)	N = 461 (95.84%)
Student	N = 43 (8.05%)	N = 13 (24.52%)	N = 30 (6.24%)
Self-employed	N = 68 (12.73%)	N = 13 (24.52%)	N = 55 (11.43%)
Salaried	N = 166 (31.08%)	N = 18 (33.96%)	N = 168 (30.77%)
Aromatherapist	N = 69 (12.92%)	N = 1 (1.89%)	N = 68 (14.14%)
Housewife	N = 93 (17.40%)		N = 93 (19.33%)
Retired	N = 16 (3.00%)	N = 3 (5.66%)	N = 13 (2.70%)
Others (civil servant, etc)	N = 79 (14.79%)	N = 5 (9.43%)	N = 74 (15.38%)
East	N = 459 (85.96%)	N = 36 (67.92%)	N = 423 (87.94%)
Central	N = 49 (9.18%)	N = 10 (18.87%)	N = 39 (8.11%)
Northeast	N = 5 (0.94%)	N = 1 (1.89%)	N = 4 (0.83%)
West	N = 21 (3.93%)	N = 6 (11.32%)	N = 15 (3.12%)

10.5. Table S2: EOs' consumption

Table S2 EO's consumption

Sales outlets	*Number of buyers*
Aromatherapy organization & beauty salon	N = 411 (76.97%)
Specialized store	N = 79 (14.79%)
Web store	N = 77 (14.42%)
Distributors & suppliers of raw materials for personal care products	N = 40 (14.42%)
Plantation	N = 40 (7.49%)
Others (gifts from friends, etc)	N = 34 (6.37%)
Supermarket	N = 9 (1.69%)

Data in table represents the place of purchase (multiple responses are provided). N is the number of respondents.

10.6. S2: Data on ingredients collected from literature (reference list)

1)Rose oil

1. Rosa-da-di

Rosa-da-di-1: Abbas G-C, Ali MN, Fatemeh S, Mahdi G-V, E LV. Classification of essential oil composition in *Rosa damascene* Mill. Genotypes using an electronic nose. Journal of Applied Research on Medicinal and Aromatic Plants 2017;4:27-34.

Rosa-da-di-2: Rakesh K, Saurabh S, Swati S, Vijai KA, Bikram S. Effect of diurnal variability and storage conditions on essential oil content and quality of damask rose (*Rosa damascene* Mill.) flowers in north western Himalayas. Scientia Horticulturae 2013;154:102-108.

Rosa-da-di-3: Hasan B, Nilgun GB. The effects of harvest date, fermentation duration and Tween 20 treatment on essential oil content and composition of industrial oil rose (*Rosa damascene* Mill.). Industrial Crops and Products 2005;21:251-255.

Rosa-da-di-4: Tayebeh S, Maryam M, Ali M. The effects of onion and salt treatments on essential oil content and composition of *Rosa damascene* Mill. Industrial Crops and Products 2012;37:451-456.

Rosa-da-di-5: Dobreva A, Velcheva A, Bardarov V, Bardarov K. Chemical composition of different genotypes oil-bearing roses. Bulgarian Journal of Agriculture Science 2013;19(6):1213-1218.

Rosa-da-di-6: Ram SV, Rajendra CP, Amit C. Chemical investigation of the volatile components of shade-dried petals of Damask rose (*Rosa Damascena* Mill.). Arch. Biol. Sci. 2011;63(4):1111-1115.

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Rosa-da-di-10: Mileva M, Krumova E, Miteva-Staleva J, Kostadinova N, Dobreva A, Galabov AS. Chemical compounds in vitro antioxidant and antifungal activities of some plant essential oils belonging to Rosaceae

family. Biologie microbilogie 2014;67(10):1363-1368.

Rosa-da-di-11: Kiran GDB, Bikram S, Virendra PJ, Virendra S. Essential oil composition of Damask rose (*Rosa damascene* Mill.) distilled under different pressures and temperature. Flavour Fragr. J. 2002;17:136-140.

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Rosa-da-di-13: Wafaa N, Marc EB, Lara HW, Claire NNO. Essential oil composition of *Rosa damascene* Mill. From different localities in Lebanon. Acta Botanica Gallica 2011;158(3):365-373.

Rosa-da-di-14: Mohamadi M, Mostafavi A, Shamspur T. Effects of storage on essential oil content and composition of *Rosa damascene* Mill. Petals under different conditions. Journal of essential oil -bearing plants 2011;14(4):430-441.

Rosa-da-di-15: Mahmoodreza M, Forough K, Hossein T, Younes G. Composition of the essential oils of *Rosa damascene* Mill. From south of Iran. Iranian Journal of Pharmaceutical Sciences 2010;6(1):59-62.

Rosa-da-di-16: Naquvi KJ, Ansari SH, Ali M, Najmi AK. Volatile oil composition of Rosa damascene Mill. (Rosaceae). Journal of pharmacognosy and phytochemistry 2014;2(5):130-134.

Rosa-da-di-17: Teodora A, Miroslava K, Lyubomir S, Maya P, Albena S, Stanka D, Mykola D. Chemical composition of essential oil from *Rosa Damascena* mill., growing in new region of Bulgaria. Food technologies 2016;5(3):492-498.

Rosa-da-di-18: Loghmani-Khouzani H, Sabzi Fini O, Safari J. Essential oil composition of *Rosa damascene* Mill cultivated in central Iran. Scientia Iranica 2007;14(4):316-319.

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Rosa-da-ab-2: Kurkcuoglu M, Baser KHC. Studies on Turkish rose concrete, absolute, and hydrosol. Chemistry of natural compounds, 2003;39(5):457-464.

Rosa-da-ab-3: Amjad F, Adnan Y, Muhammad Q, Atif R, Syed MA, Usman T. Gas chromatography analysis of the absolute rose oil from Rosa damascene landraces and scented rose species from Pakistan. International journal of agriculture & biology 2012;14:713-719.

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Rosa-gallica-di-2: Mileva M, Krumova E, Miteva-Staleva J, Kostadinova N, Dobreva A, Galabov AS. Chemical compounds in vitro antioxidant and antifungal activities of some plant essential oils belonging to Rosaceae family. Biologie microbilogie 2014;67(10):1363-1368.

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6. Rosa-kushui

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Rosa-kushui-2: Liu Y, Wang X, Fei et al. Kushui Rose (*R. setate x R. rugosa*) decoction exerts antitumor effects in *C. elegans* by downregulating Ras/MAPK pathway and resisting oxidative stress. International journal of molecular medicine 2018;42:1411-1417.

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Ginger-6: Sharma PK, Singh V, Ali M. Chemical composition and antimicrobial activity of Fresh Rhizome essential oil of *Zingiber officinale* Roscoe. Pharmacogn. J. 2016;8(3):185-190.

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*f*rom North Western Himalayas. Natural Product Communications 2011;6(1):93-96.

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Sandalwood-album-4: Subasinghe U, Gamage M, Hettiarachchi DS. Essential oil content and composition of Indian sandalwood (*Santalum album*) in Sri Lanka. Journal of Forestry Research 2013;24(1):127−130.
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Frankincense-b.car-5: Camarda L, Dayton T, Di Stefano T, Pitonzo R, Schillaci D. CHEMICAL COMPOSITION AND ANTIMICROBIAL ACTIVITY OF SOME OLEOGUM RESIN ESSENTIAL OILS FROM *BOSWELLIA* SPP. (BURSERACEAE). Annali di Chimica 2007;97:837-844.

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10.7. S3: Summary of consumer-exposed inclusion level of fragrance allergens in studied EOs.

		Pinenes	Benzyl alcohol	Benzyl benzoate	Benzyl salicylate	Cinnamyl alcohol	Citral	Citronellol	Eugenol	Farnesol	Isoeugenol	Geraniol	Limonene	Linalool
Rose	Min	0.07	0.04	0	0		0.1	2.68	0.36	0.18		0.99	0	0.13
%	Mean	0.4	0.33	0	0		0.61	13.58	1.02	1.08		5.84	0.03	1
	Median	0.37	0.43	0	0		0.58	13.4	1	1.05		5.71	0.03	0.95
	Max	0.97	0.92	0	0		1.27	26.83	1.99	2.41		11.57	0.06	2.29
Ginger	Min	0.1					4.02	0.43		0.2		0.05	0.5	0.05
%	Median	2.7					14.7	1.71		0.6		4.25	1.44	1.4
	Max	26.13					30.8	2.49		1		15	5.08	4.8
Lemon	Min	1.12					0	0.01				0.01	51.95	0.07
%	Median	12.84					0	0.01				0.05	67	0.11
	Max	31.49					0.27	0.15				0.05	84.84	0.76
Sandalwood	Min	0								1.73				
%	Mean	0.05								16.18				
	Median	0								15.47				
	Max	0.02								33.78				
Jasmine	Min		0.34	0.55	0.1	0.03		10.74	0.33	0.07	0	0.09	0	1.94
%	Mean		5.4	4.88	0.16	0.05		11.19	4.65	2.06	0.01	1.33	0.01	14.95
	Median		4.96	4.79	0.16	0.05		11.2	4.7	1.85	0.01	4.01	0	14.23
	Max		14.21	9.88	0.25	0.06		11.61	8.86	5.31	0.04	5.5	0.02	31.46
Frankincense	Min	3.51		0.22				0					2.29	0.48

%	Mean	17.98	0.8	0	12.46	0.9
	Median	17.85			12.16	0.87
	Max	33.07	12	0.2	25.11	1.49

Summary of consumer-exposed inclusion level of fragrance allergens in Rose, Ginger, Lemon, Sandalwood, Jasmine, and Frankincense.

10.8. Figure S3: The number of drops per application for Lavanda oil

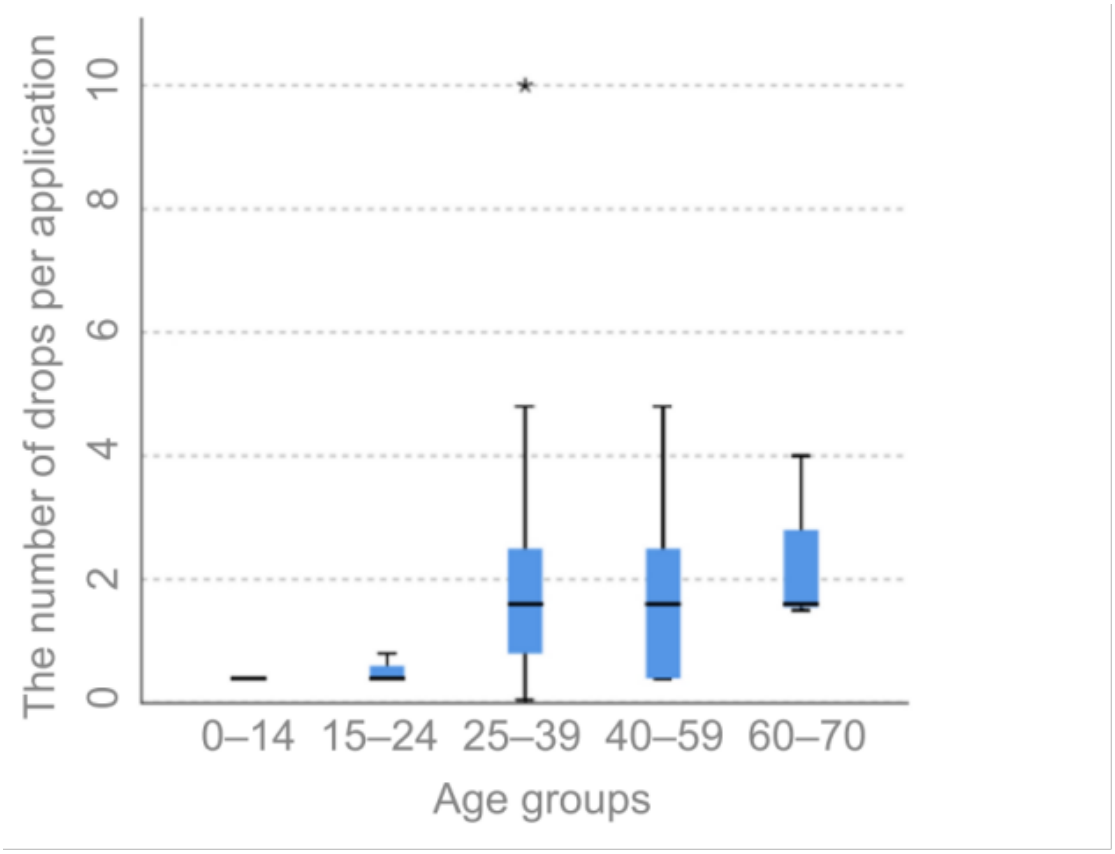

Figure S3. The number of drops per application for Lavanda oil per age group. Difference on the number of drops per application per age group was determined for 5 age groups with a Kruskall-Wallis test.

11. Acknowledgement

First and foremost, I would like to express my deep and sincere gratitude to my research supervisor, Prof. Nakai, for giving me the opportunity to do research and providing invaluable guidance throughout this research. His dynamism, vision, sincerity and motivation have deeply inspired me. He has taught me the methodology to carry out the research and to present the research works as clearly as possible. It was a great privilege and honor to work and study under his guidance. I am extremely grateful for what he has offered me. I would also like to thank him for his friendship, empathy, and great patience.

I am appreciating the assistance of Prof. Li Guangwu with the advice of the questionnaire design and an agreement to conduct survey in the Chinese Aromatic & Aromatherapy WeChat groups.

I am very much thankful to my husband and my two boys for their love, understanding, and continuing support to complete this research work. My Special thanks goes to my friend and research colleague, Saimar Pervez, for his constant encouragement.

Finally, my thanks go to all the people who have supported me to complete the research work directly or indirectly.

Xiao Jun