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空氣中人造麝香採樣方法及分析方法開發

Development of Synthetic Musks Analysis and Airborne Synthetic Musks Sampling Methods

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During these years doing my PhD thesis, I gradually realised that I am not really that kind of persons who prefer to immerse into the academia field. However, I found my passion is totally on understanding science, discovering new technologies and their relevant applications etc. To be honest, the training of PhD for me is to make me understand myself and know how to think logically as well as see problems and get the best solutions towards the problems found. Some people might say having work experience is way more important than studying in graduate schools. In my opinion, PhD training is unique and totally not replaceable with any work experience, especially when you have an awesome instructor (my advisor, Dr. Tsai), excellent lecturers, a few great coworkers, and research-oriented study environment (NTU.)

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To the future, I would love to contribute myself to this world with regards to the knowledge I learned in National Taiwan University. In addition, I would keep myself enthusiastic and passionate pursuing new things and discovering the beauty of the earth.

空氣中人造麝香採樣方法及分析方法開發

臺灣大學公共衛生學院環境衛生研究所 102學年度

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中文摘要

人造麝香（synthetic musks; artificial musks） 廣泛添加於消費個人產品個人或家用產品，如化妝品、家庭用品及清潔用品等個人照護用品，使產品具有香氣；依化學成份的不同，人造麝香主要分為硝基麝香、多環麝香、大環麝香、及脂環麝香等四類。硝基麝香與多環麝香為目前最廣為使用及討論的人造麝香。硝基麝香因其毒性，已逐漸被禁用或管制，因此多環麝香為目前主要使用的人造麝香。此兩者皆已列管於美國環保署的毒性化學物質資料中，且證據顯示人造麝香會誘發氣喘、內分泌干擾物、及與癌症有相關，人造麝香可能會經由皮膚接觸 、食入、空氣吸入等造成人體暴露。人造麝香廣泛存在於室內空氣及周界環境中，但空氣中人造麝香吸入往往因為其香味而被忽略。截至目前為止，還沒有相當完整的人造麝香於空氣中之分佈狀況，亦沒有相當敏感且易於應用的空氣中人造麝香的採樣分析方法，因此本研究著重於空氣中人造麝香的採樣方法及人造麝香的分析方法，並以建立之分析方法量測市售21種香精，另外以現場採樣評估調查目前台灣生產香氛類用品的工作場所室內人造麝香狀況。

本研究使用泡綿採樣管與玻璃纖維濾紙為採樣介質，經過微波萃取及吹氮濃縮等樣本前處理，再以三重四極柱氣相層析串聯質譜儀建立全掃描及特定多重反應監控離子對化的定性及定量條件，分析常見的10種人造麝香。相較於傳統的單一選擇離子測量，分析靈敏度有大幅度進步，回收率皆在60–120%。搭配採樣方法，採集脫附效率除DPMI因其蒸汽壓較高導致採集脫附效率為53%外，9種人造麝香採集脫附效率為64–120%，因此每分鐘3.5升採集8個小時，空氣濃度僅需達0.48 ng m^{-3} (DPMI)即可。

針對5家生產不同香氛製品的勞工作業場所進行空氣採樣的結果發現，本研究採樣工廠使用的人造麝香以多環麝香類為大宗（多環麝香以HHCB及AHTN為最常出現且濃度較高的2種，ADBI及DPMI亦有測量到），並有化妝品禁用成分被檢出（如MA、MM)。工作場所空氣中的人造麝香主要以氣狀存在，但在粒

狀物亦可觀察到人造麝香粘附的狀況，空氣中氣狀多環麝香平均濃度為3.4×10^{2} ng m^{-3},，氣狀硝基麝香為1.3×10^{2} ng m^{-3}，粒狀多環麝香為4.4×10^{2} ng m^{-3},，粒狀硝基麝香則為5.4×10^{2} ng m^{-3}。 另外本研究亦應用已開發的MRM方法定性市售21種香精的人造麝香，其中二十種都含有HHCB及AHTN，與我們的現場樣本結果符合，也與人造麝香的使用量調查相符。

人造麝香需要更多更深入的研究，無論是在環境的影響方面或是健康危害方面，需建立更完整的風險評估模式。本研究完成之作業場所常見10種人造麝香採樣分析方法，可用於未來對於人造麝香分佈調查等評估等應用。

關鍵詞：人造麝香、香精、空氣採樣、泡綿採樣器、暴露評估、氣相層析串聯式質譜儀

Development of Synthetic Musks Analysis and Airborne Synthetic Musks Sampling Methods

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Abstract

Synthetic musk creates a variety of scent by different combination of its individual compounds and has been widely used in a large variety of consumer products with relatively lower cost regarding to natural musk, especially pharmaceutical and personal care products (PPCPs). According to the structures of the compounds, synthetic musk can be divided into four groups, nitro musk, polycyclic musk, macrocyclic musk, and alicyclic musk. Being widely used with considerate consumption in the past and presence, nitro musk and polycyclic musk have been the two mainly discussed types of synthetic musk in the literatures. As for the adverse health effects, synthetic musk has been partially filed in the Hazardous Substances Data Bank (HSDB®). In addition, there were studies indicating that synthetic musks might induce asthma as well as act as endocrine disruptors and be correlated to cancers. Synthetic musk is omnipresent in the air, but the exposure via inhalation is often ignored due to pleasant smells. Furthermore, the information with the regards to the understanding for the distribution of synthetic musks in air is limited. Therefore, this study mainly aimed to develop a highly sensitive and widely applicable method for the determinations of airborne synthetic musk. Besides, with the method developed here, we analyzed twenty-one available commercially available fragrances and also focused on the comprehensive evaluation of the indoor air quality about the synthetic musk distribution in the working environment of the scented-products manufacturing sites.

Polyurethane foam (PUF) and filter were employed for active air sampling in the research. As for the sample preparation, microwave assisted extraction (MAE) and nitrogen evaporator were performed for the purpose of time-saving and better efficiency. A gas chromatography coupled with triple quadrupole tandem mass spectrometer (GC-MS/MS) with specific multiple reaction monitoring (MRM) transition pairs were the major technique applied for sample analysis in this study. Compared with using selected ion monitoring (SIM) mode traditionally, the sensitivities were improved in this study about an order at least. The recoveries have been all achieved the range between 60% and 120%. On the other hand, with the sampling preparation and sampling method established here, the collection efficiencies were within the range of 64% to 120%. In terms of air concentration, as low as 0.48 ng m^{-3} can be determined when sampling at 3.5 L min^{-1} for 8 hours. The method established was further applied to the analysis of synthetic musk compounds in air samples collected in cosmetics plants.

The field sample results showed that both polycyclic and nitro-musks were observed in the field in gaseous and particle phases. To be more specific, obviously, the airborne concentrations of polycyclic musks found in all the factories were much higher than those nitro musks. In addition, Cashmeran (DPMI), Celstolide (ADBI), Galaxolide (HHCB), and Tonalide (AHTN) were the four major synthetic musks as the dominant musk compounds in the working environment. To be detailed, the average concentrations of gaseous polycyclic musk, gaseous nitro-musk, particle-phase polycyclic musk, and particle-phase nitro musk were 3.4×10^2, 1.3×10^2, 4.4×10^2, and 5.4×10^2 ng m^{-3}, respectively.

The analysis method could be adopted onto various types of samples. 21 commercially available liquid fragrances were analyzed and identified with their compositions of synthetic musks. All of the samples were found composed of synthetic musks. HHCB and AHTN were the most commonly seen ingredients. This result is consistent with the observation from the air samples and the usage estimation from IFRA.

Synthetic musks definitely deserve further studies and insight into its environmental impacts and potential to cause harm to human beings. The methodology from sampling, sample preparation, to analysis developed in this study could be extensively applied onto various applications.

Keywords: Synthetic Musk; Fragrances, Air Sampling; Polyurethane Foam; Gas Chromatography Tandem Mass Spectrometers, Exposure Assessment

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Chapter 1 Introduction

Synthetic musk, with relatively lower cost than natural musk extracted from animals and essential oil extracted from plants, creates a variety of scent. Therefore, they have been very widely used in many consumer products, such as detergents, air fresheners, and laundry products. Besides, pharmaceutical and personal care products (PPCPs), including cosmetics, shampoos, lotions, and deodorants, all contain different types of synthetic musk.

According to the structures and the composition of this type of compounds, synthetic musk can be divided into four groups, nitro musk, polycyclic musk, macrocyclic musk, and alicyclic musk [2-5]. Being widely used in the past and presence, nitro musk and polycyclic musk have been the two mainly discussed types of synthetic musk in the literatures. Nitro musk constitutes a carbon benzene ring with 2 – 3 nitro groups. With the health concern and bio-accumulative potential, the usage of nitro musk has been reduced [6]. Instead, Galaxolide (HHCB) and Tonalide (AHTN), which belong to polycyclic musk, have become the most popular thereafter. The USEPA has listed Galaxolide as one of the high production volume (HPV) chemicals [7]. Furthermore, the polycyclic musk usage has increased dramatically; in contrast, the nitro musk usage has been dropped due to the health concern (Table 1 and Figure 5 [8]). The total usage of fragrance has climbed to 100,000 tons, and the polycyclic musks has been estimated to at least 10,000 tons and observed in a variety of products.

As for the adverse health effects, there were studies indicating that synthetic musks might induce asthma as well as act as endocrine disruptors and be correlated to cancers[9-12]. Nitro musk and two of the polycyclic musks, i.e., Tonalide and Galaxolide, have been filed in the Hazardous Substances Data Bank (HSDB®) on the

National Library of Medicine's (NLM) Toxicology Data Network (TOXNET® in the United States) [13].

Studies reported elsewhere have observed that synthetic musks have been detected in consumer products as well as in effluents, sewage, sediments, river, and bays etc. [14-23]. The levels and environmental fate of synthetic musk in a variety of matrices, in fact, have been extensively investigated. Accordingly, the exposure routes were supposed to be mainly dermal uptake and oral intake. Dermal absorption of fragrances is the most discussed way of exposure since the musk-containing products are usually in liquid forms. However, inhalation is one of the exposure routes deserves relatively high concern and attention because some investigations have shown that airborne synthetic musk was ubiquitous over a wide variety of public places, occupational settings, and homes [24-29]. So far, the knowledge of the distribution of synthetic musk is little, for a reliable, sufficient, and effective methodology related to sampling and analysis is still under development [3]. Photo-degradation is effective for decomposing synthetic musks, although it is a slow process in the indoor environment and varies seasonally [4, 30]. Meanwhile, numerous synthetic-musk-containing products are substantially applied in the indoor environment, e.g. homes, work place, public place etc. Due to the slow degradation and considerable usage, synthetic musks may accumulate indoors over time. Moreover, some studies indicated that house dust is also one of the indoor sources of synthetic musk for human exposure. The house dust might be re-suspend as 5 – 25 μm particles. The particles less than 10 μm are inhalable; while those less than 2.5 μm are respirable. Since the properties of semi-volatile compounds (SVOCs), such as synthetic musks, they are capable to deposit onto house dust. Analysis of the compounds in house dust could be an indicator of the indoor synthetic musk contamination. Both of synthetic musk concentration on the particulate matters and as gaseous phases also give a little information to correlate the usage of synthetic musk containing products, habits of the users, as well as distribution and fate of synthetic musks indoors. Both of gaseous and particulate synthetic musks might be brought into the respiratory system and deposit in alveolar [31-33].

Solid sorbents, such as PUF, Tenax TA, and XAD, were usually performed for the sampling of synthetic musk in the air. However, various volatile and semi-volatile organic compounds other than synthetic musks can also be adsorbed simultaneously. Hence, the determination is challenging, since the capacity and selectivity of the method might cause concerns.

Gas chromatography/mass spectrometers (GC-MS) or tandem mass spectrometers (MS/MS) with selected ion monitoring (SIM) mode have been applied to analyze synthetic musk in the air. Nevertheless, further applications of specific multiple reaction monitoring (MRM) transition pairs, which will be able to achieve more precise analysis, are still limited elsewhere. Hence, this research aimed to develop a highly selective and sensitive method for the determinations of low-level airborne synthetic musk by using GC-MS/MS with MRM mode.

Chapter 2 Literature Review

2.1 Natural Musk and Synthetic Musk

Synthetic musks have been used in many pharmaceutical and personal care products (PPCPs) and household products. The main function of synthetic musk is to scent or to cover the odor either of the raw materials or from the environment. Due to the high cost of extracting natural musk and animal rights, synthetic musks were designed to replace natural musks. Although synthetic musks have been considered as low toxicity, the huge consumption and usage of synthetic musks may cause problems and lift the risk of the exposure to synthetic musks.

2.1.1 Natural Musk

Musk is a class of aromatic substances secreted by male musk deer which functions as pheromones to attract mates. The gland of secreting musk so-called musk pod, is located between the genitals and umbilicus. There are a few natural sources of natural musk other than musk deer e.g. civet, muskrat, musk duck, musk shrew, musk ox etc. However, the main source of musk used to be musk deers in general. The extraction process of natural musk from musk pods was complicated, costly, and cruel, since the deers must be killed in order to obtain the musk pods. The secretion of the musk pods removed would be concentrated under the drying process, and then by using solvents, the so-called musk grain (concentration of the pod secretion) would be diluted and preserved till subsequently being added into products [34]. Natural musk has been viewed as an valued ingredient on herbal medicine and a perfume material in Asia for more than 5000 years. Natural musk today is the most expensive animal product as perfume fixatives. TRAFFIC, an international wildlife trade monitoring network of EU, reported in 1999 that natural musk was one of the most expensive commercial products, and its price climbed more than US$10/g of gold price in August 1998 [35].

The first evidence of successfully isolating and understanding natural musk appeared at the very early 19 century. Natural musk was first isolated from musk pod secretion in 1906 by Walbaum and identified with its unique structure in 1926 by Ruzicka. Wilbaum named the extract musk compound as muscone which was a ketone to be exact and claimed this compound as a main odor source of the musk gland secretion. In 1915, Sack isolated another musky ketone from civet cat and called the isolated ketone commpound civetone[34]. Moreover Ruzicka and his team accomplished the chemical formula and structures of muscone and civetone as 3-methylcyclopentadecanone and cycloheptadecen-1-one, respectively [34, 36]. Muscone, Civetone, cyclohexadecenolide (Amberettolide), and some other macrocyclic lactones in plants have been categorized as macrocyclics [34]Natural musk, Muskon in German and Muscone in English, belongs to macrocyclic ketones or lactones whose carbons are between 13-19, mostly C16 ($C_{16}H_{30}O$), in the ring structures [36, 37] as Figure 1 [13].

However, natural musk has been nearly banned and abandoned as an additive ingredient in the perfumery industry due to its limited availability, high cost, and animal rights. Instead, chemically musky alternatives were created and have been the main stream for the aroma relevant fields.

2.1.2 Synthetic musk

Synthetic musk has been critical in the modern pharmaceutical and personal care products industry. Synthetic musks have gradually replaced the use of natural musk since synthetic musk is capable to create a variety of scents and odors similar to natural animal musk and musky odors. Those compound which possess the odor of musk were identified of six structural features, benzene, tertralin, indane, nitro, steroid, macrocyclic

[38]. In general, within the six types, only tertralin, indane, and nitro derivatives were with commercial value in the markets. Tertralin and indane musk derivatives were then gathered as polycyclic musk, and nitro types were later known as nitro musk. The first synthesized musk belonged to nitro musk was synthesized and named as Musk Baur (2-(1,1-Dimethylethyl)-4-methyl-1,3,5-trinitro-benzene) by Baur in 1891. Regarding to the development of organic synthesis techniques, a variety of musk-like compounds have been synthesized. Figure 2 gives a brief idea of the history of synthetic musk. Owing to the limited availability, high cost of natural musk, synthetic musk, with relatively lower cost regarding to natural musk, creates a variety of scent. Hence, they have been widely used in many consumer products, such as detergents, air fresheners, and laundry products as well as have had industrial importance too. Besides, pharmaceutical and personal care products (PPCPs), including cosmetics, shampoos, lotions, and deodorants, all contain different types of synthetic musk.

Nowadays, synthetic musks have involved two more categories other than nitro musk and polycyclic musk. According to the structures of this type of scenting compounds, synthetic musks have been re-divided into four major groups, nitro musk, polycyclic musk, macrocyclic musk, and alicyclic musk [2-5, 39]. However, nitro musk and polycyclic musk are still the two mainly discussed groups of synthetic musks because of their massive production and usage. Nitro musk, as shown as Figure 4, constitutes a carbon benzene ring with 2 – 3 nitro groups. With the health concern and bio-accumulative potential, the usage of nitro musk has been reduced [6]. Instead, Galaxolide (HHCB) and Tonalide (AHTN), which belong to polycyclic musk, have become most popular thereafter. And, the USEPA has listed Galaxolide as one of the high production volume (HPV) chemicals [7]. The commonly-used nitro musk were musk xylene (MX) and musk ketone (MK). Polycyclic musk including celestolide

(ABDI), galaxolide (HHCB) and toxalide (AHTN) and traseloide (ATII), phantolide (AHMI), and cashmeran (DPMI) was later produced and then penetrated to the market, which has become the major use of synthetic musk instead of nitro musk according to the International Fragrance Association (IFRA) report at 2000 [40]. From 1987 to 2000, the polycyclic musk usage has increased dramatically; in contrast, the nitro musk usage has been dropped due to the health concern (Table 1 and Figure 5 [8]). But overall, the usage of synthetic musk has been raised up considerably and rapidly.

2.2 Health impacts of Synthetic musks

Synthetic musk has been applied in the world for a few decades in pharmaceutical and personal care products, household products, and many kinds of consumer products etc. as an additive to create nice scent and cover odor from materials musk, labeled as fragrance or parfum which is a mixture of various synthetic musk compounds. Those musk-contained products are easily found in our daily life and contaminate to human beings in a variety of exposure pathways.

Synthetic musk composes of several compounds. Each compound possesses its own unique physical structure and chemical characteristics. In addition, these compounds were synthesized in late 18 century and began its usage in mid-1900s. Hence, the health impact information of synthetic musk is still limited on some degrees and not well-established. However, in general, as for the adverse health effects, there have been studies indicating that synthetic musk might be a factor to raise the incidence of asthma and very likely act as endocrine disruptors [9-12]. Nitro musk and two of the polycyclic musks, i.e., Tonalide and Galaxolide, have been filed in the Hazardous Substances Data Bank (HSDB®) on the National Library of Medicine’s (NLM) Toxicology Data Network (TOXNET® in the United States) [13].

Some studies indicated that synthetic musk is relatively lipophilic and semi-volatile in a similar pattern with polycyclic aromatic hydrocarbons (PAHs) and polychlorinated biphenyls (PCBs) [24, 26, 41-43]. Accordingly, synthetic musk might embed on the suspended particulate matters in the atmospheric aerosol samples as well as present as gaseous phase, similar to other SVOCs (semi-volatile organic compounds)[44-46]. In addition, as PAHs and PCBs found in the sludge, sediment, wastewater, sewage etc., a few studies reported elsewhere have observed that synthetic musk could be detected in consumer products as well as in effluents and sewage [14-23]. On top of that, with similar physical-chemical properties to semi-volatile PCBs and PAHs, synthetic musk is accumulative hydrophilic, and lipophilic in the environment and bio-organisms based on its high octanol-water partition coefficient (K_{ow})[47]. Moreover, synthetic musk has been found in human blood and breast milk [23, 48-55] The sources of human exposure of synthetic musk are not only from the direct dermal contact and inhalation but also from diet. Although HHCB and AHTN have lower Kow, all of the synthetic musk has been found considerably in various organisms. Due to relatively large production and consumption volume with its physical-chemical properties of high Kow, BCF (bio-concentration factor, or BAF), low photo-degradation and biodegradation constants, synthetic musk is apt to be very bio-accumulative, bio-magnifying, and bio-concentrating through over the food chain[39, 47, 56-59]. The most discussed way of exposure is through skin contact since the musk-containing products are usually in liquid forms. Besides, pathway of inhalation might be critical because some investigations showed that airborne synthetic musk was ubiquitous over a wide variety of public places, occupational settings, and homes [24-29]. However, due to the lack of sufficient and effective sampling and analysis methods, still very few research has focused on the distributions of airborne synthetic musk [3].

Due to different types of synthetic musk compounds, physico-chemical properties vary amongst species. Therefore, there is little information about the toxicity of co-exposure of synthetic musk. In contrast, although individual synthetic musk toxicological data has been reported, the information is still limited and the human toxicological data is rarely seen on certain degrees. Discussing on the toxicity, synthetic musk has been recognized with very little acute and sub-acute toxicity. Mostly, biological long-term accumulative and chronic effects havee been focused due to the unique properties of synthetic musk.

Nitro musk, MX (Musk Xylene), MK (Musk Ketone), MM (Musk Moskene) and MT (Musk Tibetine), showed the extremely low acute oral and dermal toxicity. The animal experimental data suggested the LD50 (lethal dose) is greater than 5000 mg/kg [13, 60-63]. However, MA (Musk Ambrette) which has been banned is with higher oral LD50 of 339 mg / kg [64]. As for the toxicity of polycyclic musk, HHCB and AHTN might associate with liver injury, increase of body weight etc, but the LD50s were much more than 0.57 g/kg in general [9, 65, 66].

Regarding to the sub-chronic toxicity, synthetic musk has been relevant to adverse effect to nerve-system and reproductive system. One of the nitro musk, musk Ambrette, has been recognized causing neurotoxicity, testicular atrophy and phototoxicity on the laboratory animals [55, 67-72]. From literature reviewing, dermal no observed adverse effect level (NOAEL) could be determined that MK and MT was 75 mg/kg bw/day, MX and MM was 24 mg/kg bw/day. Therefore, the daily nitro-musk exposure could be derived from the previous data that the average exposure to the nitro musk fragrance was between 0.03 and 0.04 mg / kg bw with a safety factor of 100 [72]. AHTN and HHCB has been studied for their sub-chronic oral and dermal toxicity. Although AHTN and HHCB were possibly a factor to gain weight on the livers, and a few hepatic changing of laboratory animals, the impact to the livers was recognized as reversible with no significantly histopathologic changing on the liver biopsy. Thus, from the experimental data, the NOAELs for HHCB and AHTN were recommended as 150 mg/kg bw and 15 mg/kg bw, respectively. Accordingly, the daily exposure of HHCB and AHTN were estimated as 0.11 mg/kg bw with a safety factor of 1400 and 0.043 mg/kg bw with a safety factor of 350. [66, 73-75].

The most concerned health issue of synthetic musk is its chronic toxicity, carcinogenicity, and genetic impacts. According to the long-term feeding synthetic musk laboratory data, MA would cause weight loss, blood changes, and muscular atrophy [64]. An increase of incident of tumors and cancer were observed in the MX-fed mice [76]. MK might result in reduction of birth weight. HHCB, AHTN, MX, and MK have been proved to be related to the developmental toxicity [77].

Although there hasn’t been much research suggesting synthetic musk is truly harmful straight to human health [78], synthetic musk has actually been proved that it is capable to inhibit drug transporter proteins (efflux transporters). Drug transporter proteins exist in many kinds of organisms, including human, and their substrate specificity ranges widely. These transporter proteins are able to connect to a variety of substance. By the competition between substrates, therefore the activity of the drug transporter protein would be inhibited and further causes human cells exposed to toxicants or suppress the performance of drugs. The inhibition wouldn’t be ceased immediately after removing the synthetic musk and would last 24 – 48 hours approximately [79, 80]. Due to the lipophilic and not easily degradable, synthetic musk might stay in the organisms for long time, i.e. the half life of MK in human tissue of 70 days [81], and be passed to the next generation via breast milk feeding.

Currently, musk ambrette is the only one of the synthetic musk being banned. Given the fact that polycyclic musk is structurally more durable in the environment and highly lipophilic transmitting in the food chain, and the rest of nitro musk is stilling in use. With the consideration of the potential harm of synthetic musk, continuously studying on the toxicology of synthetic musk, environment distribution and fat should be carried on.

2.3 Synthetic Musk in the Environment

Synthetic musk has been reported in sediments, aquatic biota, water, sludge, organisms as well as human adipose tissue and breast milk. Yamgishi et al. reported the synthetic musk (musk xylene and musk ketone) in the freshwater fish, marine shellfish, river water and the wastewater collected from sewage treatment plants along the Tama River and Tokyo Bay in 1983. Over 80% of their samples were found MX and MK within. The highest concentrations of both compounds were observed in freshwater fish, suggesting that bioaccumulation might be occurred in the aquatic ecosystem [82]. Winkler et al in 1998 then conducted a survey about the synthetic musk in suspended particulate matter in the water of River Elbe in Germany showing that HHCB and AHTN contamination was in the same order of magnitude as a PAH contamination [83]. According to the review of Brausch and Rand, the synthetic musk in the surface water of MK, MX, ADBI, HHCB, and AHTN ranged from 4.8 – 390, 1.1 – 180, 3.1 – 520, 64 – 12500, and 52 – 6780 ng L^{-1}, respectively[84]. The highest level of the surface water samples overall was reported at Berlin, Germany. Hebere et al. collected 30 surface water samples from rivers, lakes, and canals in Berlin and analyzed the polycyclic and nitro musks by using Solid-phase Microextraction (SPME) and Gas Chromatography-Mass Spectrometer (GC-MS). The result showed that polycyclic musks as HHCB, AHTN, and ADBI presenting in all of the samples up to μg L^{-1}, and MK was also found in many of the 30 samples; while MM and MX were only detected in one sample, and MA wasn't found in any samples [85]. Kafferlein et al. published a review to illustrate the occurrence in the environment of synthetic musk, especially MX in water [86]. A few studies investigated the synthetic musk in water environment. Balk et al summarized their data from more than 200 surface water samples taken in Germany, The Netherlands and Switzerland. They concluded that AHTN and HHCB were 0.07 μg L^{-1}[75, 87, 88]. But the polycyclic musk compounds other than AHTN and HHCB were occasionally reported since AHTN and HHCB have dominated the fragrance market. Furthermore Peck et al studied synthetic musk from 2003 and reported the concentration of polycyclic musk in Lake Michigan, ranging from under detection limits (DPMI) to 7.2 ng L^{-1} (HHCB). They also indicated that the concentration of surface water was significantly influenced by waste water treatment plant (WWTP) effluent. WWTP effluent has been recognized as a major source of synthetic musk fragrances to the environment and been reported the concentration worldwide. Similarly, AHTN and HHCB are the most frequently reported compounds and their levels were 1 to 5 μg L^{-1} [29, 89-100]. As mentioned previously, the highest level of surface water appeared in Germany in 1999 [85] which might result from the incomplete removal mechanism by the waste water treatment process. In 2011, Clara et al screened the occurrence of polycyclic musks in wastewater and receiving water during waste water treatment. They observed AHTN and HHCB, the most commonly seen synthetic musks, ranging from concentrations of 0.41–1.8 and 0.9–13 μg L^{-1}, respectively. Household waste water was recognized as a major source of synthetic musk, compared to the industrial waste water around Europe. Also they determined the synthetic musk removal efficiencies of waste water treatment between 50% and 95%, depending on the treatment types. The discharges with non-fully removed synthetic musk would be the major sources to the surface water [101]. On the other hand, according to the study of sorption behavior of synthetic musk, synthetic musk could be adsorbed in very short time, especially onto the sewage sludge [102]. Therefore, synthetic musk might move from water to solid and could be detected in solid matter, suspended particulate matter, sludge, and sediment, up to 63, 000 μg/kg dry weight (sewage sludge) [29, 42, 92, 103-108].

As for the occurrence in the bio-organisms, plants and animals, there have been a few studies reporting the concentrations and bioaccumulation mechanisms. Table 3 presents the synthetic musk detected in animals. It could be later interpreted that the eco-system has been contaminated by synthetic musk, and bioaccumulation might have been happened. Diet could be one of the exposure pathways in the context of the given findings of synthetic musks detected in animals. Indeed, synthetic musks were observed in the human beings, such as in human breast milk (Table 4 [50]), blood, and adipose tissues etc. A few studies further elucidated that synthetic musk might penetrate and accumulate into infants via placenta and breast milk feeding [12, 49-53, 109-118]. On the other hand, synthetic musk is different from the other POPs, e.g. PCBs on the issue of accumulation in human bodies. Concentrations of most of the POPs in human breast milk are strongly related to mothers' age, number of children previously breast-fed, the lactation duration, usage of the compounds, and the diet [119]. Synthetic musks exposure to human beings is highly correlated to the dermal application and consumers' habits without the influence of age [112]. Inhalation is another critical and indispensable exposure route of synthetic musks since their concentration in indoor air were much higher than the concentrations of PCBs in households [28].

Referring to the issue of synthetic musks in the air, the literature is still limited onto the research on the dermal absorption of synthetic musks, such as the synthetic musks in the PPCPs, rather than those in the air for inhalation. However, Kallerborn et al. in 1999 studied ambient air and a few indoor environments with their level of synthetic musks at the south of Norway. The polycyclic musks outdoors could reach 223 pg m^{-3} (HHCB), and nitro musks reached 64 pg m^{-3} (MX). The synthetic musks indoors extraordinarily targeted high concentration, for example, HHCB and MX were10 times (2470 pg m^{-3}) and 8 times (500 pg m^{-3}) more than they in the ambient air, respectively (Table 5 [120]). There was more data about the indoor environments with the concentrations of synthetic musk as Table 6. As mentioned previously, the synthetic musk level in human is highly correlated to the consumers' habits which is relevant the types and usage of consumer products. In the case of the concentrations of Table 6, the average of the five synthetic musk compounds investigated in the hair dresser was higher than the other five places [121]. This phenomenon implied that the workers/employees who work in the relevant industry might have more exposure than those in other industry. In addition, Peck and his team sampled and analyzed the commonly-seen synthetic musks in Lake Michigan and at the city of Milwaukee. HHCB and AHTN could be detected in the air of the surrounding of the Lake between 1.1 and 4.1 ng m^{-3}. Overall the concentration of polycyclic musks was much higher than the concentration of nitro musks (MX: 0.032 – 0.014 ng m^{-3}) [122]. Further in 2006, they collected 181 air samples with high-volume air samplers from urban, suburban, and rural sites in Iowa and the Great Lakes, USA. Overall, the concentrations of synthetic musks in the urban sites were on the order of 1 – 5 ng m^{-3}). HHCB and AHTN remained the most frequently seen synthetic musk compounds. This study revealed that the synthetic compound contamination has been ubiquitous in the environment, especially in the air [123].

Synthetic musks belong to semi-volatile organic compounds. Therefore synthetic musks could adsorb on solid matters, i.e. dust. Fromme et al. collected 74 gaseous samples and 30 household dust samples from the apartments and kindergartens in Berlin, Germany. In spite of that the gaseous synthetic musks indoors varied from 12 – 299 ng m^{-3}, synthetic musks turned out on the household dust up to 47 mg kg^{-1}[28].

Regarding to the specific workplaces with higher concentration of synthetic musks as mentioned previously, Chen et al. evaluated the air quality of a cosmetic plant in Guangzhou and its surroundings regarding to five synthetic musks, DPMI, ADBI, AHMI, HHCB, and AHTN. Obviously, inside of the manufacturing area, the sum of the five studied polycyclic musks in gas phase rocketed to more than 5,000 ng m^{-3}, and individual musk as HHCB accounted for over 80% of total amount of the studied polycyclic musks (details in Table 7). Given the fact that the personnel in the manufacturing area suffered from high synthetic musks. Hence, the occupational exposure to synthetic musks should be taken into consideration of occupational health programs. On the other hand, a cosmetic plant was recognized as a major source contributing for the synthetic musk concentration to the surroundings [124]. The more distance from the major contamination source, the less synthetic musk detected in the ambient air.

2.4 Sampling Methods for Synthetic Musks

In terms of its semi-volatile characteristic, synthetic musks are normally collected by a few sampling media, i.e. polyurethane foam (PUF), Tenax TA, XAD-2, and filters. Table 8 lists the sampling methods and analysis methods of the past studies of synthetic musks. As can be seen, mostly PUF was the sampling absorbent, and some of the studies collected gaseous and particulate synthetic musks by PUF and glass fiber filters. Different combinations of sampling media are led by different research aims and target compounds. As for each sampling medium,

PUF sampler itself has been identified as reliable both active and passive air sampling media based on the theory and applications [125-130]. US EPA also develop a standard method to collect pesticides, PCBs and etc. suspending in the air [125]. PUF could be coupled with Tenax which is a porous polymer resin and trap volatiles and semi-volatile compounds. Tenax benefits to sampling in a highly humid environment due to its low affinity for water. PUF could also be used with XAD which has been applied onto collect semi-volatile organic compounds (SVOCs) in the ambient air. US EPA has developed methods, including TO-10, TO-4, and TO-13, by using XAD conjunct with PUF to collect pesticide, PAHs, phthalate and other SVOCs. In this study, PUF with pre-glass-fibre-filter samplers were employed. The glass-fibre filter is used to separate particle-phase and gas-phase compounds. This arrangement enables the finding of gaseous and solid phase partition of the pollutants investigated. The particle-associated compounds, which are suspected to be semi-volatile, will be accumulated on the filters.

Polyurethane foam (PUF) has been widely used for the evaluation of environmental concentration and personal exposure to persistent organic compounds (POPs), e.g. polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), polycyclic musk (PCMs) etc.[129], by active air sampling (AAS) and passive air sampling (PAS). Solid sorbents, such as PUF, Tenax TA, and XAD, were usually performed for the sampling of synthetic musk in the air too. Those POPs mentioned above appear as volatile or semi-volatile forms (VOCs/SVOCs) and can be possibly trapped by PUF air samplers. Moreover, some

VOCs and SVOCs, such as formaldehyde, which are considered as a group of chemicals inducing short-term and long-term adverse health effect can be trapped by PUF too due to its high volatility. PUF is commercially available and relatively cheap. In terms of adsorption capability, it is possible that PUF can be used to trap most of the POPs, VOCs, and SVOCs which are three of the most crucial groups of air pollutants indoors. Accordingly, PUF is capable to be joint with different absorption/adsorption media to enrich the collection efficiency of specific compounds, such as semi-volatile PAHs. As for different phases, PUF is capable to assemble with pre-filter in order to distinguish the different chemical composition between particle phase and gas phase. Given the fact that PUF offers the flexibility and possibility to screen the species and the concentrations of the pollutants, it enables to establish the relationship between indoor/outdoor air quality and health effects. In terms of using solid sorbents, matrix effect might happen since the attached or absorbed target compounds have to be extracted by solvent, e.g. hexane, acetone/hexane, methanol, etc. Moreover, matrix effect to the analysis of synthetic musk might be led since different sample types comprise various chemicals and need appropriate sample preparation, i.e. PPCPs, environmental, and biological samples. Due to the matrix effect, the analysis of synthetic musk within different sample types including airborne form is challenging. Other than synthetic musk, the main problem of the methodology is the capacity and selectivity to a variety of volatile and semi-volatile organic compounds, which might also be extracted in the solvents simultaneously. Therefore, a sensitive method with selectivity will be helpful for the analysis.

2.5 Analytical Instrument for Analyzing Synthetic Musks

There are several ways to minimize the matrix effect and achieve better separation of synthetic musk from sampling to analysis. In terms of analysis other than sampling and sample preparation, on one hand, better separation might be worked by modifying the temperature program prolonging chromatography procedure. But for the complex samples, such as PPCPs, water, waste water, extraction of air samplers, etc., it might be very time-consuming and not be easy to separate the target compounds away from the matrix with only one MS or one-dimensional gas chromatography. Another method is to employ advanced technology such as a two-dimensional gas chromatography with time-of-flight (TOF) mass spectrometer (GCxGC-MS) which may capable to separate synthetic musk compounds from samples by tandem columns. However, this technique might be less workable for very complex samples and lead similar problems as changing the temperature program. The other method which is more common is through gas chromatography/mass spectrometers (GC-MS) or tandem mass spectrometers (MS/MS) with selected ion monitoring (SIM) mode. This pattern has been applied to analyze synthetic musk in the air to overcome the obstacle mentioned above. Further applications of specific multiple reaction monitoring (MRM) transition pairs, which will be able to achieve more precise analysis, are still limited elsewhere. Hence, this research aimed to develop a highly selective and sensitive method for the determinations of low-level airborne synthetic musk by using GC-MS/MS with MRM mode.

On the other hand, from above saying in order to give some facts of the complexity of the commercialised and some stands for choosing MRM method, we applied GCxGC-MS method by using commercialised fragrances. From literatural reviewing, giving the fact that Tonalide and musk xylene are recognised co-eluted and difficult to distinguish these two compounds by SIM mode/ MRM transition monitoring is one of the possible solutions to perform analysis based on unique transition parent and product ion pairs. However, on the MRM chromatography in 2D version, the two compounds were still overlapped. In this case, a two-dimensional gas chromatography with time-of-flight (TOF) mass spectrometer (GCxGC-MS) (LECO, USA) was applied for further separation. The specialized feature of GCxGC-MS is mainly at the GCxGC, the enhancive separation technique at the 2nd dimension of gas chromatography. As shown in the Figure 6, this technique simply separates the eluents from the first column (conventional one dimensional GC separation) by two-stage modulator which operates cold and hot pulses of nitrogen gas. The analyte are focused by cold pulse in the first jet of the dual stage-quadjet modulator in the second oven and then released by the immediately applied hot pulse. When the heated analytes move to the 2nd jet, a cold pulse would be applied as soon as their arrival, which would helps the analytes refocused before getting into mass spectrometer. The cycle of cold and hot pulsed could be manipulated over and over again during the separation. Time-of-flight mass spectrometer (TOF) as a mass detector of GCxGC/TOF-MS, TOF MS is literally faster than conventional quadrupole MS with analysing accurate mass. In other words, TOF MS in general produces much more spectra for a peak with higher resolution.Therefore, TOF-MS coupled wih various separation technology is mainly applied in identification rather than quantification. In addition, by the progress of mass spectrometry, tandem mass spectrometer system is now becoming a widely used technique for both identification and quantification.

Basically, a GC-MS offers a sample to be separated by gas chromatography and detected by fragments which were generated by ionisation via mass spectrometry. GC-MS systems are capable to identify possible composition of a sample by retention time

(GC) and mass spectra (MS). However, in general, samples are always complicated. Given this fact matrix effect is often happened during analysis. Indeed, a not-ambiguous-identification and a well-defined-quantification are hardly achieved by conventional GC-MS for complex matrix with simple sample preparation. GC-MS/MS with multiple reaction monitoring might be suited to deal with the complex samples where trace-level chemicals are. MRM in GC-MS/MS separate compounds eluted from gas chromatography in two stages. The first quadrupole which is conventional single quadrupole MS system use 70 eV to make precursor ions. The second quadrupole is a chamber supplying collision energy to hit the precursor ions into product ions. The third quadrupole functionalises as a filter and focus those product ions into detectors and then amplifying into electronic signals. Apparently, gas chromatography coupled with triple quadrupole mass spectrometer is much more selective and precise, compared to conventional a gas chromatography coupled with single quadrupole mass spectrometer. In the past, Selective Ion Monitoring (SIM, or Selected reaction monitoring (SRM)) was the solution to enhance the selectivity and sensitivity to detect certain component within a complex-matrix sample. Although SIM works well for the purpose of extracting critical mass information from matrix, it is limited if the matrix is very complicated with interference by a few fragments from other compounds. MRM mode definitely increases the sensitivity and selectivity since two abundant ionised fragments at the first stage (Q1) are chosen. These certain ionised fragments are then collided and generated a few daughter ions of each parent ion. The most abundant daughter ion of each parent ion is selected and detected. A parent ion and its daughter ion therefore form an MRM pair. MRM specialized to cope with the samples in fairly complicated matrix or with the ones where analytes appear as very low amount (low concentration), such as food samples as well as air samples.

Chapter 3 Materials and Methods

3.1 Reagents and chemicals

All synthetic musk standards, including musk ambrette (MA), musk ketone (MK), musk moskene (MM), and musk xylene(MX) with 10 μg mL^{-1} in cyclohexane as well as Cashmeran (DPMI), Celestolide (ADBI), Galaxolide (HHCB), Phantolide (AHMI), Tonalide (AHTN), and Traseolide (ATII) with 100 μg mL^{-1} in cyclohexane were purchased from LGC Standards (London, UK). Table 2 illustrates the physical and chemical properties of synthetic musk studied in this research. Cyclohexane, acetone, and other solvents with analytical grade were provided by Merck (Taipei, Taiwan).

In addition, for the pre-test and identification the synthetic musk compounds in the commercialised fragrances, there were 21 commercialised fragrance products bought in the local markets.

3.2 Labware

All of the glassware used in the experiments was carefully cleaned with non-scented neutral detergent, rinsed with deionized water and acetone followed by drying in the hood.

3.3 Air Sampling Equipment

Brand new pre-cleaned-and-ready-to-use polyurethane foam (PUF) plug coupled with glass fiber filter sampling sets (PUF/Glass Fiber Filter, 22 X 100 mm size, 1-section, 76 mm sorbent; SKC 226-126) were from SKC Inc (USA). GilAir™ Plus (2000 c.c – 5000 c.c min^{-1}) and Gillian 3500 (700 c.c – 3500 c.c. min^{-1}) pumps (Sensidyne, USA) connected with PUF samplers were performed for the method validation and field sampling.

3.4 Instrument

The chemical analysis was performed by Agilent 7000B Gas chromatography coupled with triple quadrupole tandem mass spectrometer. The system was operated by the MassHunter software with Wiley and NIST library search.

As for the gas chromatography, the injection volume was set up to 2 μL and the injection port was reached 250 ° C in order to vaporize the samples into gaseous phase. On top of that, the column selected was a DB-5MS (J & W Scientific, Folsom, CA. 30m x 0.25 mm id, crosslinked 5% phenyl methyl silicone, 0.25 mm film thickness). The overall separation with helium at 1 mL min^{-1} was processed by the temperature program set up from 70° C to 280° C. The initial temperature was 70 ° C for 0.5 minutes followed by an increase of 30 ° C per minute to 200 ° C and 225 ° C at 3 ° C per minute. Afterwards, the column would be heated upto 280 ° C at an increase of 40 ° C per minute holding for a minute.

As for the mass spectrometry, EI mode with 70 eV was selected as ionization process. Full scan from 50 to 300 amu, selected ion mode (SIM mode), and multiple reaction monitoring (MRM) were fully implemented for identification and quantitative analysis. 1.6 scans per single second was setup, and the total analysis time was 15.54 minutes at 1 mL/min of helium as carrier gas.

The specialized mode of Agilent 7000 B is Multiple Reaction Monitoring (MRM). Basically, the elutes ran through the first quadrupole mass analyser (Q1) and bypassed Q2 where an extra energy, so-called collision energy, is offered to impact the precursor (parent ion) ionised fragments from Q1 into product ions (daughter ions) followed by Q3. The difference from GC-MS to GC-MS/MS is MRM pairs, that GC-MS/MS detected those ions after two impacts by electronic impaction and collision energy. Table 13 shows the collision energy and the two MRM pairs of each synthetic musk compound.

There are a few instrumental options of analysing synthetic musks. Generally, GCxGC-MS (two-dimensional gas chromatography coupled with mass spectrometer) and GC-MS/MS are frequently in comparison. The LECO GCxGC-MS here is employed applied the same GC temperature program as the one used for GC-MS/MS analysis. However, there are two major differences. First, GCxGC-MS uses two columns to lift the separation of the samples. The first column is Rtx-5MS (DB-5MS) which belongs to low polarity for general purpose of analysing SVOCs; while the second column is Rtx 200 with mid polarity for all purpose and herein for further separation as the second dimension of GCxGC-MS. The second oven where the Rtx-200 column was located was set up 50 ° C higher than the first GC oven.

3.5 Validation of air sampling method

In this study, active low volume PUF with filter sampling system were applied, according to the US EPA Method TO-10A for semi-volatile organic compound [131, 132]. Active sampling offers a few benefits of time saving and pumping known volume, compared to passive sampling. The laboratory validation here was performed and followed the guideline of the US EPA Method TO-10A. Briefly, by placing 1 mL of 2 μg mL^{-1} 10-synthetic-musk-mixture standard solution into an impinger, the sampling efficiency (SE) was determined by two tandem PUF samplers assembled to the impinger with pumping into highly-purified nitrogen at the flow rate of 3.5 L min^{-1}. The air sampling validation set is shown as Figure 9.

The entire validation process was carried out in a cleaned hood filled with filtered air (without particles and VOCs), and the sampling time was 8 hours. All the validation experiments were performed in triplicates.

All samples were extracted by microwave-assisted extraction (MAE). The PUFs and glass fibre filters after sampling were placed separately into two GreenChem^{TM} Extraction vessels. 60 mL of 1:1 cyclohexane: acetone (v/v) were required in order to cover the 10 cm tall PUF plug in each vessel and then extracted for 60 mins at 85°C of the Microwave-Accelerated Reaction System, Model MARS-X (CEM Corporation, USA). Compared to the traditional extraction methods for synthetic musk, such as Soxhlet extraction (SE), simultaneous distillation-solvent extraction (SDSE), and ultrasound probe (UP), microwave-assisted extraction is more effective, efficient, and environmental friendly because of less solvent consumption [133, 134].

Regarding to confirmation of the efficiency of MAE extraction and concentration outcome of nitrogen evaporation, 1 ml 10-synthetic-musk-standard mixture of 0.2 μg/mL were spiked onto PUF and filter respectively and added 60 mL of acetone:cyclohexane 1:1 mixture. In comparison between the traditional Soxhlet extraction method and MAE extraction with nitrogen evaporation concentration, MAE extraction is more accessible, easy, solvent-less and faster. Hu et al. made a comparison towards two major synthetic musk in the sediment with these two extraction techniques as Table 9 [133].

Additionally, regarding to our target compounds, synthetic musks, and MAE, the solvents for extraction and the later concentration procedure would be very critical. Hu et al. mentioned that the mixture of hexane and acetone worked more efficiently on extraction than the one with hexane and dichloromethane [133]. Moreover Smyth et al. (2007), Svoboda et al (2007), Sofuoglu et al (2010), and Weinberg et al (2011) used the mixture of hexane and acetone for extraction as well [26, 43, 135, 136]. Regarding to DCM as a toxicant, the mixture of cyclohexane and acetone 1:1 was employed for extraction instead of hexane because cyclohexane and hexane are structurally similar and not different on extraction [137]. In this case, PUF and filter were separately put into a GreenChem vessel with certain spiked amount, 1 ml of 0.2 μg/mL 10-synthetic-musk-standard mixture, and 60 ml of acetone: cyclohexane 1:1. In details, given the fact to the selected solvents that acetone functionalizes to increase the polarity during the MAE process because cyclohexane isn't polar, and microwave is only capable to heat the polar molecule. In other words, acetone enhances the efficiency of MAE. Further, acetone could speed up the volatility and bring the solvent out of the extraction liquid. Cyclohexane is less volatile than acetone. Give the fact that cyclohexane is more difficult to desolventize than hexane[138], it is capable to keep synthetic musk in the extraction during the nitrogen evaporation.

On the other hand, we compared the MAE methodology with a variety of combination of temperature, duration, and times of extraction as Table 10. The optimized condition is to extract the samples under 85°C for 60 mins. Thus, the MAE procedure was begun from room temperature to 85 °C in 7 mins and maintained in 85°C for 60 mins. Afterwards, the extraction of each PUF and filter would go through concentration procedure. Nitrogen evaporator with gentle stream was processed, and the extractions were first concentrated to 0.5~1 mL and then rinsed back to 2 mL with cyclohexane for further instrumental analysis.

It is noteworthy that surrogates are normally included in the treatment and analytical procedure to evaluate the loss of the analytes [30]. For example, deuterated musk xylene and AHTN standards are commercially available. However, deuterated AHTN has been reported to undergo partial deuterium to hydrogen exchange during analysis which may cause inaccurate surrogate recovery [139]. Besides, it was reported that no ideal surrogate standard could be found regarding the sampling of musks by PUF and filter [124]. Nevertheless, it has been stated that the procedural calibration might offer higher recoveries than the surrogate corrected recoveries [140].Hence, instead of surrogates, spiked samples were analyzed in every batch in this study to determine the recoveries [124].

3.6 Field air sampling

Field air sampling were performed at four cosmetics plant and a site of manufacturing household product to validate the application of the method developed in this study (sampling site and samples details listed in Table 11). The cosmetics products manufactured include facial wash, lotion, cream, shampoo, body wash, and toner etc.; whilst the household products in the site we visited are dish wash and laundry detergents. All of the settings used fragrance/parfum to scent their products during the process. Mixtures of highly concentrated synthetic musk were added as fragrance. All samplers were cleaned and wrapped by aluminum foil in sealed jars individually before sampling. With pumps and tubes appropriately assembled, the samplers were positioned at 1.2 - 1.5 meters high above the ground floor with 0.3 - 0.5 meters away from the reaction tanks. The samplers must face downwards against the dusts. Total sampling duration was approximately 480 min, and the average sampling volume was ca. 1.6 m^3. Figure 8 shows the way of connecting a PUF sampler set to a pump, and Figure 10 illustrated the arrangement of the samplers during the sampling on site.

After collecting, each sample (the whole sampling tube) was carefully foiled, returned to the jars, and shipped back to the lab for further sample preparation and anaysis. Sample preparation was performed within 12 hours after the field sampling. All the quantifications of the airborne synthetic musks were calibrated by the extraction efficiency and sampling efficiency obtained from external calibration curves of the spiked standards.

Chapter 4 Results and Discussion

4.1 Optimization of GC-MS/MS in this Study

As reported elsewhere, the analysis of airborne synthetic musk was mostly processed by GC-MS with selected ion monitoring (SIM) mode [28, 106, 120, 141-143]. To the best of authors' knowledge, there were only three studies specifically discussed MRM transition pairs of synthetic musk by using human breast milk samples, house dust, and sediments [4, 144, 145]. However, these three studies didn't comprehensively reveal the ten synthetic musk compounds which we involved in this study. Moreover, regarding to air sampling, there was no study analyzing synthetic musk by performing triple quadrupole GC-MS/MS with a set of MRM transition pairs with MDLs.

Figure 11 shows the chromatograms of full scan mode and MRM mode (a and b, respectively). Due to full scan, the chromatographs might contain a few peaks other than synthetic musks. By selecting specific MRM transition pairs for each synthetic musk compound with appropriate collision energy, the matrix effect could be minimized. Hence, the MRM mode worked out in this study is quite useful for the environmental samples with complex media. Table 13 summarizes of the MRM pairs of the synthetic musk compounds studied in this research.

As mentioned above, GC-MS with selected ion monitoring (SIM) mode was mostly performed for the analysis of synthetic musks. In addition, synthetic musk compounds were reported capable to be separated by a fine tune in a temperature program for water sample[140]. On the other hand, it is noteworthy that Tonalide, Galaxolide, and musk xylene were nearly co-eluted in this study. Nevertheless, the issue of co-elution in this study was entirely solved by performing the MRM transition monitoring which results in more specific and sensitive analysis of synthetic musks .

This suggests that the GC-MS/MS with MRM mode could be useful for complex sample matrix.

On one hand, in order to demonstrate different techs for analyzing synthetic musks in various matrix and illustrate the strength of using GC-MS/MS rather than other instrument, this a two-dimensional gas chromatography coupled with time-of-flight mass spectrometer (TOF-MS) and a well-tested method for GC×GC-MS were carried out. Bester (2009) indicated that high resolution or tandem mass spectrometric techniques are rarely used for synthetic musk analysis since the sensitivity of the low resolution mass spectrometers usually is sufficient, and a better gas chromatographic separation could make sure the peak is identified correctly, such as a comprehensive two-dimensional gas chromatography (GC×GC) with a TOF-MS [142]. Given the facts of GC×GC-MS that it might work well when the matrix is not so complicated. Further separation by cold and hot snaps cycles of GC×GC-MS could be helpful for our synthetic musk standard mixture. As for the 10-synthetic musk-standard mixture, the above statement might be correct and was proved in Figure 12. GC×GC-MS is capable to separate the compounds with similar elution time. GC×GC-MS allows direct sample injections and is capable to identify unknown constituents. But for those compounds which might occupy very small percentage in a product, GC×GC-MS might have issues of its selectivity to the analytes and needs of interpreting as well as turning rather smeared chromatographs into convincible and reliable data. From our data analyzing the commercial fragrance (100:1 diluted), GC×GC-MS is very unlikely to resolve different m/z within a sample. Take one of the commercial fragrance purchased, white musk for a instance, with less sample injection volume of 0.2 µl since we didn't know its real composition within this commercial fragrance, the chromatograph as Figure 13 was fairly blurred all over the full scanned mass range. Moreover, the library search didn't offer much help on defining the composition of the commercial fragrances with their two dimensional gas chromatographically mass spectrometry data. According to the result with NIST library search, we could find HHCB, MX and more than hundreds of chemicals. However, it might be difficult to quantify the synthetic musk within a sample. In other words, GC×GC-MS is more apt to being a tool of identification of unknown compounds rather than quantification [146]. Alternatively, GC-MS/MS is way more appropriate for this study, regarding to our research aims of identifying, quantifying the synthetic musk in the air and any kinds of samples.

On the other hand, as for chemical compositions, nitro musk and polycyclic musk possess a variety of compounds which might lead to the differences on analytical sensitivities. The type of GC column is one of the determinants for separating the compounds within a sample. Better separation usually brings better effect for further mass detection. Xie et al compared two capillary GC columns for separating polycyclic musk compounds telling that DB5-MS column which we employed in this study could lead better performance on separating synthetic musks [147]. As for the impact modes, there are usually two ways to go, electron impacts (EI) and chemical impact (CI). GC-MS with electron impact (EI) is recommended for analyzing both polycyclic musk and nitro musk. However, it was observed that EI mode of GC-MS was more sensitive for the analysis of polycyclic musk than nitro musk, while GC-MS with NCI (negative chemical impact) tends to more suitable for nitro musk analysis [147]. From our study here, both polycyclic musks and nitro musks are our target group of compounds for the purpose of realizing the synthetic musk in the air of fragrance relevant industry. Indeed, EI mode was the first option here.

The development of MRM pairs is also useful to identify various sample types, including liquid samples. It was employed in this study not only for the air samples but also for those commercially available fragrances. As for identification of commercial fragrances, with the MRM pairs we developed in this study, we could find synthetic musk composition in 21 commercial fragrances. From Table 12, HHCB and AHTN were found in every single commercial fragrance, except sandal wood fragrance. More details are described in the later section.

As for quantification, the linear range of the analysis was determined to be 1 ng mL^{-1} to 5 μg mL^{-1} by performing the MRM mode. Regarding method detection limits (MDLs), the USEPA defines MDLs as ‘the minimum concentration that can be determined with 99% confidence that the true concentration is greater than zero. Hence, the MDLs for nitro musk and polycyclic musks were found to be 0.05 – 0.31 ng mL^{-1} and 0.02 – 0.10 ng mL^{-1}, respectively (Table 13). In terms of air concentration, as low as 0.48 ng m^{-3} (in terms of Cashmeran) can be determined when sampling at 3.5 L min^{-1} for 8 hours by the method established. The concentration reported elsewhere showed that the concentrations of synthetic musk frgrances in indoor air ranged from below 10 ng m^{-3} to 299 ng m^{-3} and 1750 pg m^{-3} to 540 pg m^{-3} in clean lab [108, 120, 147-149]. Compared with these ranges, our method of simultaneously analyzing nitro musk and polycyclic musk could be achieved with relatively higher sensitivity by performing MRM transition monitoring in this study. The results from this study improved the sensitivities about an order at least.

4.2 Commercially available fragrances

According to our data shown in Table 12, the optimized analysis method helped to identify the synthetic musk composition within the 21 commercially available fragrance samples. Obviously, different fragrances are mixed by various synthetic musk with different compositions and percentages, which create unique scents. HHCB and

AHTN are the most found synthetic musk compound in the fragrance. This result is consistent with the fact that HHCB and AHTN is widely used in the market. All the samples contained polycyclic musk; while nitro musk is only found in 10 out of 21 samples. Musk ambrette (MA), the most concerned musk compound, was found in one sample, green tea fragrance, although MA has been banned for years. Compared the two types of synthetic musk, the ratio and usage of polycyclic is larger than the ones of nitro musk. Meanwhile, from Table 12, different manufacturers might have different mixing procedure and strategy to create a specific type of fragrance (i.e. white musk).

Consumers cannot fully understand what kinds of synthetic musk compounds they are exposed tofrom the labels on the fragrance products. Referred to a report released in 2010 “NOT SO SEXY: The health risks of secret chemicals in fragrance”, it revealed 38 secret chemicals in 17 name-brand products (Perfumes, colognes, and body spray), with an average of 14 secret chemicals per product. In addition, by laboratory testing, 15 name-brand products out of total 17 contain HHCB; one has MK; five have AHTN[118]. That report also indicated the gap of knowledge about the toxicity and the health impact of synthetic musk. Though there is little evidence of adverse human endocrine system effect resulted from synthetic musk, van der Berg et al emphasized that the oestrogenic effect of synthetic musk is cell- and oestrogen receptor-type specific, and polycyclic musk is anti-estrogenic (ERb-selective), antiandrogenic and antiprogestagenic with the potential to mimic the endocrine system in vivo. Synthetic musk may interact with other chemicals performing combined effect and causing health impacts [150].

Our result of identification the commercialized products pointed out all the fragrances are synthetic musk involved. These synthetic musk fragrances have been extensively used in a variety of consumer products and have contaminated lives and environment in a world-wide scale. For long-term consideration, correct labeling and less usage of synthetic musk should be taken place.

4.3 Air sampling efficiency

As mentioned above, the air sampling method was validated by following the guideline of the US EPA Method TO-10A. For sample preparation, MAE was performed, and concentration was through nitrogen evaporation. The extraction efficiency for both PUF and filter was between 64% - 122% (referred to Table 10). The individual extraction efficiencies of polycyclic musks on PUF were from 64 % to 122%, while nitro musk were varied from 96%, to 114%. As for filter, the extraction efficiencies of polycyclic musk and nitro musk were 67% to 118% and 75% to 100%, respectively.

As shown in Table 14 and Table 15, we found the sampling efficiencies were all located in the range of 62% - 93% (Cashmeran was 64%). The findings suggested that the retention percentage varied from compound to compound, and the difference among the musk compounds may be attributable to their vapor pressures [26]. This might explain why the extraction efficiency and sampling efficiency for Cashmeran, which has the highest vapor pressure, were both the lowest.

To determine if breakthrough occurred, two PUF plugs were placed in the primary and secondary traps and were attached to the pump. According to USEPA method TO-10A [132], the sum of the amounts of compound found from both the primary and secondary plugs should be within ±10% of the original amounts added. It was found that all the synthetic musks tested in this research were within the acceptable range. In addition, it was also reported elsewhere that the musk compounds were mostly retained in the first PUF plug, except for DPMI [26].

In this study, PUF and glass fiber filter were both applied for the air sampling. As also shown in Table 15, the amounts of the synthetic musks collected on the filters were much lower than the amount trapped on the PUF, except for MK. This might indicate that synthetic musks were more likely to appear in gaseous state in the environment.

4.4 Analysis of field air samples

Field air sampling was performed at four cosmetics plants and a household product manufacturing site in this study. Analysis of field blanks was also performed. For both glass fibre filter and PUF cartridge, no significant contamination was observed (i.e., the integrated areas from chromatogram were lower than the detection limits).

Given the fact that PUF was suitable for collecting various semi-volatile organic compounds [151, 152], the chromatogram of the sample with scan mode demonstrated unknown peaks which might interfere the identifications of the synthetic musks (Figure 11a). As MRM mode was applied afterwards, Figure 11b discovered the clear appearances of Cashmeran (DPMI), Celstolide (ADBI), Galaxolide (HHCB), and Tonalide (AHTN) without the effects from complex sample matrix.

Different numbers of sampling spots was chosen depending on the environmental condition and working procedures in the investigating plants. As shown in Table 16 and 17, both gaseous and particulate forms of synthetic musks were determined. And, the concentrations in gaseous form were generally higher than particulate form in the cosmetic factory. This phenomenon is also consistent with the synthetic musk consumption worldwide and our identification result of commercial fragrances as Table 12.

Compared to nitro musks, the airborne concentrations of polycyclic musks found in all the factories were much higher. In addition, Cashmeran (DPMI), Celstolide (ADBI), Galaxolide (HHCB), and Tonalide (AHTN) were the four major synthetic musks determined. The average concentrations of gaseous polycyclic musk, gaseous nitro-musk, particle-phase polycyclic musk, and particle-phase nitro musk were 3.4×10^{2}, 1.3×10^{2}, 4.4×10^{2}, and 5.4×10^{2} ng m^{-3}, respectively.

For each sampling spot, different production process was taking placing at the moment of sampling on site. Since the fragrance required for each product might different from each other, various compositions of synthetic musks were found among samples (Table 16 and Table 17). In terms of the sampling sites, the result depicted the difference from plant to plant. The highly yielded volume and relatively opened space production line (in contrast of clean rooms in Plant A, D and partially C) resulted in overall higher synthetic musk concentration than the rest of the sampling plants both in gaseous and particulate phases at Plant B and E. The outcome also inferred that polycyclic musk and nitro musk are very likely applied into the routine production. Regarding to the potential of causing adverse effect reproductive systems, phototoxicity, and negative impacts to the ecosystem and environment, nitro musk was observed in this study. MA was found in Plant A and B; MM was found in Plant A and D; MX was found in Plant D and E; MM was found in all the five sites we surveyed. Accordingly, MA and MM have been banned from the use in cosmetic products, and MX and MK have been set up their maximum limits in cosmetic products by EU [9].

There is little research on evaluating the synthetic musk in the air of working environment. Only Chen et al published a paper in 2007 investigating five polycyclic musk compounds in the air of a cosmetic plant in China. We compared our data to the result of Chen et al. as Table 18. From Chen's study, HHCB, AHTN, ADBI, AHMI, and DPMI presented in the environment of the studied cosmetic plant. Obviously, HHCB and AHTN were the dominant synthetic musk compounds. In the meantime, synthetic musk appeared as gas phase rather than as particulate phase. In this study, the concentration of these five compounds of polycyclic musk were found higher in Plant B, C, and E, which might be relevant to the air and environmental controlling conditions. Plant B, C, and E belong to relatively conventional industry. B and C have built clean rooms in order to suit the regulation of manufacturing cosmetic products, but their major producing areas and main procedures were not in the clean rooms. The manufacturing tanks were not closed-type. Likewise, Plant E manufactures household products, and its manufacturing area and storage area were half-opened, and the tanks are half-opened as well; while its filling and packing area was not fully closed. Plant B, C, and E were not comprehensively temperature and humidity controlled; whilst all the manufacturing and filling areas of Plant A and D were in clean rooms. Apparently, clean room and the type of manufacturing tanks are two factors causing the concentration of synthetic musk varying. In addition, the recipe (formula) of each product, product types, procedure, temperature, humidity, and ventilation etc. are all the factors to result in the difference of synthetic musk among sampling sites.

In terms of the occurrence of synthetic musk in Taiwan, this issue has been discussed recently and gotten the public concern. Synthetic musk is categorized as an emerging pollutant in the environment[153]. Although some of the reports and studies have indicated potential effects and ecotoxicity concerns of synthetic musks [154], this type of compounds have been used as an essential ingredient in PPCPs and household products hugely, at the concentrations of several thousands of μg/g [155]. Without being aware of the potential harm in the past, synthetic musk has been ubiquitously spread out in the environment. Especially HHCB and ATHN has been detected worldwide in the air[28, 156], water[42], sediment[8, 103, 145], and animals[57, 107, 157]. These compounds have been reported in various countries and areas as well, such as Europe, USA, and Asia [20, 48-50, 153, 158-162]. In Taiwan, there haven’t been many groups working on the synthetic musks evaluation. However, Ding and his team reported the occurrence of synthetic musks in the environments regarding to the sampling methods they developed, which enhance the efficiency and accuracy of sampling and analyzing synthetic musks. According to his research, the synthetic musks varied up to10.8 ng/g in the fish [163], 5.9 ng/g in the sediment, 2.8 ng/g in the sludge[164], 2.7 ng/g in the oysters[165], 63.9 ng/L in the aqueous samples[166], 140 ng/L surface water[167]. The synthetic musk concentration in the air hasn't been involved in any published paper and reports in Taiwan so far. Our study has presented the concentration of airborne synthetic musks in a few indoor working environments. Meanwhile, our sampling methodology of synthetic musks could be widely applied onto any studies of evaluating airborne synthetic musks. As for the analysis methodology, we have proved that the specific MRM pairs could be employed not only on the PUF/Filter samples, but also onto liquid samples. This methodology absolutely could lift the productivity and the efficiency without worry of too much sample preparation which might cause a lot of loss of target compounds during the procedure. The collecting efficiency of sampling in this study is 64%-120%. The recovery of the extraction and concentration is 64%-122%.

As for comparison to other studies of studying MDLs of processing synthetic musk samples, some of our data is obviously higher than any other reported values. This phenomenon could result from that the sensitivity and the lower detection limits have been achieved in this study. Take MDLs of sample preparation procedure for instance, our MDLs reported as 0.02-0.2 ng mL^{-1}, is at least equal or better than a few reported values 0.01-0.03 ng mL^{-1}[168], 4 – 25 ng L^{-1}[140], 6 – 84 ng L^{-1}[169], 1 – 66.7 ng L^{-1} [14]. However, based on the PUF sampling methods, gas chromatography with mass spectrometer as well as indoor air, our result shows that 0.48 ng m^{-3} (in terms of

Cashmeran) can be determined when sampling at 3.5 L min^{-1} for 8 hours, which is much better than the other similar designed reported MDL, 10 ng m^{-3} [147, 149].

By far, there is no guideline or exposure limits to indoor air quality or occupational environment. As can be seen in our result, particulate-HHCB and particulate-AHTN as well as DPMI, ADBI, and AHMI in both gas phase and particle phase are with higher concentration than those values reported by Chen et al. Compared to either indoor or outdoor air, our data is remarkably higher.

Chapter 5 Conclusion

Synthetic musk is ubiquitous in the environment worldwide. It is relatively cheap, easy to make, capable to create a variety of scent. Therefore, they have been widely used in many consumer products and pharmaceutical and personal care products (PPCPs). In terms of the demand of monitoring the synthetic musks in the environment, this research developed a highly sensitive and widely applicable method for the determinations of airborne synthetic musk. PUF and filter were employed for active air sampling of synthetic musks. MAE and nitrogen evaporator were performed for sample preparation. GC-MS/MS with specific MRM transition pairs was applied for sample analysis. Compared with using SIM mode traditionally, the sensitivities were improved about an order at least. In terms of air concentration, as low as 0.48 ng m^{-3} can be determined when sampling at 3.5 L min^{-1} for 8 hours. The MRM transition pairs found in this research, as well as the instrumental conditions established, can be applied to examine the contents of synthetic musks in other forms of sample matrix. Obviously, the combination of the sampling device, MAE & nitrogen evaporation, and well-defined chemical analysis by GC-MS/MS is highly recommended in the application of evaluating the indoor airborne synthetic musks on various sites.

Regarding to the potential toxicity, massive usage, and omnipresence of synthetic musks this group of compounds has drawn the concern of public. Indeed, there has been always a demand to determine the concentration of synthetic musks in various media as well as the exposure and impact to human beings and environment. Our result shows the developed methodology could be extensively used onto a variety of sample matrix, especially onto air samples. In the mean time, our result also indicated HHCB is very commonly seen with high concentration compared to other synthetic musk compounds. Studies reported have observed that synthetic musk could be detected in consumer products, effluents, sewage, sediment, air, biota, animals, and human beings. The exposure routes include oral intake, dermal exposure, and inhalation. The most discussed way of exposure is through skin contact since the musk-containing products are usually in liquid forms. Besides, inhalation might be very critical because some investigations showed that airborne synthetic musk was ubiquitous over a wide variety of public places, occupational settings, and homes. Our method could specify the airborne synthetic musk in occupational settings and the synthetic musks in the commercial fragrances although the matrix was complicated.

There is still limitation in this study. To be specified, PUF is a kind of whole air sampling media. Various volatile and semi-volatile organic compounds other than synthetic musks can also be adsorbed simultaneously. Hence, the determination is challenging, since the capacity and selectivity of the method might cause concerns. In other words, PUF is rather not specific to certain compounds. However, this defeat could be made up by MRM transition pairs. Further, MRM transition pairs for chemicals should be developed, especially in the field of environmental science. On the other hand, the reason we chose traditional nitrogen evaporation of the sample concentration instead of auto-NO_2-evaporator (TurboVap) and rotary concentration since our experience showed that more loss happened during these two types of concentrators. Also the low temperature that traditional nitrogen evaporator can achieve could keep the SVOCs non-volatile and stay in the extraction solutions although the tradeoff is time-consumption.

Another limitation occurred in this study was that there is no appropriate surrogates for synthetic musks. With regards to the use of surrogates might bring relatively convincible information, there is the need for further discovery of finding proper surrogates and their applicable MRM ion pairs in the future instead of the current commercial deuterated musk xylene and AHTN standards which have been proved to lead inaccurate surrogate recoveries.

In addition, the particle size cut-off measuring is one of the flaws of this study, because there are certainly more and more discussion and research interests raised on the spotlight of PM2.5. Unfortunately, regarding to the research on airborne synthetic musk, to the best of authors' knowledge, all the available studies on particle phase of airborne musks discussed the concentrations without the concerns on size distributions. In this case, we would like to focus more on the correlation of particle size and embedded synthetic musks. To provide more detailed information, we will consider applying a size-selective impactor inlet to exclude non-respirable airborne particulate matter for future study.

So far, there is none of studies reporting the occurrence of airborne synthetic musk in Taiwan. This study is preliminary to open a new perspective of indoor air quality regarding to PPCPs. Although we only accomplished some parts of the synthetic musk indoor air scenario in the cosmetics and scent-relevant working environments. Our aim is to target more microenvironments in order to understand how synthetic musk distribute and act with other compounds in the indoor air. On the other hand, none of guideline towards synthetic musk indoors and in the occupational settings has been established yet. This study gave a few useful details to look into the occupational health in specific industry where massive usage of synthetic musks has been applied and indoor environments. Regarding to the fact that synthetic musks could be one of the factors to induce the incidence of asthma and other allergy, without appropriate ventilation and personal protection, workers and inhabitants indoors might suffer from adverse impacts caused by synthetic musks readily and long-term wise.

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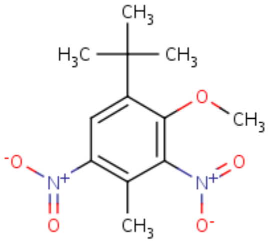
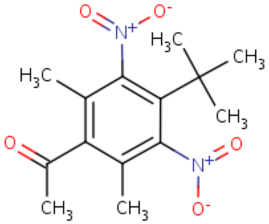
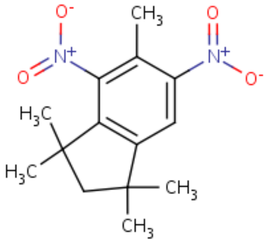
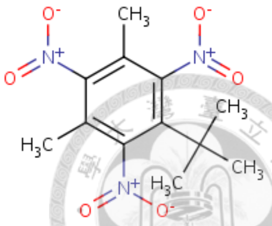
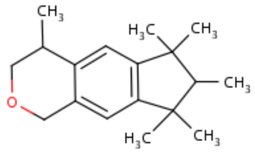
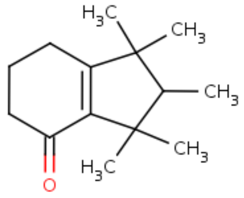
Table 1 Annual Global Use of Nitro and Polycyclic musk fragrances

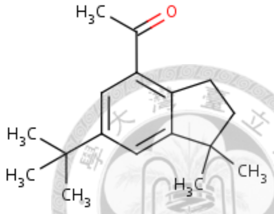
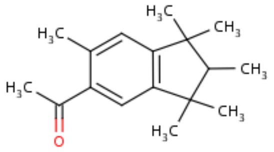
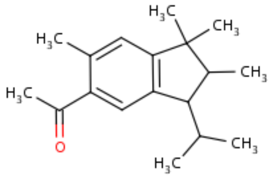
	Nitro-musk fragrances	Polycyclic musk fragrances
1987	2,450	4,300
1996	2,000	5,600
2000	800	10,000

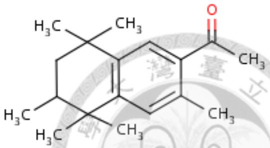
Reference [8](in tones)

Table 2 Physico-chemical properties of the synthetic compounds studied

Compound Name	**Synonyms**	**CAS number**	**Molecular Formula**	**Molecular Weight**	**Vapor Pressure (mmHg)@25° C**	**log K_{ow}**	**Structure**
Nitro-musk							
Musk Ambrette (MA)	2,6 -Dinitro-3-methoxy-4-tert-butyltoluene 6-tert-butyl-3-methyl-2,4-dinitro anisole	83-66-9	$C_{12}H_{16}N_2O_5$	268.265	1.31×10^{-5}	4.0	
Musk Ketone	Acetophenone, 4'-tert-butyl-2',6'-dimethyl-3',5'-dinitro- 2-Acetyl-5-tert-butyl-4,6-dinitroxylene 1-(4-(1,1-Dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl) ethanone Ethanone, 1-(4-(1,1-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl)-	81-14-1	$C_{14}H_{18}N_2O_5$	294.303	5.84×10^{-7}	4.30	
Musk Moskene	4,6-Dinitro-1,1,3,3,5-pentamethylindan 1H-Indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6-dinitro-; 1,1,3,3,5-Pentamethyl-4,6-dinitroindane 1,1,3,3,5-Pentamethyl-4,6-dinitro-2h-indene	116-66-5	$C_{14}H_{18}N_2O_4$	278.303	8.4×10^{-5}	5.8	

Musk Xylene	Benzene, 1-tert-butyl-3,5-dimethyl-2,4,6-trinitro- 5-tert-butyl-2,4,6-trinitroxylene 5-tert-butyl-2,4,6-trinitro-m-xylene 2,4,6-Trinitro-1,3-dimethyl-5-tert-butylbenzene 2,4,6-Trinitro-3,5-dimethyl-tert-butylbenzene	81-14-1	$C_{12}H_{15}N_3O_6$	297.263	6.35×10^{-7}	4.4	
Polycyclic Musk							
Galaxolide **HHCB**	1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8,-hexamethyl-cyclopenta[g] 2-benzopyran Cyclopenta[g]-2-benzopyran, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl- Hexahydrohexamethyl cyclopentabenzopyran Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]2- benzopyran 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylindeno(5,6- c)pyran	1222-05-5	$C_{18}H_{26}O$	258.44	5.45×10^{-4}	5.9	
Cashmeran **DPMI**	6,7-Dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone 6,7-Dihydro-1,1,2,3,3-pentamethyl-4-(5H)indanone 1,2,3,5,6,7-Hexahydro-1,1,2,3,3-pentamethyl-4H-inden-4-one 4H-Inden-4-one, 1,2,3,5,6,7-hexahydro-1,1,2,3,3-pentamethyl-	33704-61-9	$C_{14}H_{22}O$	206.32	0.003	4.9	

Celestolide **ADBI**	1-(6-tert-butyl-1,1-dimethyl-2,3-dihydroinden-4-yl)ethanone 4-Acetyl-6-*tert*-butyl-1,1-dimethylindan 1-[6-(tert-butyl)-1,1-dimethyl-2,3-dihydro-1h-inden-4-yl]ethan-1-one 1-(6-tert-butyl-1,1-dimethyl-indan-4-yl)-ethanone 4-Acetyl-6-tertiary butyl-1,1-dimethyl indane 1-(6-tert-butyl-1,1-dimethyl-2,3-dihydro-1h-inden-4-yl)ethanone 4-Acetyl-6-tert-butyl-1,1-dimethylindane	13171-00-1	$C_{17}H_{24}O$	244.37	6.52×10^{-4}	6.6	
Phantolide **AHMI**	1-(1,1,2,3,3,6-Hexamethyl-indan-5-yl)-ethanone 1-(Dihydro-1,1,2,3,3,6-hexamethyl-1h-inden-5-yl)-ethanone;ahmi;phantolide;phantolid(r) 1-(2,3-Dihydro-1,1,2,3,3,6-hexamethyl-1h-inden-5-yl)-ethanone	15323-35-0	$C_{17}H_{24}O$	244.376	1.11×10^{-4}	6.7	
Trasolide **ATII**	5-Acetyl-3-isopropyl-1,1,2,6-tetramethylindane 1-(2,3-Dihydro-1,1,2,6-tetramethyl-3-(1-methylethyl)-1h-inden-5-yl)ethan-1-one ethanone	68140-48-7	$C_{18}H_{26}O$	258.404	4.5×10^{-5}	6.3	

Tonalide **AHTN**	2'-acetonaphtone, 5,'6',7',8'-tetrahydro-3',5',5',6',8',8'-hexamethyl- 6-acetyl-1,1,2,4,4,7-hexamethyltetraline Ethanone, 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-napthalenyl)- 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2- naphthyl)ethan-1-one	21145-77-7	$C_{18}H_{26}O$	258.4	5.12×10^{-4}	5.7	

Reference [4, 14, 24, 26, 58, 140, 141, 147, 170]

Table 3 Recent HHCB and AHTN concentrations in wildlife

Species	Tissue	Location	Year	*N*	HHCB	AHTN	Ref.
Fish							
Atlantic salmon	Skin-on filet	New York	2003	6	<1–3.2	<1–1.6	[171]
Smallmouth bass	Liver	New York	2003	3	4.3–5.4	1.6–1.9	[171]
Hammerhead shark	Blubber	Japan	2004	5	16–48	< 9.1	[172]
Eel	Filet	Germany	1996 –1997	165	< 30– 4800	< 20 – 2300	[29]
Carp	Whole	Nevada	2000 – 2001	12^{a}	1.4 – 4.5	1.4 –3.6	[173]
Thornback ray	Filet	Norway	1999	1	8.3	0.77	[174]
Thornback ray	Liver	Norway	1999	1	0.63	1.2	[174]
Haddock	Filet	Norway	1999	2	1.5 – 1.7	1.1 – 1.8	[174]
Haddock	Liver	Norway	1999	3	47 – 250	10 – 23	[174]
Atlantic cod	Filet	Norway	1999	3	0.14 – 0.51	0.073 – 0.24	[174]

Atlantic cod	Liver	Norway	1997–1999	13	2.4–530	0.92–760	[174]
Saithe	Filet	Norway	1999	1^{b}	5.2	2.1	[174]
Saithe	Liver	Norway	1999	1	2.6	0.37	[174]
Farmed trout	Filet	Denmark	1999	50	<0.52–53	0.44–16	[175]
Farmed trout	Filet	Denmark	2003–2004	87	<0.52–28	<0.61–7.5	[175]
Birds							[171]
Common merganser	Liver	New York	1999	2	3.7–4.2	1.6–1.7	
Greater and lesser scaup	Liver	New York	1995–1999	2	1.9–2.7	1.0–1.1	[171]
Mallard	Liver	New York	1995	1	2.7	1.1	[171]
Mammals Finless porpoise	Blubber	Japan	1999–2002	9	13–150	o9.1–9.6	[172]
Polar bear	Liver	Alaska	1997–2000	5	< 1	< 1	[171]
Sea otter	Liver	California	1993–1999	8	< 1 –3.2	< 1	[171]
Harbor seal	Liver	California	1996–1997	3	4.4–5.5	< 1 –2.3	[171]

California sea lion	Liver	California	1993–1996	3	1.5–4.4	< 1 – 2	[171]
River otter	Liver	Michigan	1997	3	2.4–3.0	< 1 – 1.2	[171]
Bottlenose dolphin	Blubber	Florida	1994–2000	4	4.2–21	NA	[171]
Striped dolphin	Blubber	Florida	1995–1997	3	8.1–25	NA	[171]
Pygmy sperm whale	Blubber	Florida	2000	1	6.6	< 1	[171]
Atlantic sharpnose dolphin	Liver	Florida	2004	3	4.6–5.2	1.4–1.7	[171]
Mink	Liver	Illinois	1997	4	2.2–5.3	1.1–2.7	[171]

(ng g^{-1} wet mass)

Table 4 The synthetic musks in human breast milk

Locations	Survey Time	n	Statistic	HHCB	AHTN	ADBI	ATII	MX	MK	References
China	2006 – 2007	110	Median	63	5	–	–	17	4	[49]
			Range	<5 – 782	<5 – 139	–	–	<5 – 198	<4 – 105	
			Detection Ratio	99%	75%	–	–	83%	60%	
Japan	2006 – 2008	20	Range	<50 – 440	<50 – 190	—	—	—	—	[115]
			Detection Ratio	60%	30%	—	—	—	—	
Germany	1995	55	Mean	—	—	—	—	41	10	[117]
			Detection Ratio	—	—	—	—	100%	87%	
Germany	1996	5	Median	37	22	6	N.D.	30	10	[113]
			Range	16 – 108	11 – 158	1 – 18	—	10 – 30	5 – 15	
			Detection Ratio	100%	100%	100%	0%	100%	100%	
Germany	1997 – 1998	40	Median	64	22	1.6	1.5	6.1	4.6	[52]
			Range	21 – 1316	16 – 148	1.0 – 14.1	1.1 – 51.3	1.3 – 47.9	2.1 – 82.9	
			Detection Ratio	88%	33%	38%	25%	95%	45%	
Germany	2005	39	Median	—	—	—	—	8	N.D.	[176]
			Range	—	—	—	—	<LOQ – 240	<LOQ – 6	
			Detection Ratio	—	—	—	—	21%	8%	

Sweden	2000 – 2003	101	Median	63.9	10.4	<2.0	<3.0	9.5	<5.0	[110]
			Range	2.8 – 268.0	<3.0 – 53.0	<2.0 – 11.0	<3.0 – 12.6	<6.0 – 83.9	<5.0 – 24.4	
			N < LOQ	0	26	75	77	33	83	
Demark	1999	10	Median	147	17.5	5.98	<0.22	<3.1	<5.0	[175]
			Range	38.0 – 422	5.58 – 37.9	<0.39 – 11.2	<0.22 – 2.58	<3.1 – 46.4	<5.0 – 26.9	
USA	2004	38	Median	220	46.8	–	–	30.0	74.5	[112]
			Range	<5 – 917	<5 – 144	–	–	<2 – 150	<2 – 238	
			Detection Ratio	97%	56%	–	–	36%	85%	

(ng g^{-1} lipid)
N.D.: Not Detected

Table 5 Sample list and concentration values for the Norwegian air samples

	Musk Method (pg/m^3)											
Sample no.	A		B		C		D		E		F	
Sample type	Ambient air		Ambient air		Ambient air		Ambient air		Indoor air		Blank	
Sample volume (m^3)	1110		907		1020		1190.5		108		-	
Sample period	18-20 Nov. 1998		7-9 Dec. 1998		9-11 Dec. 1998		15-17 Dec. 1989		17-20 Dec. 1998		20 Dec. 1998	
Ionization	NICI	EI	NICI	EI	NICI	EI	NICI	EI	NICI	EI	NICI	EI
MX	17	46	35	64	17	20	23	54	530	500	4	6
MK	6	7	24	45	5	4	6	4	120	110	1	2
AHTN	Int	44	30.7	76	76	41	110	46	1110	600	<dl	4
HHCB	Int	130	676	223	116	110	105	116	4790	2470	<dl	15
ATII	-	10		15		19		6	-	430	-	1

Int: Interference
dl: detection limit

Table 6 First Indoor Air Synthetic Musks Measuring Report on Different Sites in Norway
Sampling sites, sample volumes and concentration levels determined during the first indoor air synthetic musk measuring campaign in Norway

Sample	Sampling Location	Site Status	Volume (m^3)	ATII	AHTN	HHCB	MX	MK
Laboratory (1998)	Norwegian Institute for Air Research	Restricted Access	108	0.4	0.6	2.5	0.5	0.1
Laboratory (1999)	Norwegian Institute for Air Research	Restricted Access	70.47	0.3	1.9	5.6	0.3	0.1
Rest Facilities	Norwegian Institute for Air Research	Accessible for all employees	76.12	0.8	5.8	19.0	0.6	0.2
Hair Dresser	Downtown of Kjeller	Public Accessible	36.27	5.2	13.4	44.3	1.0	0.3
Toilet	Norwegian Institute for Air Research	Accessible for all employees	77.4	0.8	6.2	18.9	0.4	0.1
Cafeteria	Norwegian Institute for Air Research	Accessible for all employees	81.89	4.8	11.6	35.3	N.D.	N.D.
Method Blank	–	–	Cal. for 100	0.001	0.1	0.3	0.005	0.001

(ng m^{-3})
N.D.: Not Detected

Table 7 Concentrations of polycyclic musks in air of the cosmetic plant and its surroundings

Sampling Locations	TH (Upwind direction, about 25 km away from the cosmetic plant)		OD (Downwind direction, about 200 m away from the cosmetic plant)		M (Out of the workshop of the cosmetic plant)		ID (In the workshop of the cosmetic plant)	
Synthetic Musk Compounds	Particulate-phase	Gas-phase	Particulate-phase	Gas-phase	Particulate-phase	Gas-phase	Particulate-phase	Gas-phase
DPMI	-	0.32±0.17	-	0.55±0.26	1.32±0.17	1.31±0.60	2.55±1.09	119.20±40.43
ADBI	-	0.24±0.25	-	0.31±0.22	0.35±0.23	0.50±0.26	0.84±0.36	34.45±9.50
AHMI	-	-	-	-	-	0.23±0.24	0.83±0.26	32.63±10.16
HHCB	0.87±0.13	2.14±0.97	1.16±0.18	11.52±3.01	3.36±1.04	88.32±28.78	100.46±30.81	4504.97±941.10
AHTN	0.85±0.05	1.01±0.40	1.19±0.18	2.51±0.73	1.25±0.19	22.07±11.14	22.61±9.84	724.82±143.07
Sum	1.71±0.16	3.72±1.49	2.35±0.25	14.89±3.24	6.39±1.35	108.43±39.30	127.40±41.12	5416.07±1079.11

(ng m^{-3})

Table 8 Overview of typical procedure for the determination of synthetic musk fragrances in the air

Synthetic musk compounds	Sampling Media	Sample preparation (Extraction)	Analysis	Column	Recovery (%)	MDL (pg m^{-3})	Ref.
MK, MX, AHTN, ATII, HHCB	PUF and GFF	Hexane/diethyl ether (9:1, v/v)	GC–MS-NCI/EI	DB-5MS (30 m × 0.25 mm, 0.2 μm) Ultra 2 (25 m × 0.2 mm, 0.11 μm)	>80	Polycyclic musks: 20–50 (NCI), 5–10 (EI) Nitro musks: 0.2–0.5 (NCI), 6–12 (EI)	[120]
MK, MX, HHCB, ADBI, AHMI, AHTN, ATII, DPMI	XAD-2 and GFF	Hexane/acetone (1:1, v/v)	GC–MS-EI	HP5-MS (30 m × 0.25 mm, 0.25 μm)	56–86	–	[122, 123]
AHTN and HHCB	PUF/XAD-2 and GFF	Hexane/diethyl ether (4:1, v/v) for PUF/XAD-2 DCM for GFF	GC–MS-EI	HP5-MS (30 m × 0.25 mm, 0.25 μm)	94–114	3000 – 965,000	[149]
MK, ADBI, AHMI, AHTN, ATII, HHCB	PUF	Hexane/diethyl ether (9:1, v/v)	GC–MS-EI	HP5-MS (30 m × 0.25 mm, 0.25 μm)	91–100	10,000	[97]
DPMI, ADBI, AHMI, ATII, HHCB, AHTN	PUF and GFF	DCM	GC–MS-EI	HP-5 (30 m × 0.32 mm, 0.25 μm)	57–108	–	[124]
MA, MK, MM, MX, ADBI, AHMI, AHTN, ATII, DPMI, HHCB	PUF and GFF	Cyclohexane/acetone (1:1, v/v)	GC-MS/MS EI	DB-5MS (30 m × 0.25 mm, 0.2 μm)	64 – 111	480 (based on 8 hrs sampling)	

Table 9 Comparisons of microwave-assisted extraction (MAE), soxhlet extraction (SE)

	Recovery (RSD%)	LOD (μg/kg)	LOQ (μg/kg)	R^2	RRTs (RSD%)	Solution (mL)	Time
MAE							
HHCB	88 (5)	0.4	1.6	0.92	18.33 (0.5)	30	20 mins
AHTN	94 (5)	0.6	2.5	0.92	18.44 (0.5)	30	20 mins
Soxhlet							
HHCB	102 (5)	0.3	0.8	0.94	18.33 (0.4)	150	24 hours
AHTN	88 (4)	0.3	1.0	0.94	18.44 (0.4)	150	24 hours

Table 10 Recoveries of different temperature, duration, and time of MAE

Synthetic musk compound	MA		MK		MM		MX		HHCB	
	Conc.	EE %	Conc.	EE %	Conc.	EE %	Conc.	EE %	Conc.	EE %
0.2 μg/mL standard mixture (Direct analysis)	0.15		0.15		0.15		0.15		0.17	
1 ml of 0.2 μg/mL standard mixture spike										
PUF 100°C for 60 mins	0.21	139%	0.28	184%	0.17	111%	0.16	103%	0.17	95%
Filter 100°C for 60 mins	0.12	80%	0.16	107%	0.12	76%	0.11	72%	0.15	87%
PUF 85°C for 30mins	0.18	119%	0.23	151%	0.16	101%	0.15	97%	0.20	113%
Filter 85°C for 30mins	0.14	91%	0.17	110%	0.13	84%	0.13	85%	0.16	91%
PUF 85°C for 60mins	0.17	116%	0.22	114%	0.15	99%	0.15	96%	0.16	92%
Filter 85°C for 60mins	0.13	83%	0.18	116%	0.12	79%	0.12	75%	0.16	94%
PUF 85°C for 60mins, 2nd extraction	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
Filter 85°C for 60mins, 2nd extraction	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

Synthetic musk compound	DPMI		ADBI		AHMI		ATII		AHTN	
	Conc.	EE %	Conc.	EE %	Conc.	EE %	Conc.	EE %	Conc.	EE %
0.2 μg/mL standard mixture (Direct analysis)	0.19		0.17		0.17		0.16		0.18	
1 ml of 0.2 μg/mL standard mixture spike										
PUF 100°C for 60 mins	0.14	73%	0.22	128%	0.20	118%	0.23	142%	0.23	128%
Filter 100°C for 60 mins	0.12	62%	0.18	102%	0.17	97%	0.18	111%	0.16	90%
PUF 85°C for 30mins	0.12	63%	0.19	113%	0.18	104%	0.20	123%	0.19	108%
Filter 85°C for 30mins	0.13	66%	0.18	106%	0.17	101%	0.18	112%	0.16	92%
PUF 85°C for 60mins	0.12	64%	0.19	111%	0.18	103%	0.20	122%	0.20	115%
Filter 85°C for 60mins	0.13	67%	0.19	108%	0.18	103%	0.19	118%	0.17	96%
PUF 85°C for 60mins, 2nd	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

extraction										
Filter 85°C for 60mins, 2nd extraction	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

(conc.: µg/mL)

EE %: Extraction Efficiency

N.D.: Not Detected

Table 11 Summary of Five sampling sites

Plant A (Cosmetics)						
Sampler number and material	A1PUF+ A1Filter	A2PUF+ A2Filter	A3PUF+ A3Filter			
Sampling Spot	Filling Room	Manufacturing Room	Laboratory			
Sampling Flow rate	3500 cc/min	3500 cc/min	3500 cc/min			
Sampling Duration	483 mins	477 mins	477 mins			
Sampling Volume	1690 L	1669 L	1669 L			
PlantB (Cosmetics)						
Sampler number and material	B1PUF+ B1Filter	B1aPUF+ B1aFilter	B1bPUF*	B2PUF+ B2Filter	B3PUF+ B3Filter	B4PUF+ B4Filter
Sampling Spot	The largest manufacturing tank area (Scented lotion)	The largest manufacturing tank area (Scented lotion)	The largest manufacturing tank area (Scented lotion)	Manufacturing tank area (non-scented lotion)	Manufacturing tank area (highly viscous products)	Storage room (Semi-finished products)
Sampling Flow rate	3500 cc/min	3500 cc/min	3500 cc/min	3500 cc/min	3500 cc/min	3500 cc/min
Sampling Duration	488 mins	484 mins	484 mins	393 mins	484mins	482 mins
Sampling Volume	1708 L	1694 L	1694 L	1375 L	1694 L	1687 L
Plant C (Cosmetics)						
Sampler number and material	C1PUF + C1Filter	C2PUF + C2Filter	C3PUF+ C3Filter	C4PUF+ C4Filter	C5PUF+	C6PUF+ C6Filter
Sampling Spot	Manufacturing room (Emulsification)	Storage room (liquids)	Storage room (semi-finished products)	Filling room	Semi-opened filling room (wash-type products)	Storage room (semi-finished wash-type products)
Sampling Flow rate	3500 cc/min	3500 cc/min	3500 cc/min	3500 cc/min	3500 cc/min	3500 cc/min
Sampling Duration	410 mins	415 mins	417 mins	157 mins **	213mins	410 mins
Sampling Volume	1435 L	1451 L	1459 L	549 L	745 L	1435 L
Plant D (Cosmetics)						
Sampler number and material	D1PUF+ D1Filter	D2PUF + D2Filter	D3PUF*			
Sampling Spot	Filling room (Scented bag) Entrance	Filling room (Scented bag)	Filling Room (Scented bag)			
Sampling	3500 cc/min	3500 cc/min	3500 cc/min			

Flow rate						
Sampling Duration	458 mins	392mins**	392mins**			
Sampling Volume	1602 L	1370 L	1370 L			
Plant E (Household)						
Sampler number and material	E1PUF+ E1Filter	E2PUF+ E2Filter	E3PUF+ E3Filter	E4PUF+ E4Filter	E5PUF+ E5Filter	E6PUF+ E6Filter
Sampling Spot	Storage Room (Raw synthetic musk material)	Filling site I (laundry detergent)	Filling site II (laundry detergent)	Manufacturing site I (laundry detergent)	Manufacturing site II (laundry detergent)	Storage room (Raw materials)
Sampling Flow rate	3500 cc/min	3500 cc/min	3500 cc/min	3500 cc/min	3500 cc/min	3500 cc/min
Sampling Duration	188 mins	430 mins	429 mins	439 mins	431mins	420 mins
Sampling Volume	658 L	1505 L	1501 L	1535 L	1507 L	1470 L

*Tandem PUF for testing breakthrough (Data wasn’t shown in this study)；

**Pumps shutdown because of huge amount of particulate matters；

Note: Without sample storage test. All samples were extracted right after delivering back to office at the same day.

Table 12 Identification of 21 commercially available fragrances

	Nitro-musk				Polycyclic Musk					
Commercial Fragrance	Musk Ambrette (MA)	Musk Ketone (MK)	Musk Moskene (MM)	Musk Xylene (MX)	Galaxolide (HHCB)	Cashmeran (DPMI)	Celestolide (ADBI)	Phantolide (AHMI)	Traseolide (ATII)	Tonalide (AHTN)
Musky										
While Musk A	N.D.	N.D.	N.D.	N.D.	✓	✓	✓	✓	N.D.	✓
White Musk B	N.D.	N.D.	✓	N.D.	✓	✓	✓	✓	✓	✓
White Musk C	N.D.	✓	✓	✓	✓	✓	✓	N.D.	✓	✓
White Musk D	N.D.	✓	✓	✓	✓	✓	✓	✓	N.D.	✓
Musk	✓	✓	✓	N.D.	✓	✓	✓	✓	✓	✓
Rose Musk	N.D.	N.D.	N.D.	N.D.	✓	N.D.	N.D.	N.D.	N.D.	✓
Flowery										
Ginger Lily A	N.D.	✓	N.D.	N.D.	✓	✓	✓	✓	N.D.	✓
Ginger Lily B	N.D.	N.D.	N.D.	N.D.	✓	✓	N.D.	✓	N.D.	✓
Jasmine	N.D.	N.D.	N.D.	✓	✓	N.D.	N.D.	N.D.	N.D.	✓
Lily	N.D.	N.D.	N.D.	N.D.	✓	✓	✓	N.D.	✓	✓
Osmanthus	N.D.	✓	N.D.	✓	✓	N.D.	N.D.	✓	N.D.	✓
Rose Queen	N.D.	N.D.	N.D.	N.D.	✓	✓	N.D.	N.D.	N.D.	✓
Tuberose	N.D.	N.D.	N.D.	N.D.	✓	N.D.	✓	✓	N.D.	✓
Sakura	N.D.	N.D.	N.D.	N.D.	✓	✓	✓	✓	✓	✓
Lavender	N.D.	N.D.	N.D.	N.D.	✓	✓	N.D.	✓	✓	✓
Fruity										
Green Apple	N.D.	N.D.	N.D.	N.D.	✓	N.D.	N.D.	✓	✓	✓

	Nitro-musk				Polycyclic Musk					
Commercial Fragrance	Musk Ambrette (MA)	Musk Ketone (MK)	Musk Moskene (MM)	Musk Xylene (MX)	Galaxolide (HHCB)	Cashmeran (DPMI)	Celestolide (ADBI)	Phantolide (AHMI)	Traseolide (ATII)	Tonalide (AHTN)
<u>Woody</u>										
Sandal wood	N.D.	N.D.	✓	N.D.	N.D.	N.D.	✓	N.D.	N.D.	✓
Coffee	N.D.	✓	N.D.	N.D.	✓	N.D.	N.D.	N.D.	N.D.	✓
Green Tea	✓	N.D.	N.D.	N.D.	✓	✓	✓	✓	✓	✓
<u>Other</u>										
Man’s Ocean	N.D.	✓	✓	N.D.	✓	N.D.	✓	✓	✓	✓
Baby Peach	N.D.	N.D.	N.D.	N.D.	✓	✓	✓	✓	N.D.	✓

N.D.: Not Detected

Table 13 Analysis conditions of target compounds by gas chromatography coupled with triple quadrupole tandem mass spectrometer (GC-MS/MS)

Synthetic musk Compound	**Reference GC-MS detection ions [6, 106]**	**Reference MRM transitions (collision energy) [51]**	**Reference Method Detection Limit (MDL), ng mL^{-1} [6]**	**MRM transitions of this study**	**Collision Energy (eV)**	**Method Detection Limit (MDL), ng mL^{-1}**
Cashmeran	135,191,163,		0.48	191→135*	10	0.03
(DPMI)	206			206→163	10	
Celestolide	173,229,244	244→229 (5)	0.20	244→229*	10	0.02
(ADBI)		229→130(20)		244→173	15	
Phantolide	145,187,229,244	244→229 (8)	0.19	244→229*	5	0.02
(AHMI)		229→145 (20)		229→187	5	
Musk	91,251,253	268→253 (15)	1.0	268→253*	5	0.05
Ambrette (MA)		253→106 (18)		253→106	5	
Trasolide	131,173,215	258→215 (5)	0.25	258→215*	5	0.02
(ATII)		215→131 (20)		215→173	5	
Galaxolide	171,213,243,	258→243 (5)	0.21	243→213*	5	0.10
(HHCB)	258	243→143 (20)		258→243	5	
Musk Xylene	43,282,297	297→282 (5)	1.1	282→265*	5	0.31
(MX)		282→91 (25)		297→282	5	
Tonalide	243,258,282,297	258→243 (5)	0.27	243→187*	5	0.03
(AHTN)		243→159 (15)		243→201	5	
Musk Moskene	263,264,278	278→263 (5)	0.23	263→221*	10	0.20
(MM)		263→156 (25)		278→263	5	
Musk Ketone	279,280,294	279→117 (5)	0.88	279→191*	10	0.05
(MK)		294→279 (23)		279→117	35	

* Quantifier pair

Table 14 Collection efficiency (%) of active low volume PUF and glass filter sampling with different flow rates (1 mL 0.2 μg mL^{-1} standards in a impinger with flow rate of 3.5, 2, and 1 L min^{-1}.)

	ADBI	AHMI	AHTN	ATII	DPMI	HHCB	MA	MK	MM	MX
1 mL 10-synthetic-musk-standard mixture of 0.2 μg/mL Flow rate of pump: 3.5 L/min										
Total collection efficiency（PUF A+B +Filter）	105%	93%	96%	108%	64%	111%	78%	120%	67%	64%
Collection efficiency of PUF A+Filter）	76%	67%	68%	77%	64%	79%	78%	120%	67%	64%
Collection efficiency of PUF (A)	47%	41%	50%	45%	49%	68%	78%	61%	67%	64%
Collection efficiency of filter	29%	26%	18%	32%	15%	10%	N.D.	59%	N.D.	N.D.
1 mL 10-synthetic-musk-standard mixture of 0.2 μg/mL Flow rate of pump: 2 L/min										
Total collection efficiency（PUF A+B +Filter）	91%	56%	67%	97%	27%	111%	74%	117%	64%	61%
Collection efficiency of PUF A+Filter）	62%	56%	44%	66%	14%	61%	74%	117%	64%	61%
Collection efficiency of PUF (A)	33%	30%	26%	34%	11%	51%	74%	59%	64%	61%
Collection efficiency of filter	29%	26%	18%	32%	3%	10%	N.D.	59%	N.D.	N.D.
1 mL 10-synthetic-musk-standard mixture of 0.2 μg/mL Flow rate of pump: 1 L/min										
Total collection efficiency（PUF A+B +Filter）	88%	80%	66%	95%	10%	111%	146%	59%	64%	60%
Collection efficiency of PUF A+Filter）	60%	54%	42%	64%	8%	66%	146%	59%	64%	60%
Collection efficiency of PUF (A)	30%	27%	24%	31%	7%	56%	73%	0%	64%	60%
Collection efficiency of filter	30%	27%	19%	32%	1%	10%	73%	59%	N.D.	N.D.

Table 15 Collection efficiency (%) of active low volume PUF and glass filter sampling with flow rate 3.5 L min^{-1}
(1 mL 0.2 μg mL^{-1} standards in a impinger with flow rate of 3.5 L min^{-1}.)

	Celestolide ADBI	Phantolide AHMI	Tonalide AHTN	Traseolide ATII	Cashmeran DPMI	Galaxolide HHCB	Musk Ambrette MA	Musk Ketone MK	Musk Moskene MM	Musk Xylene MX
Collection efficiency of PUF and filter	68.7 ± 2.79	65.2 ± 2.54	62.0 ± 3.57	68.7 ± 3.29	64.1 ± 3.49	65.9 ± 19.03	66.8 ± 7.20	92.68 ± 4.34	67.9 ± 4.34	66.8 ± 2.76
Collection efficiency of PUF	42.1 ± 3.50	39.9 ± 3.25	43.2 ± 3.85	37.1 ± 3.42	49.0 ± 3.97	55.6 ± 19.04	66.8 ± 7.20	41.5 ± 5.75	67.9 ± 4.34	66.8 ± 2.76
Collection efficiency of filter	26.6 ± 0.77	25.3 ± 0.75	18.8 ± 0.56	26.8 ± 0.85	15.6 ± 0.49	10.0 ± 0.36	N.D.	51.2 ± 1.93	N.D.	N.D.

Table 16 Gaseous form of synthetic musk determined in cosmetics plants

Synthetic Musk	ADBI	AHMI	AHTN	ATII	DPMI	HHCB	MA	MK	MM	MX
Plant A										
A1	1.9×10^{2}	2.0×10^{2}	1.9×10^{2}	2.0×10^{2}	N.D.	2.7×10^{2}	2.0×10^{2}	1.1×10^{2}	1.4×10^{2}	N.D.
A2	N.D.	N.D.	1.7×10^{2}	1.9×10^{2}	N.D.	2.0×10^{2}	N.D.	1.1×10^{2}	1.4×10^{2}	N.D.
A3	1.9×10^{2}	N.D.	1.7×10^{2}	2.0×10^{2}	N.D.	2.1×10^{2}	N.D.	1.1×10^{2}	N.D.	N.D.
Plant B										
B1	2.4×10^{2}	N.D.	9.6×10^{2}	N.D.	1.0×10^{3}	1.6×10^{3}	N.D.	1.1×10^{2}	N.D.	N.D.
B2	1.9×10^{2}	2.0×10^{2}	8.0×10^{2}	N.D.	3.7×10^{2}	2.9×10^{3}	N.D.	1.1×10^{2}	N.D.	N.D.
B3	2.3×10^{2}	N.D.	7.3×10^{2}	N.D.	8.6×10^{2}	1.2×10^{3}	N.D.	1.1×10^{2}	N.D.	N.D.
B4	3.1×10^{2}	N.D.	7.9×10^{2}	N.D.	4.2×10^{2}	1.2×10^{3}	N.D.	1.4×10^{2}	N.D.	N.D.
B5	2.4×10^{2}	N.D.	6.1×10^{2}	N.D.	5.1×10^{2}	1.0×10^{3}	2.0×10^{2}	1.1×10^{2}	N.D.	N.D.
B6	2.4×10^{2}	N.D.	6.9×10^{2}	N.D.	6.7×10^{2}	1.1×10^{3}	N.D.	1.1×10^{2}	N.D.	N.D.
Plant C										
C1	N.D.	N.D.	1.6×10^{2}	2.0×10^{2}	1.5×10^{2}	1.4×10^{2}	N.D.	1.1×10^{2}	N.D.	N.D.
C2	N.D.	2.3×10^{2}	2.6×10^{2}	N.D.	1.8×10^{2}	4.9×10^{2}	N.D.	1.3×10^{2}	N.D.	N.D.
C3	2.2×10^{2}	N.D.	3.5×10^{2}	N.D.	1.8×10^{2}	8.9×10^{2}	N.D.	1.3×10^{2}	N.D.	N.D.
C4	5.8×10^{2}	6.2×10^{2}	4.5×10^{2}	N.D.	N.D.	2.7×10^{2}	N.D.	N.D.	N.D.	N.D.
C5	4.3×10^{2}	4.6×10^{2}	4.0×10^{2}	N.D.	N.D.	2.7×10^{2}	N.D.	2.5×10^{2}	N.D.	N.D.
C6	N.D.	2.4×10^{2}	2.3×10^{2}	N.D.	N.D.	2.4×10^{2}	N.D.	1.3×10^{2}	N.D.	N.D.
Plant D										
D1	1.2×10^{2}	N.D.	1.3×10^{2}	N.D.	1.8×10^{2}	2.5×10^{2}	N.D.	5.7×10^{1}	8.3×10^{1}	8.4×10^{1}
D2	1.7×10^{2}	N.D.	2.0×10^{2}	N.D.	2.5×10^{2}	3.5×10^{2}	N.D.	6.7×10^{1}	N.D.	1.0×10^{2}
D3	N.D.	7.9×10^{1}	6.5×10^{1}	8.2×10^{1}	N.D.	1.1×10^{2}	N.D.	N.D.	N.D.	N.D.
Plant E										
E1	1.7×10^{2}	1.6×10^{2}	4.2×10^{2}	N.D.	1.5×10^{2}	1.9×10^{3}	N.D.	1.4×10^{2}	N.D.	N.D.
E2	7.5×10^{1}	7.2×10^{1}	3.4×10^{2}	N.D.	3.7×10^{1}	6.8×10^{2}	N.D.	7.0×10^{1}	N.D.	8.8×10^{1}
E3	7.5×10^{1}	7.3×10^{1}	3.1×10^{2}	N.D.	5.0×10^{1}	6.0×10^{2}	N.D.	6.5×10^{1}	N.D.	N.D.
E4	7.3×10^{1}	7.1×10^{1}	5.0×10^{2}	N.D.	5.8×10^{1}	1.5×10^{3}	N.D.	6.8×10^{1}	N.D.	8.6×10^{1}
E5	7.4×10^{1}	7.2×10^{1}	2.6×10^{2}	N.D.	3.4×10^{1}	6.1×10^{2}	N.D.	6.6×10^{1}	N.D.	8.7×10^{1}
E6	7.3×10^{1}	N.D.	1.5×10^{2}	N.D.	2.4×10^{1}	4.0×10^{2}	N.D.	6.3×10^{1}	N.D.	8.9×10^{1}
Maximum	5.8×10^{2}	6.2×10^{2}	9.6×10^{2}	2.0×10^{2}	1.0×10^{3}	2.9×10^{3}	2.0×10^{2}	2.5×10^{2}	1.4×10^{2}	1.0×10^{2}
Minimum*	7.3×10^{1}	7.1×10^{1}	6.5×10^{1}	8.2×10^{1}	2.4×10^{1}	1.1×10^{2}	2.0×10^{2}	5.7×10^{1}	8.3×10^{1}	8.4×10^{1}

Average*	2.0×10^2	2.1×10^2	3.9×10^2	1.7×10^2	3.0×10^2	7.7×10^2	2.0×10^2	1.1×10^2	1.2×10^2	8.9×10^1

(ng m^{-3})
* without counting N.D. values
N.D.: Not Detected

Table 17 Particulate form of synthetic musk determined in cosmetics plants

Synthetic Musk	ADBI	AHMI	AHTN	ATII	DPMI	HHCB	MA	MK	MM	MX
Plant A										
A1	N.D.	N.D.	3.7×10^{2}	N.D.	N.D.	7.8×10^{2}	N.D.	N.D.	N.D.	N.D.
A2	N.D.	N.D.	3.7×10^{2}	N.D.	N.D.	7.7×10^{2}	N.D.	N.D.	N.D.	N.D.
A3	N.D.	N.D.	3.7×10^{2}	N.D.	N.D.	7.9×10^{2}	N.D.	N.D.	N.D.	N.D.
Plant B										
B1	3.0×10^{2}	N.D.	3.7×10^{2}	N.D.	4.4×10^{2}	8.5×10^{2}	N.D.	N.D.	N.D.	N.D.
B2	3.0×10^{2}	N.D.	3.7×10^{2}	N.D.	N.D.	8.4×10^{2}	N.D.	N.D.	N.D.	N.D.
B4	3.7×10^{2}	3.9×10^{2}	4.6×10^{2}	N.D.	N.D.	1.0×10^{3}	N.D.	N.D.	N.D.	N.D.
B5	3.0×10^{2}	N.D.	3.8×10^{2}	N.D.	N.D.	9.0×10^{2}	N.D.	N.D.	N.D.	N.D.
B6	3.0×10^{2}	N.D.	3.7×10^{2}	N.D.	N.D.	8.3×10^{2}	N.D.	N.D.	N.D.	N.D.
Plant C										
C1	N.D.	N.D.	3.7×10^{2}	N.D.	N.D.	7.4×10^{2}	N.D.	N.D.	N.D.	N.D.
C2	N.D.	N.D.	4.3×10^{2}	N.D.	N.D.	8.8×10^{2}	N.D.	N.D.	N.D.	N.D.
C3	N.D.	3.6×10^{2}	4.3×10^{2}	N.D.	N.D.	8.8×10^{2}	N.D.	2.1×10^{2}	N.D.	N.D.
C4	N.D.	9.7×10^{2}	1.1×10^{3}	N.D.	N.D.	2.3×10^{3}	N.D.	N.D.	N.D.	N.D.
C6	N.D.	N.D.	4.3×10^{2}	N.D.	N.D.	8.7×10^{2}	N.D.	2.2×10^{2}	N.D.	N.D.
Plant D										
D1	N.D.	N.D.	1.1×10^{2}	N.D.	N.D.	2.4×10^{2}	N.D.	N.D.	N.D.	N.D.
D2	N.D.	N.D.	1.3×10^{2}	N.D.	N.D.	2.8×10^{2}	N.D.	N.D.	N.D.	N.D.
Plant E										
E1	N.D.	N.D.	2.6×10^{2}	2.5×10^{2}	9.0×10^{2}	6.7×10^{2}	N.D.	N.D.	N.D.	N.D.
E2	N.D.	N.D.	1.1×10^{2}	N.D.	2.2×10^{1}	2.4×10^{2}	N.D.	N.D.	N.D.	N.D.
E3	N.D.	N.D.	1.2×10^{2}	N.D.	5.9×10^{2}	2.6×10^{2}	N.D.	N.D.	N.D.	N.D.
E4	N.D.	N.D.	1.1×10^{2}	N.D.	3.2×10^{2}	2.5×10^{2}	N.D.	N.D.	N.D.	N.D.
E5	N.D.	N.D.	1.1×10^{2}	N.D.	5.2×10^{2}	2.4×10^{2}	N.D.	N.D.	N.D.	N.D.
E6	N.D.	N.D.	1.2×10^{2}	N.D.	6.0×10^{2}	2.4×10^{2}	N.D.	N.D.	N.D.	N.D.
Maximum	3.7×10^{2}	9.7×10^{2}	1.1×10^{3}	2.5×10^{2}	9.0×10^{2}	2.3×10^{3}	N.D.	2.2×10^{2}	N.D.	N.D.
Minimum*	3.0×10^{2}	3.6×10^{2}	1.1×10^{2}	2.5×10^{2}	2.2×10^{1}	2.4×10^{2}	N.D.	2.1×10^{2}	N.D.	N.D.
Average*	3.2×10^{2}	5.7×10^{2}	3.3×10^{2}	2.5×10^{2}	4.8×10^{2}	7.1×10^{2}	N.D.	2.1×10^{2}	N.D.	N.D.

(ng m^{-3})

*N.D. values weren’t counted in.

N.D. Not Detected

Table 18 Comparison between a reference and this study

	Synthetic Musk	
	Gaseous	Particulate
Chen et al. [124]		
HHCB	4504.97 ± 941.10	100.46 ± 30.81
DPMI	119.20 ± 40.43	2.55 ± 1.09*
ADBI	34.45 ± 9.50	0.84 ± 0.36
AHMI	32.63 ± 10.16	0.83 ± 0.26
AHTN	724.82 ± 143.07	22.71 ± 9.84
Plant A		
HHCB	226.61（198.68-274.23）	776.15（767.75-785.23）
DPMI	N.D.	N.D.
ADBI	125.61（N.D.-190.04）	N.D.
AHMI	67.01（N.D.-201.04）	N.D.
AHTN	178.06（168.01-191.89）	368.29（365.23-372.13）
Plant B		
HHCB	1515.50（1035.13-2894.04）	886.35（834.46-997.77）
DPMI	641.59（366.98-1022.57）	88.40（N.D.-442.01）
ADBI	239.63（188.20-305.80）	316.85（300.39-373.39）
AHMI	33.13（N.D.-198.78）	77.20（N.D.-385.99）
AHTN	762.98（613.65-956.30）	391.17（372.84-458.53）
Plant C		
HHCB	382.55（136.41-890.17）	1142.90（744.60-2338.70）
DPMI	85.29（N.D.-181.40）	N.D.
ADBI	204.57（N.D.-582.01）	N.D.
AHMI	258.31（N.D.-620.63）	266.04（N.D.-966.72）
AHTN	308.29（156.63-453.94）	556.79（366.52-1131.30）
Plant D		
HHCB	236.00（106.12-351.29）	259.07 (238.84-279.29)
DPMI	141.44（N.D.-248.88）	N.D.
ADBI	94.93（N.D.-167.04）	N.D.
AHMI	26.31（N.D.-78.93）	N.D.
AHTN	131.02（64.80-199.10）	117.78（108.40-127.16）
Plant E		
HHCB	943.02（404.78-1866.03）	317.41（240.64-671.68）
DPMI	58.71（24.50-148.67）	491.04（22.17-896.73）
ADBI	90.28（73.04-172.27）	N.D.
AHMI	75.40（N.D.-164.71）	N.D.
AHTN	328.27（151.18-495.58）	139.73（113.77-263.08）

(ng m^{-3})
N.D.: Not Detected

Table 19 Gaseous and particulate forms of synthetic musk determined in cosmetics plant B

Sample no.	Celestolide ADBI	Phantolide AHMI	Tonalide AHTN	Traseolide ATII	Cashmeran DPMI	Galaxolide HHCB	Musk Ambrette MA	Musk Ketone MK	Musk Moskene MM	Musk Xylene MX
	Gaseous (PUF)									
1	2.4×10^{2}	N.D.	9.6×10^{2}	N.D.	1.0×10^{3}	1.6×10^{3}	N.D.	1.1×10^{2}	N.D.	N.D.
2	2.3×10^{2}	N.D.	7.4×10^{2}	N.D.	8.6×10^{2}	1.2×10^{3}	N.D.	1.1×10^{2}	N.D.	N.D.
3	3.1×10^{2}	N.D.	7.9×10^{2}	N.D.	4.2×10^{2}	1.2×10^{3}	N.D.	1.4×10^{2}	N.D.	N.D.
4	2.4×10^{2}	N.D.	6.1×10^{2}	N.D.	5.1×10^{2}	1.0×10^{3}	2.0×10^{2}	1.1×10^{2}	N.D.	N.D.
5	2.4×10^{2}	N.D.	6.9×10^{2}	N.D.	6.8×10^{2}	1.1×10^{3}	N.D.	1.1×10^{2}	N.D.	N.D.
Average	2.5×10^{2}	N.D.	$7.\times10^{2}$	N.D.	7.0×10^{2}	1.2×10^{3}	3.9×10^{1}	1.2×10^{2}	N.D.	N.D.
Sample no.	**Particulate (Filter)**									
1	3.0×10^{2}	N.D.	3.7×10^{2}	N.D.	4.4×10^{2}	8.5×10^{2}	N.D.	N.D.	N.D.	N.D.
2	3.0×10^{2}	N.D.	3.7×10^{2}	N.D.	N.D.	8.4×10^{2}	N.D.	N.D.	N.D.	N.D.
3	3.8×10^{2}	3.9×10^{2}	4.6×10^{2}	N.D.	N.D.	10.0×10^{2}	N.D.	N.D.	N.D.	N.D.
4	3.0×10^{2}	N.D.	3.8×10^{2}	N.D.	N.D.	9.0×10^{2}	N.D.	N.D.	N.D.	N.D.
5	3.0×10^{2}	N.D.	3.7×10^{2}	N.D.	N.D.	8.3×10^{2}	N.D.	N.D.	N.D.	N.D.
Average	3.2×10^{2}	7.7×10^{1}	3.9×10^{2}	N.D.	8.8×10^{1}	8.9×10^{2}	N.D.	N.D.	N.D.	N.D.

(ng m^{-3})

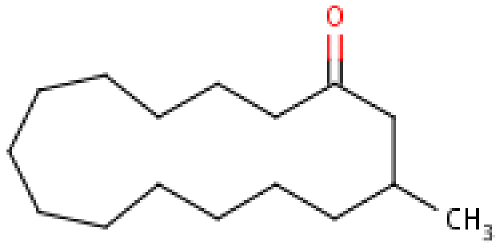


Figure 1. Macrocyclic Musk

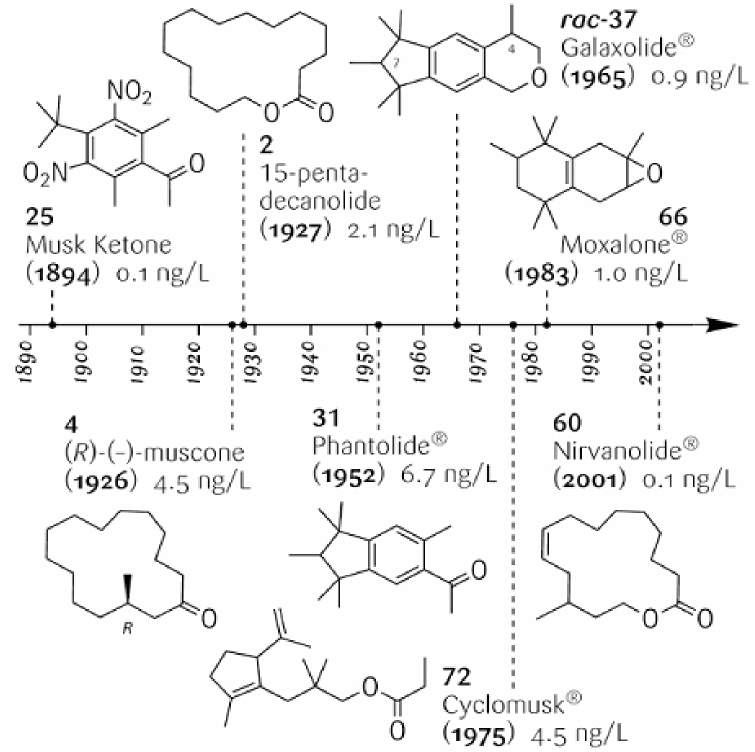


Figure 2. The History of Synthetic Musk

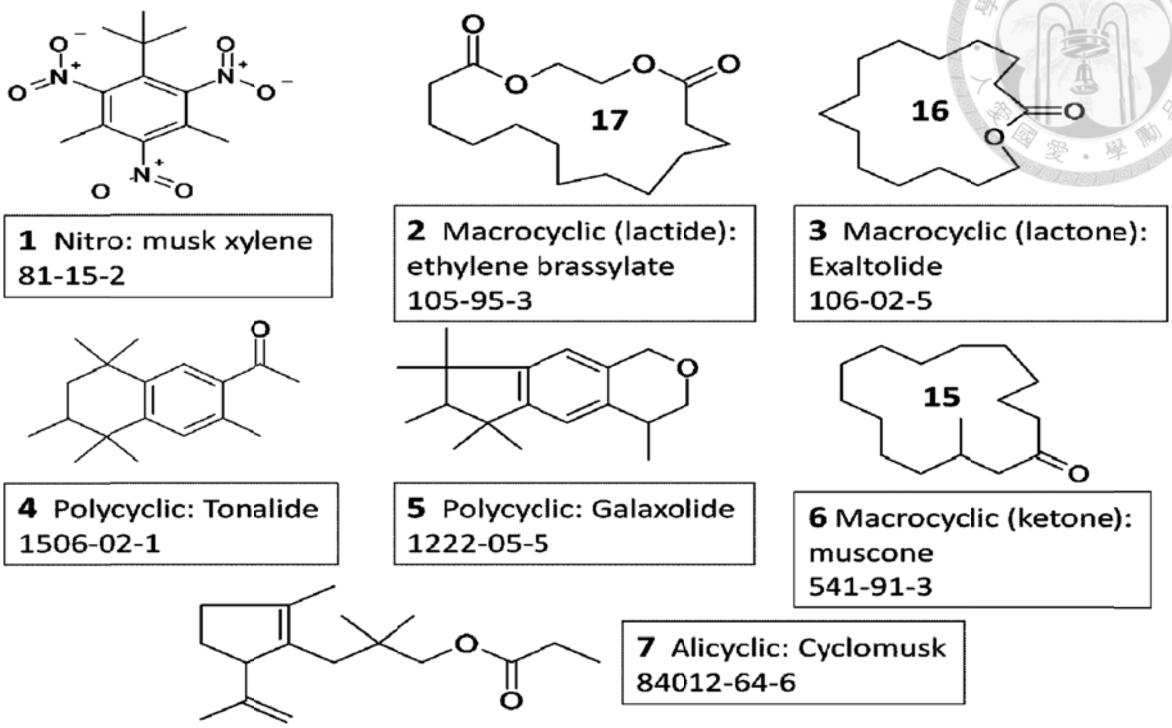


Figure 3. Types of Synthetic Musk

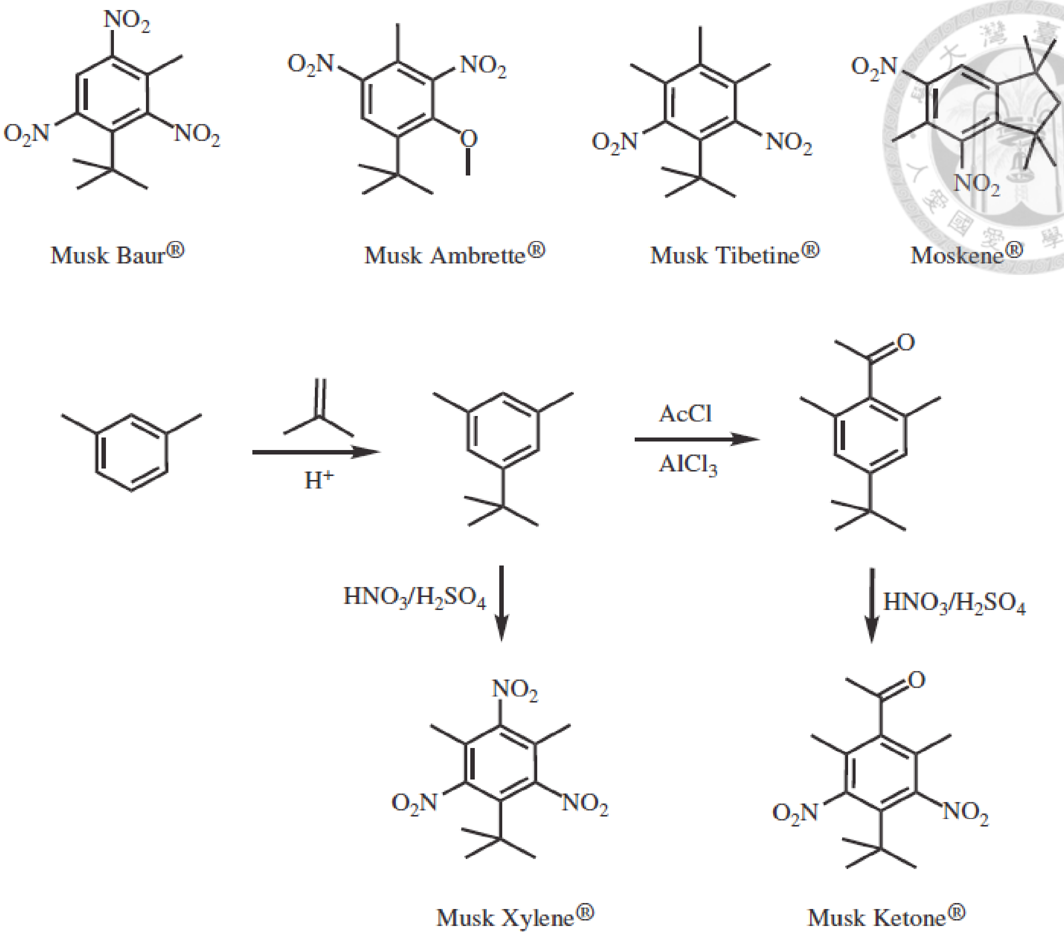


Figure 4. Nitro musk compounds

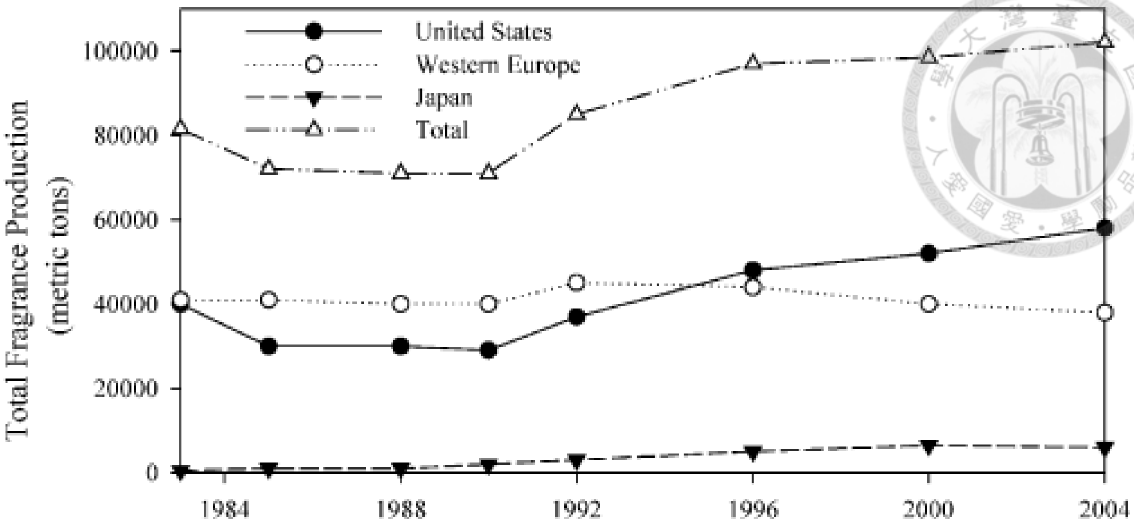


Figure 5. Total fragrance production in the United States, Western Europe, and Japan from 1983 to 2004.

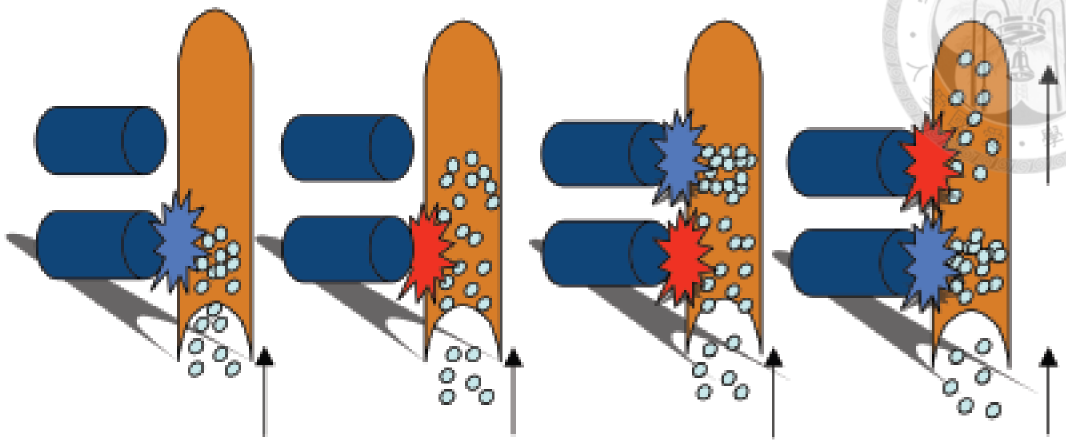


Figure 6. Schematic of two-stage moldulator operation.

Cold and hot pulses of nitrogen are shown as blue (cryogenically cooled) and red (heated). (a) Eluent from the first column enters the second column and analytes are focused by the first cold jet. (b) The cold jet turns off and the hot jet (nitrogen gas) simultaneously and immediately comes on allowing the analytes to move up the column. (c) As the hot jet from (b) turns on the second cold jet turns on at the same time and refocuses the analytes released by hot jet. (d) The second hot jet comes on and analytes are released to the detector; at this point the first cold jet comes back on, to prevent breakthrough of first dimension column eluent, and the cycle starts all over again. This continuous modulation cycle repeats for the duration of the run[1].

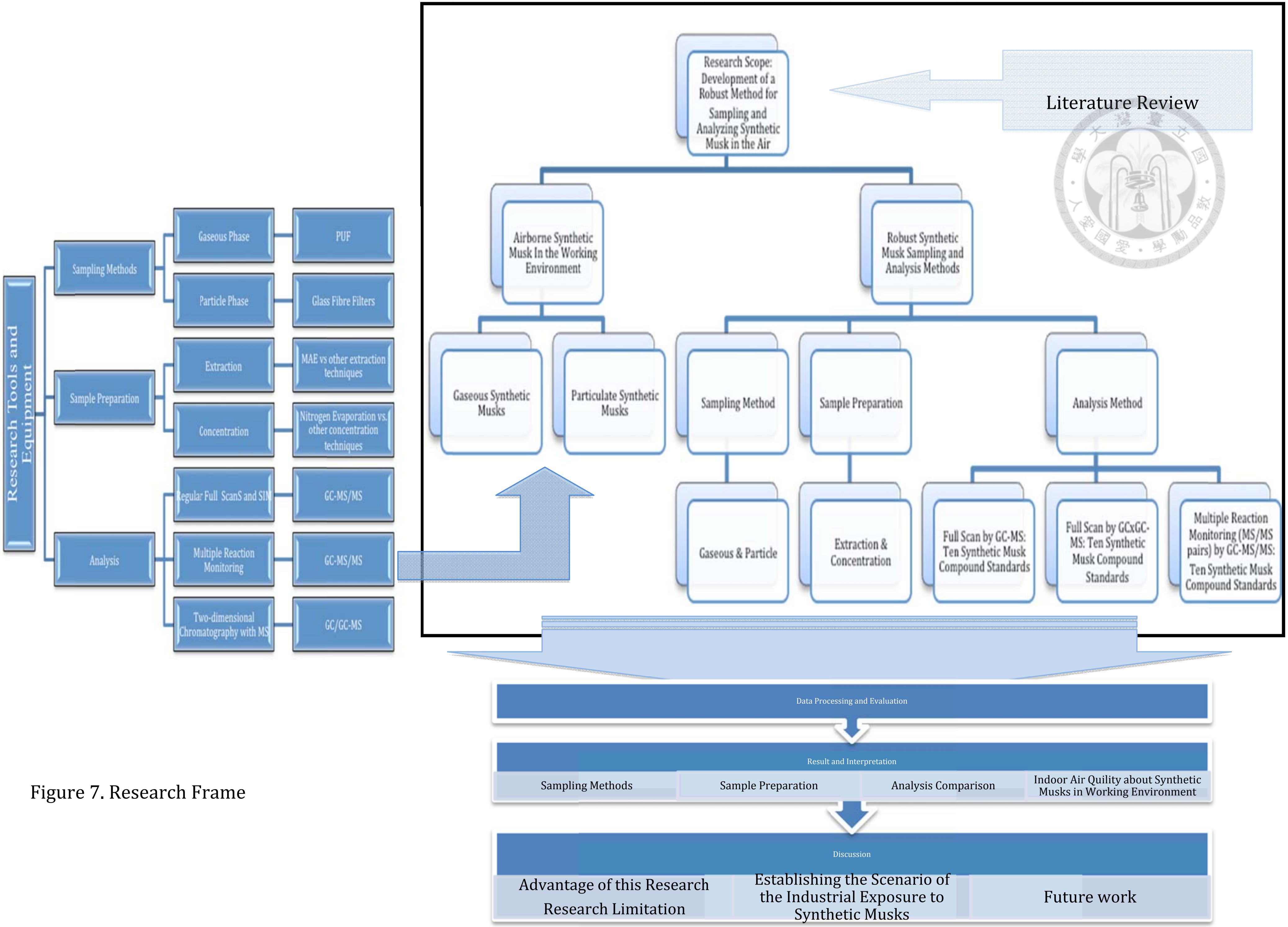


Figure 7. Research Frame

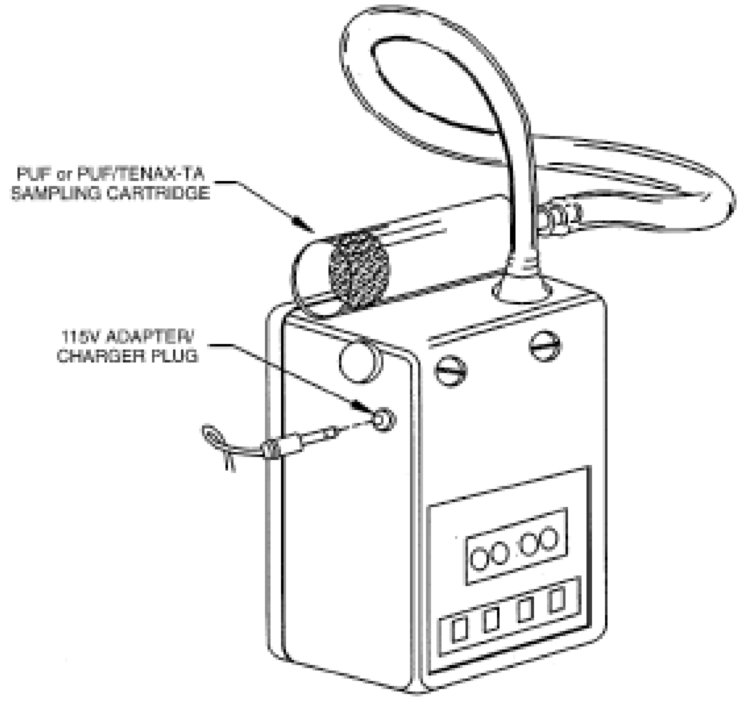


Figure 8. Sampling Set (PUF sampler with Filter connected to a pump)

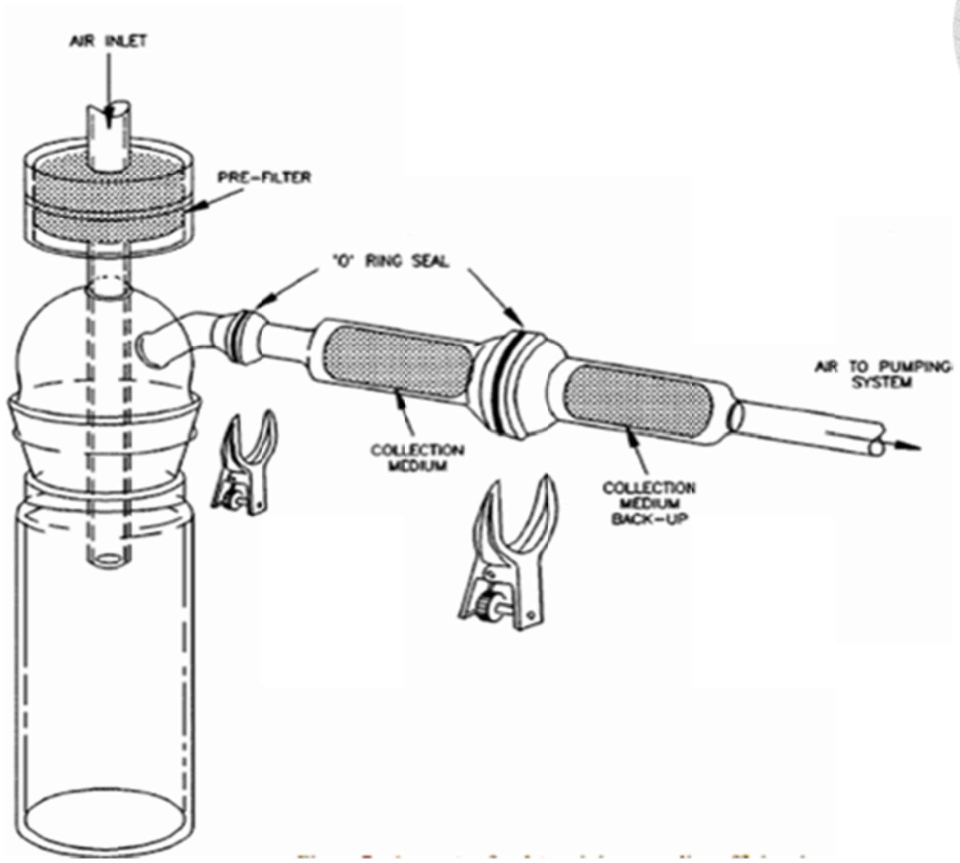


Figure 9. Validation of PUF Sampling

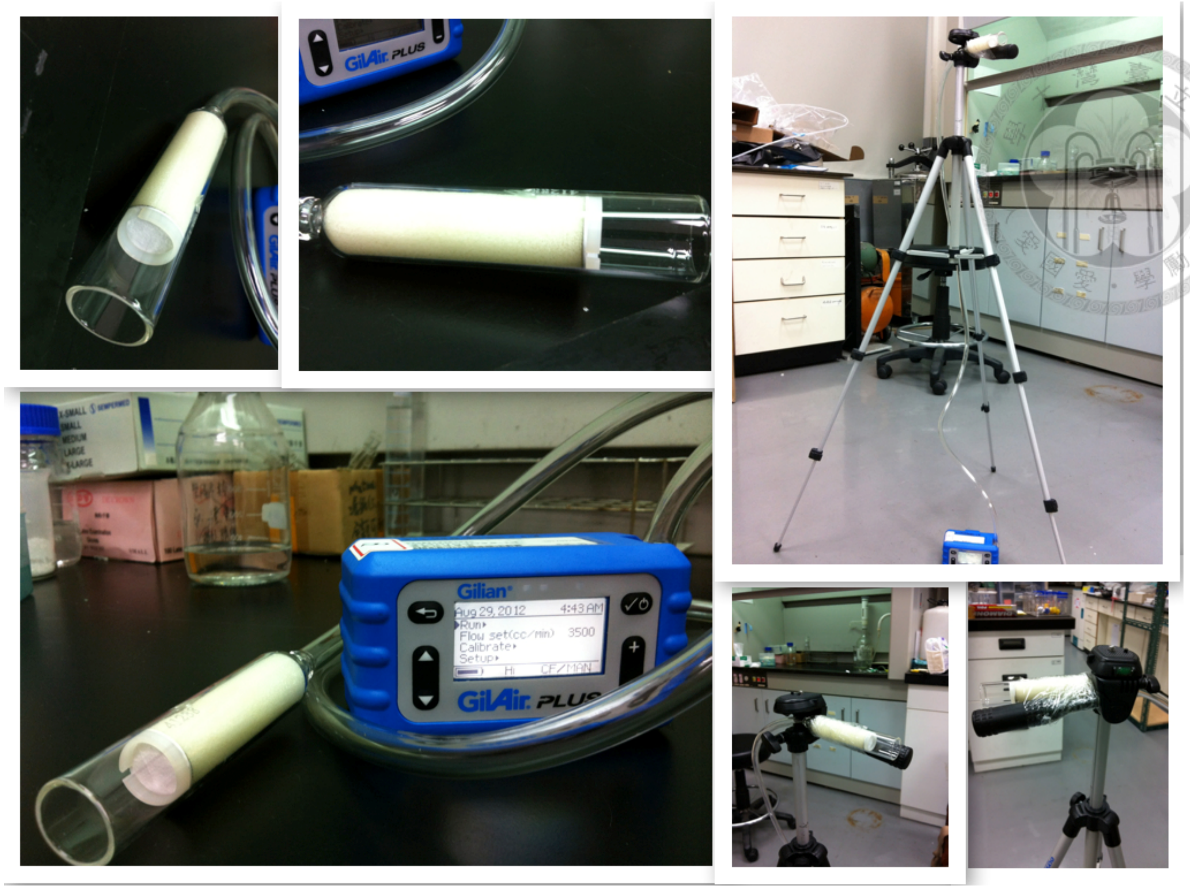


Figure 10. Simulating scene of field sampling

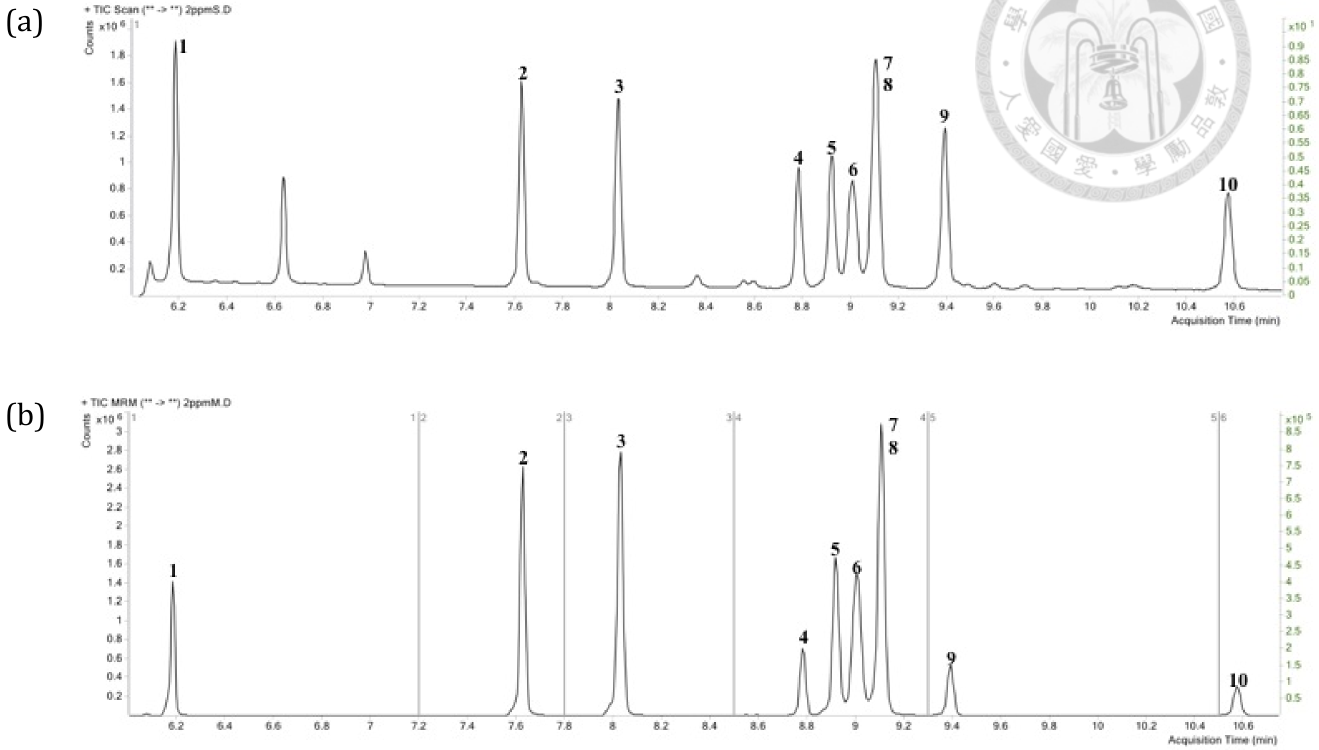
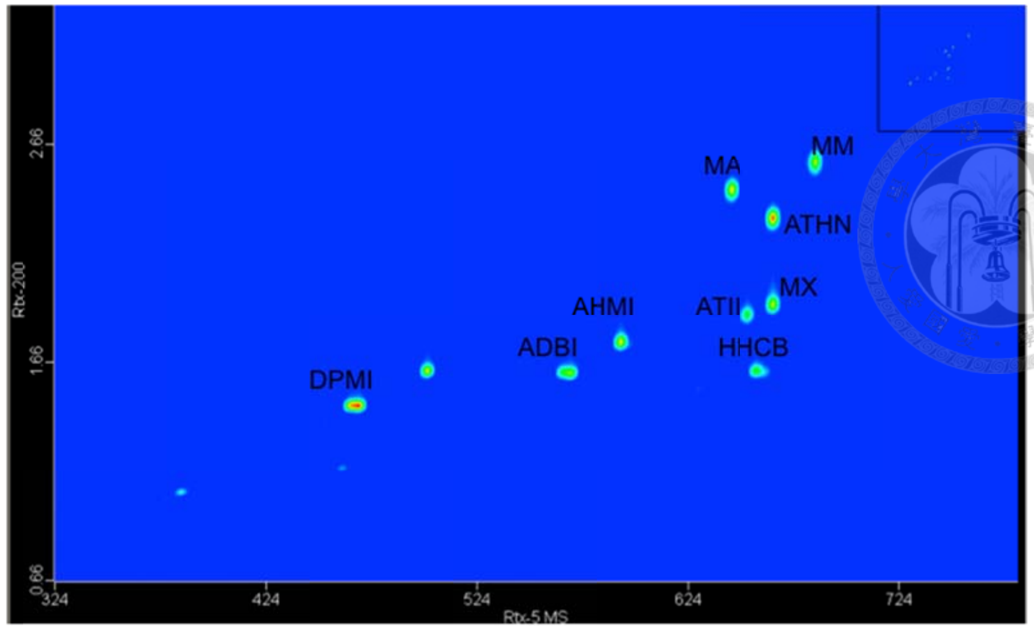


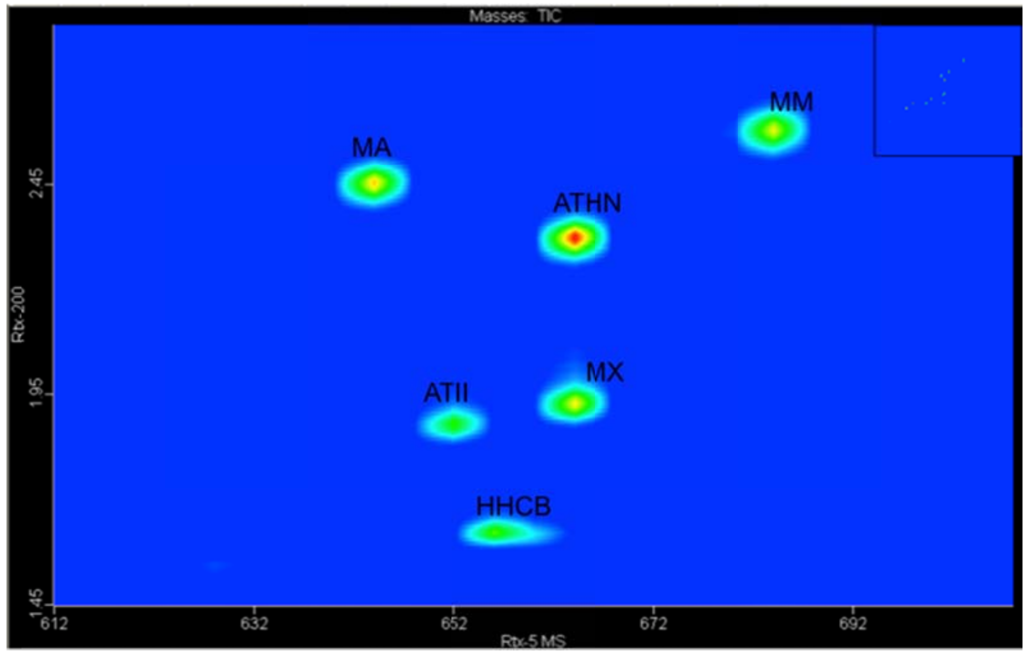
Figure 11. Chromatogram of ten synthetic musk standards.

1. Cashmeran (DPMI); 2. Celstolide (ADBI); 3. Phantolide (AHMI); 4. Musk ambrette (MA); 5. Traseolide (ATII); 6. Galaxolide (HHCB); 7. Musk xylene (MX); 8. Tonalide (AHTN); 9. Musk moskene (MM); 10. Musk ketone (MK). (a) Full scan mode acquisition-TIC; (b) MRM mode;

(a)


MM
MA
ATHN
MX
AHMI
ATII
ADBI
HHCB
DPMI
2.66
1.66
0.66
Rtx-200
324
424
524
624
724
Rtx-5 MS

(b)


Masses: TIC
MM
MA
ATHN
MX
ATII
HHCB
2.45
1.95
1.45
Rtx-200
612
632
652
672
692
Rtx-5 MS

(c)

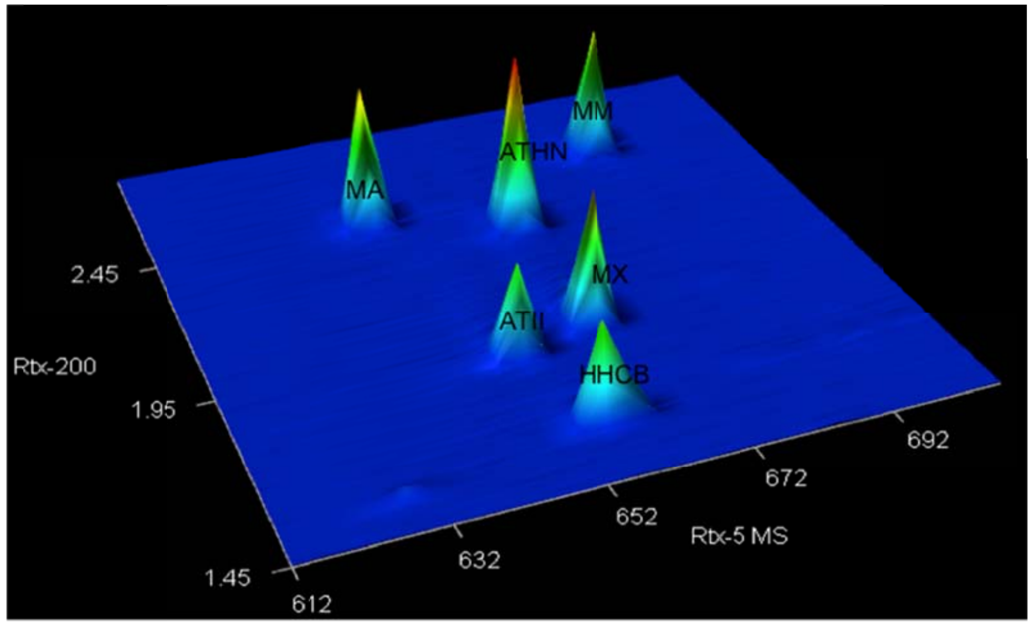

MM
ATHN
MA
MX
ATII
HHCB
2.45
Rtx-200
1.95
1.45
612
632
652
672
692
Rtx-5 MS

Figure 12. Gas chromatographs of synthetic musk standard mixture.

(a) Ten synthetic musk compounds; (b) Six synthetic musk compounds eluted within the same time segment; (c) three dimensional version of (b).

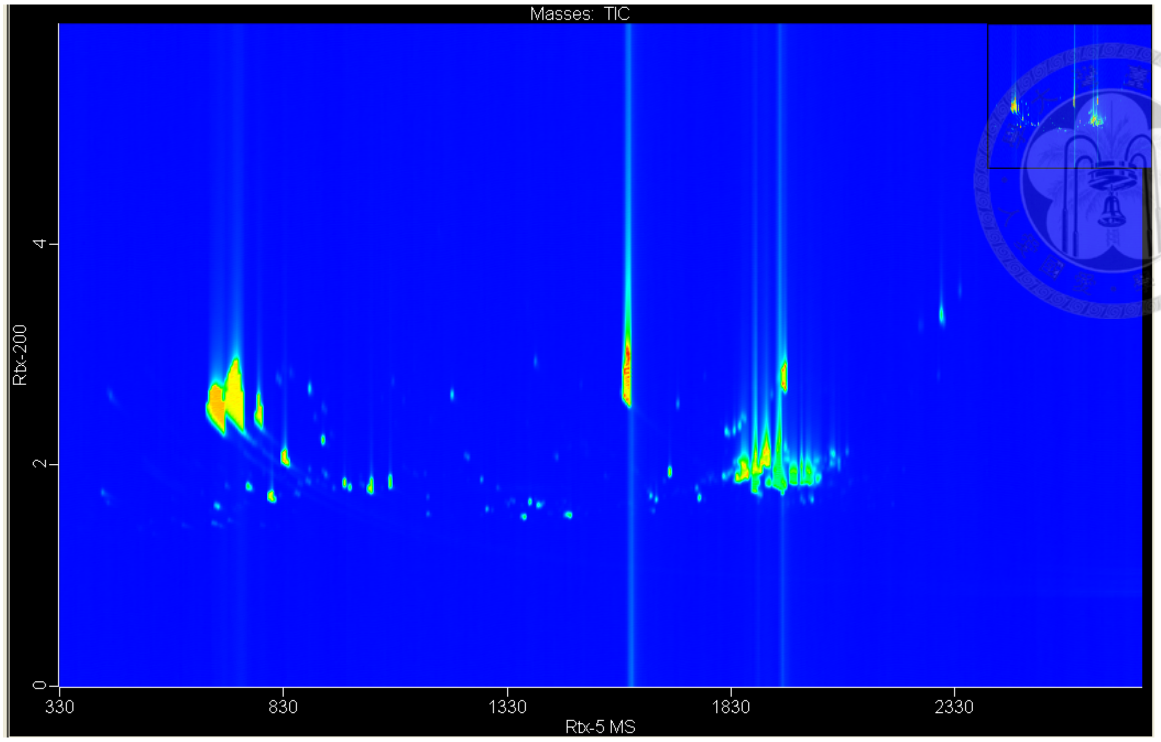


Figure 13. White Musk.

Injection volume of 0.2 µl, splitless; Rtx-5MS for 1st dimension, and Rtx-200 for 2nd dimension.