

# The Role of Musk and Musk Compounds in the Fragrance Industry

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**Abstract** An overview of the role of musk and musk compounds in the fragrance industry is given. Discovery and syntheses of representatives occurring naturally in animals and plants as well as of artificial substances possessing musk-like odor properties are reviewed. Examples of the three major classes – nitro musks, polycyclic musks, and macrocyclic musks – are covered. The importance of these compounds as fragrance ingredients of cosmetics and detergents is shown. The impact of environmental and toxicological data on the actual use and ongoing developments of this important class of fragrances are described.

**Keywords** Musk · Musk deer · Nitro musks · Polycyclic musks · Macrocyclic musks

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## 1 Introduction

Musk is a gland secretion produced by the male musk deer (*Moschus moschiferus* L.) which has been used as fragrance material for centuries [1, 2]. In addition, the term “musk” also refers to a diverse spectrum of chemically defined substances which are quite different in their chemical structures but exhibit a common, distinct, and typical flavor. These musk compounds comprise representatives occurring naturally in animals and plants as well as artificial substances possessing musk-like odor properties [3, 4].

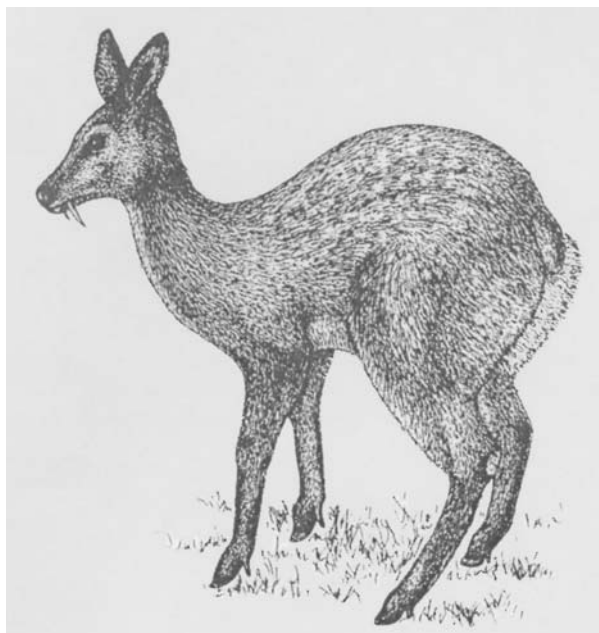
The use of musk flavor has a long history dating back to ancient times. Until the end of the nineteenth century the popular fragrance was only obtained from natural sources. Nowadays synthesized compounds are almost exclusively used [5]. They can be divided into three major classes: aromatic nitro musks, polycyclic substances, and macrocyclic musk compounds [6].

Representatives of the first two groups are broadly applied in industry [7]. They are components of fragrance compositions, which are added to cosmetics (e.g., perfumes, soaps, and creams) and to detergents. The detection of nitro musks in fish and human matrices (milk, fat) initiated a public debate on the use of these compounds. Later, the polycyclic musk compounds, which were increasingly used to replace the nitro musks, were also detected in environmental and human samples [8–10]. Therefore, macrocyclic musk compounds are expected to be of increasing importance in the future [5].

## 2

### Natural Musk

An animal secretion called “musk” is the carrier of the natural musk aroma. It is produced by the male musk deer (*Moschus moschiferus* L.) in a gland situated in the prenuptial region between the abdomen and the genitals [1, 11–13]. The musk deer (Fig. 1) belongs to the family Moschidae and reaches approximately the size of the central European roe deer. It lives in upper regions of Eastern Asia, e.g., India, Tibet, China, Siberia, and Mongolia [3, 11–15].



**Fig. 1** Musk deer (*Moschus moschiferus* L.) [11]

In order to get access to the natural musk, the animal must be killed to remove the gland, also called musk pod (Fig. 2). The fully developed pods (50–70 g) contain about 40% musk [11]. Upon drying, the reddish-brown paste turns into a black, granular material (musk grain) which is used for alcoholic solutions. The aroma of the tincture, which is described for example as animal-like, earthy, and woody, becomes more intensive during storage. Only after considerable dilution does the obtained extract exhibit a pleasant odor [1, 2, 14]. No other natural product possesses such a complex aroma associated with many often contradictory descriptions [16]. The commercially used products are differentiated according to their provenance. The best qualities, called Tonkin musk, originate from Tibet and China [1, 14].

Discovery and use of musk date back to ancient China and pre-historic India. In these societies musk was of extraordinary cultural importance and was also used as a universal drug [15]. The crusaders eventually brought musk from the Orient to Europe. There it was also used as drug as well as ingredient of perfumes. It was highly appreciated due to its properties to enhance, harmonize, and round off perfume compositions [1, 15]. Comparable to ancient times, musk is still today one of the most expensive natural products [15]. In 1998 the value of 1 g of musk ranged from 30 to 50 US \$. Thus, its price was higher than that of gold (10 US \$ g<sup>-1</sup>) [17].

Owing to the limited availability, the high price, and attempts to save the musk animals, the fragrance industry increasingly replaces natural musk by chemically synthesized musk compounds [1, 15].

Trade of musk from Afghanistan, Bhutan, India, Myanmar, Nepal, and Pakistan has been forbidden since 1979 by the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) and the import of musk from other countries is restricted by control of documents. Despite these regulations,



Fig. 2 Musk pods [62]

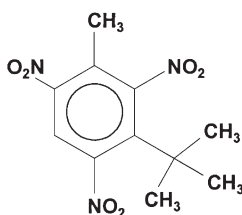
musk animals are still an endangered species. The main reason is the use of musk in traditional Asian medicine. About 500–1000 kg musk per year are used in China for production of drugs, resulting in the death of about 100,000 animals [17].

The main sources of musk used by the fragrance industry today are China, Arabia, and Russia [17]. In the European Union the trade of musk from China and Russia has been forbidden since 1999 [18]. In recent years, France has been the only European country using natural musk (annual amount in the kg range) [17].

### 3 History of Compounds with Musk Odor

Owing to the limited availability and the high price of natural musk, there were early attempts to find replacements. First indications date from 1759, when the chemist Markgraf detected products with musk-like odors in the course of the nitration of amber oil. Although these results were of no immediate practical importance, they stimulated and influenced future investigations [15]. In 1890, several years before the isolation and structural elucidation of the natural carrier of the musk aroma, Baur succeeded in synthesizing the first chemically defined substance with musk odor by nitration of *meta-tert*-butyl-toluene [3, 5, 15]. 2-(1,1-Dimethylethyl)-4-methyl-1,3,5-trinitro-benzene (Fig. 3) was patented and commercialized as “Musc Baur” [19]. Later, other members of this class of compounds, called nitro musks, were synthesized and gained considerable commercial importance.

In contrast to the development of synthetic musk compounds, the first major success of research activities on the natural musk constituents was only reported in 1906 [3]. Walbaum isolated a ketone, which he named muscone, as the major odor-contributing constituent of the secretion from the musk gland [20]. In 1915 Sack isolated another ketone with musk odor from the secretion of an animal called civet cat (*Viverra civetta* L.), which he named civetone [21]. In 1926 Ruzicka et al. eventually succeeded in characterizing muscone as 3-methylcyclopentadecanone and civetone as cycloheptadecen-1-one and confirmed their structures by synthesis [22–25]. This was the discovery of a new class of compounds, the macrocyclics [26]. One year later Kerschbaum detected additional macrocyclic lactones in angelica root oil and in ambrette seed oil [3, 27]. In 1928 Stoll and Ruzicka synthesized these compounds and identified them as cyclohexadecenolide (e.g., Ambrettolide) in ambrette seed oil and as cyclopentadecanolide (e.g., Exal-



**Fig. 3** Chemical structure of 2-(1,1-dimethylethyl)-4-methyl-1,3,5-trinitro-benzene (“Musc Baur”)

tolide) in angelica root oil [3, 26]. In 1942 Stevens and Erickson identified cyclopentadecanone (e.g., Exaltone) and cycloheptadecanone (e.g., Dihydrocivetonone) obtained from the American musk rat (*Ondatra zibethica* L.) [26].

The importance of these macrocyclic fragrance compounds of animal and plant origin stimulated the development of improved syntheses meeting the demands of industrial applications. However, the yields and the prices did not fulfill the expectations [15, 26]. Therefore, there was a search for compounds which could be synthesized more easily. This was achieved in the 1950s by the synthesis of the so-called polycyclic musk compounds, another nitro-free group of musks [3, 5]. In 1951 the synthesis of 6-acetyl-1,1,2,3,3,5-hexamethyldihydroindene (AHDI) (e.g., Phantolide) was described. Starting from this first industrially important member of this class of musks a broad spectrum of polycyclic musk compounds has been developed [6].

## 4 Synthetic Musk Compounds

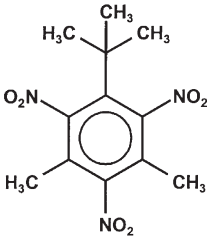
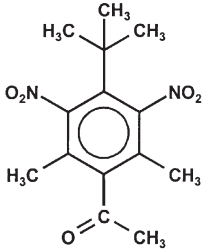
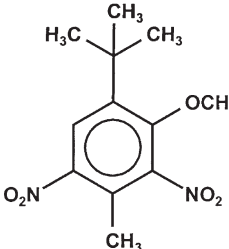
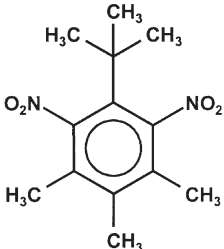
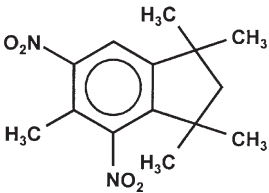
Musk compounds traditionally belong to the most important substances used in the fragrance industry [28]. On one hand this is due to their odor properties which can be divided into types such as animal-like, flowery, and fruity. On the other hand, they are appreciated because of their abilities to improve the fixation of compounds and to round off fragrance compositions [3, 29]. Increased fixation improves the effectiveness of fragrances by slowing down the release of volatiles, thus contributing to a defined and stable quality over an extended period [2]. They are also known to bind fragrances to fabrics. Therefore, they are added as perfumery ingredients not only to cosmetics but also to detergents [30].

Synthetic musks comprise a broad spectrum of different substances. Commercially, only nitro derivatives, polycyclic, and macrocyclic compounds are of importance [4]. For many years the nitro musks dominated the market. Since 1983 their share has decreased continuously by 5% per year. In 1987 the total amount (7000 tonnes) of musk compounds produced worldwide comprised 61% polycyclic, 35% nitro musks, and 3–4% macrocyclic compounds [28].

### 4.1 Nitro Musk Compounds

The era of nitro musk compounds began with the discovery of the so-called “Musc Baur” by Baur at the end of the nineteenth century [19]. In the following years, other aromatic nitro compounds were synthesized, which gained considerable importance as replacements for natural musk. These artificial substances exhibit musk-like odors although they are structurally very different from the naturally occurring musk compounds [3, 5, 6, 15]. The best known nitro musks (musk ketone, musk xylene, musk ambrette, musk tibetene, musk moskene) are listed in Table 1. They are two- or threefold nitrated benzene derivatives with additional alkyl, keto, or methoxy groups. Musk moskene, synthesized in 1932 and identified as a dinitroindane derivative in 1955, can be seen as intermediate between nitro musks and the nitro-free indane substances (polycyclic musks) [5, 6].

**Table 1** Commercially important nitro musks

CAS Name CAS No.	Trivial name	Molecular formula	Chemical structure
1-(1,1-Dimethylethyl)- 3,5-dimethyl- 2,4,6-trinitrobenzene 81-15-2	Musk xylene, Musk xylof	$C_{12}H_{15}N_3O_6$	
1-[4-(1,1-Dimethyl- ethyl)-2,6-dimethyl- 3,5-dinitrophenyl]- ethanone 81-14-1	Musk ketone	$C_{14}H_{18}N_2O_5$	
1-(1,1-Dimethylethyl)- 2-methoxy-4-methyl- 3,5-dinitro-benzene 83-66-9	Musk ambrette	$C_{12}H_{16}N_2O_5$	
1-(1,1-Dimethylethyl)- 3,4,5-trimethyl- 2,6-dinitrobenzene 145-39-1	Musk tibetene	$C_{13}H_{18}N_2O_4$	
2,3-Dihydro- 1,1,3,3,5-pentamethyl- 4,6-dinitro-1H-indene 116-66-5	Musk moskene	$C_{14}H_{18}N_2O_4$	

Comparable to the other musk substances, nitro musks are appreciated because of their odors, their role in fixation, and their versatile technological applicabilities [7, 15]. For many years they were the musk compounds produced in highest amounts, especially because of their low prices [6]. However, starting from 1983 the production rate decreased mainly because of reports on photoallergic reactions elicited by musk ambrette [28]. In 1981 musk xylene and musk ketone were detected for the first time in fish and water in Japan; the presence of both compounds in these samples was explained by their potential for bioaccumulation in aquatic systems [31, 32]. In 1983 musk xylene was also detected in fish in the USA. However, a final interpretation of these results was not possible due to potential laboratory contamination [33].

In 1993 the detection of  $\mu\text{g kg}^{-1}$  (on wet weight basis) amounts musk xylene, musk ketone, and musk ambrette in fish initiated a broad public debate on the use of nitro musk compounds. Subsequent investigations of samples from humans (milk, fat) revealed the presence of musk xylene and musk ketone and in a few samples of musk ambrette and musk moskene [34–36].

In order to locate potential sources of contamination, the content of nitro musk compounds in low-priced cosmetics and detergents marketed in Germany was surveyed in 1992. It was found that 55% of the investigated cosmetics (perfumes, shaving lotions, shower gels, shampoos, creams) and 41.5% of the detergents contained nitro musks. There were significant differences in the amounts detected, e.g., musk ketone concentrations in cosmetics ranged from 4.0 to 2200  $\text{mg kg}^{-1}$ . Musk ketone dominated in cosmetics; musk xylene was the main representative in detergents (Fig. 4). Musk ambrette could only be found in one cosmetic product [37]. This is in agreement with results reported by the Food and Drug Administration (FDA) [38, 39]. It reflects the voluntary compliance of the

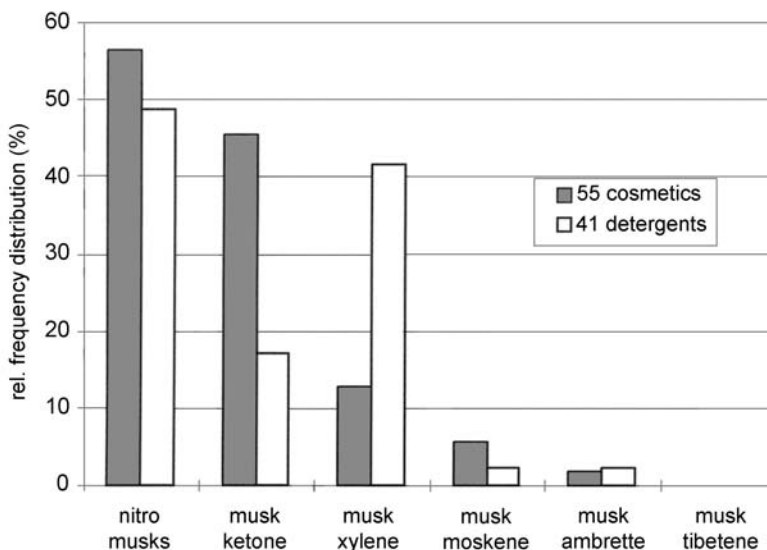


Fig. 4 Frequency distribution of nitro musks in cosmetics and detergents in 1992 [37]

fragrance industry with the 1985 recommendation of the International Fragrance Association (IFRA) not to use musk ambrette in any fragranced products coming into contact with the skin [37–39].

In 1993 the public discussion on nitro musks resulted in a recommendation of the German Cosmetic, Toiletry, Perfumery and Detergent Association (IKW) not to use musk xylene for the production of cosmetics, detergents, and other household products. The decision was based on the bioaccumulation of this compound and its potential carcinogenicity [5, 40].

In 1995 the strong photo-allergenicity of musk ambrette resulted in a prohibition of this compound in the production of cosmetics in the European Union [41]. Since 1998 musk moskene and musk tibetene are also included in the list of compounds which according to directive 76/768/EEC are not allowed to be used in cosmetics [42]. Recently, the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP) of the EU Commission recommended the implementation of limits for the use of musk xylene and musk ketone in cosmetics [43, 44].

In Switzerland the prohibition of musk ambrette and limits for the other nitro musks were already implemented by 1995. The maximum concentrations of nitro musks are 50 mg kg<sup>-1</sup> in deodorants and skin care products, 200 mg kg<sup>-1</sup> in aqueous-alcoholic products, and 500 mg kg<sup>-1</sup> in Eaux de Cologne and Eaux de Toilette. Shampoos and perfumes must be free of nitro musks [45, 46].

The intensive debate on nitro musks is also reflected in the commercial use of this group of musk compounds [47, 48]. In 1996 investigations of low-price cosmetics and detergents (mainly produced in Germany) revealed only 7 (12.5%) out of a total of 56 cosmetics to contain musk ketone, xylene, and tibetene. In the 33 detergents no nitro musks could be detected. A comparison with data obtained in 1992 showed that almost all producers of cosmetics (Fig. 5) and detergents in Germany had stopped using nitro musks. On the other hand, in 1995 the investigation of a spectrum of 42 high-priced, exclusive cosmetics mainly produced in France demonstrated the use of nitro musks in more than 50% of the products (Fig. 5) [49].

As shown in Table 2, there has been a significant decline in the usage of nitro musks by the European fragrance industry between 1992 and 1998 [50]. Worldwide the proportion of nitro musks (related to the total production of musk compounds) decreased from 35% in 1987 to about 12% in 1996 [6].

## 4.2

### Polycyclic Musk Compounds

The polycyclic musk compounds were not discovered until the 1950s [5]. They are nitro-free substances, which can be divided into indane derivatives, tetraline derivatives, tricyclic compounds, and coumarin derivatives [6, 29]. The most important representatives are listed in Table 3. Analogous to the nitro musk compounds they are artificial compounds which do not occur in nature and have no chemical relationship to the natural musk compounds. Their use began after the synthesis of 6-acetyl-1,1,2,3,3,5-hexamethyl-dihydroindene (AHDI) (e.g., Phantolide) in 1951 [6]. They are appreciated not only because of their attractive odor properties but also because their synthesis is cheaper than that of the macrocyclic



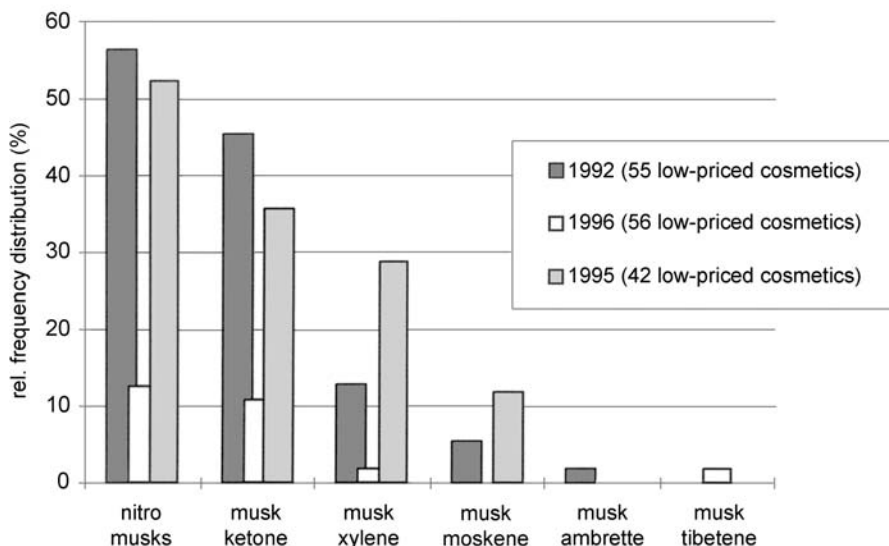


Fig. 5 Frequency distribution of nitro musks in cosmetics [37, 49]

Table 2 Industrial use of musk xylene and other nitro musks in Europe (in tonnes) [50]

Year	Musk xylene	Musk ketone	Musk moskene	Musk tibetene
1992	174	124		
1995	110	61	5	0.8
1998	86	40		

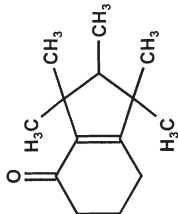
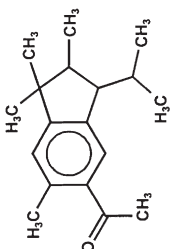
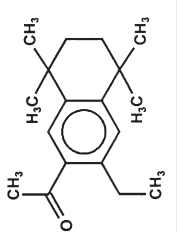
compounds, another group of nitro-free musks. Compared to the nitro musk compounds, they are superior in terms of resistance to light and alkali and in their abilities to bind to fabrics [3, 5, 6, 15]. Accordingly, they are mainly used in cosmetics and detergents. The most important representatives of this class of musks are 7-acetyl-1,1,3,4,4,6-hexamethyltetrahydronaphthalene (AHTN) and 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[g]-2-benzopyrane (HHCB) followed by 4-acetyl-1,1-dimethyl-6-*tert*-butyldihydroindene (ADBI) and 5-acetyl-1,1,2,6-tetramethyl-3-isopropyl-dihydrindene (ATII) [5, 51]. HHCB was used in higher amounts than AHTN in the early 1970s, due to more advanced production procedures and lower price. Since the 1980s these parameters have been comparable for both compounds [15]. 1500 tonnes AHTN and 3800 tonnes HHCB are used per year in the USA and in Europe [51]. These production volumes amount to about 95% of the commercially used polycyclic musk compounds [52]. In contrast, 7-acetyl-1,1,4,4-tetramethyl-6-ethyltetrahydro-naphthalene (ATTN) (Table 3) is only of historical importance. Owing to its neurotoxic properties, production and use have been terminated as from the beginning of the 1980s [5].

The decrease of the production rate of nitro musks was paralleled by an increase for the polycyclic compounds. A market share of 61% in 1987 corre-

Table 3 Commercially important polycyclic musks

CAS name CAS no.	Trade name(s)	Chemical name (abbreviation)	Molecular formula	Chemical structure
1,3,4,6,7,8-Hexahydro- 4,6,6,7,8,8-hexamethyl- cyclopenta[ <i>g</i> ]-2-benzopyrane 1222-05-5	Galaxolide Abballide Pearlode	1,3,4,6,7,8-Hexahydro- 4,6,6,7,8,8-hexamethylcyclopenta[ <i>g</i> ]- 2-benzo-pyrane (HHCB)	C <sub>18</sub> H <sub>26</sub> O	
1-(5,6,7,8-Tetrahydro- 3,5,5,6,8,8-hexamethyl- 2-naphthalenyl)-ethanone 1506-02-1	Tonalide, Fixolide	7-Acetyl-1,1,3,4,4,6-hexamethyl- tetrahydro/naphthalene (AHTN)	C <sub>18</sub> H <sub>26</sub> O	
1-[6-(1,1-Dimethylethyl)- 2,3-dihydro-1,1-dimethyl- 1 <i>H</i> -inden-4-yl]-ethanone 13171-00-1	Celestolide, Crysolide	4-Acetyl-1,1-dimethyl-6- <i>tert</i> . butyldihydroindene (ADBI)	C <sub>17</sub> H <sub>24</sub> O	
1-(2,3-Dihydro-1,1,2,3,3,6- hexamethyl-1 <i>H</i> -inden-5-yl)- ethanone 15323-35-0	Phantolide	6-Acetyl-1,1,2,3,3,5-hexamethyl- dihydroindene (AHDI)	C <sub>17</sub> H <sub>24</sub> O	

Table 3 (continued)

CAS name CAS no.	Trade name(s)	Chemical name (abbreviation)	Molecular formula	Chemical structure
1,2,3,5,6,7-Hexahydro-1,1,2,3,3,3-pentamethyl-4H-inden-4-one 33704-61-9	Cashmeran	6,7-Dihydro-1,1,2,3,3-pentamethyl-4(5H)indanone (DPMI)	$C_{14}H_{22}O$	
1-[2,3-Dihydro-1,1,2,6-tetramethyl-3-(1-methyl-ethyl)-1H-inden-5-yl]-ethanone 68140-48-7	Traseolide	5-Acetyl-1,1,2,6-tetramethyl-3-isopropyl-dihydroindene (ATII)	$C_{18}H_{26}O$	
1-(3-Ethyl-5,6,7,8-tetrahydro-5,8,8-tetramethyl-2-naphthalenyl)-ethanone 88-29-9	Versalide	7-Acetyl-1,1,4,4-tetramethyl-6-ethyltetrahydro-naphthalene (ATTN)	$C_{18}H_{26}O$	

sponding to an amount of about 4300 tonnes per year increased to 70% in 1996 corresponding to 5600 tonnes per year [5, 28]. This development was mainly due to the role of HHCB and AHTN as replacements for the nitro musks [5, 6, 53].

An investigation of cosmetics and detergents in 1994/95 revealed HHCB and AHTN to be the mainly used polycyclic musks. The concentration of HHCB, e.g., in cosmetics ranged from 0.5 to 500 mg kg<sup>-1</sup> and of AHTN from 1.1 to 520 mg kg<sup>-1</sup>. Other representatives of this group play only a minor role [10].

The first report on the presence of polycyclic musks in fish and water dates back to 1994 [8]. One year later the compounds were also found in samples from humans (milk, fat) [9]. HHCB and AHTN were analyzed in highest amounts. The values were higher than those determined for the nitro musk compounds [8, 9].

Meanwhile many producers of cosmetics and detergents stopped using polycyclic musk compounds [5]. The effect on the overall use of these compounds in Europe is shown in Table 4 [50]. In the meantime, the polycyclic musk compounds are also being evaluated by the SCCNFP of the EU Commission [7, 54, 55]. A decision of the EU Commission on the regulatory status of HHCB and AHTN is expected [7].

### 4.3

#### Macrocyclic Musk Compounds

The development of the macrocyclic musk compounds began in 1926 with the structural characterization of muscone and civetone by Ruzicka and others [15, 22, 24–26]. They demonstrated the compounds to be cyclic macromolecules, the existence of which had been considered impossible according to the so-called “Baeyer’s strain theory” [3, 15, 56].

After this breakthrough additional macrocyclic compounds exhibiting musk-like odors were isolated from natural materials, their structures were elucidated, and syntheses were developed [15, 16, 26]. The natural macrocyclic musk compounds turned out to be ketones (animal sources) and lactones (plant materials) [5, 15]. They are 15- or 17-membered ring systems. The type of odor is influenced by the ring size. Starting from 14 ring atoms, a weak musk scent is perceived. Compounds with 15–16 ring atoms exhibit strong musk odor [26].

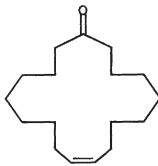
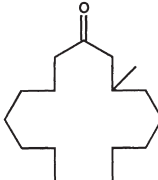
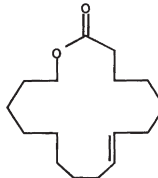
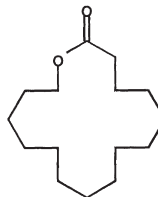
Owing to their outstanding properties (stability to light and alkaline conditions, fixation, and high quality odors), macrocyclic musk compounds are of high value for the fragrance industry. Accordingly, there have been many attempts to improve syntheses of naturally occurring macrocyclic musks for industrial application and to develop new, more easily accessible members of this class [3, 15, 26]. The synthesized macrocyclic compounds can be divided into ketones, diketones, lactones, oxalactones (ether lactones), dilactones, ketolactones, and esters. Some of the most prominent examples are listed in Table 5.

In addition to the naturally occurring representatives, a wide array of other substances not being found in nature has been synthesized [26, 57–59]. One of the most important compounds of this group (production of about 300 tonnes per year) is the dilactone ethylene brassylate [59]. Ethylene brassylate is an inexpensive musk compound because of its easy synthesis and the low costs of the starting materials [5, 60]. Another inexpensive macrocyclic musk compound is Habanolide, the unsaturated version of Exaltolide [61].

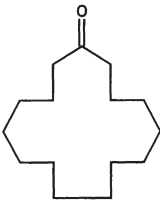
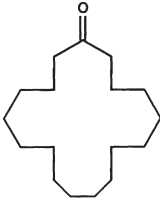
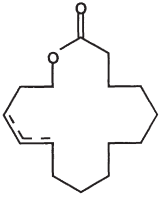
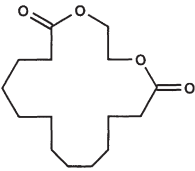
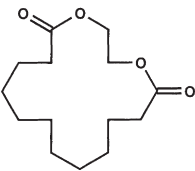
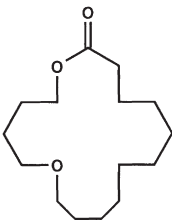
**Table 4** Industrial use of polycyclic musks in Europe (in tonnes) [50]

Year	HHCB	AHTN	ADBI	AHDI	ATII
1992	2400	885			
1995	1482	585	34	50	40
1998	1473	385	18	19	2

**Table 5** Commercially important macrocyclic musks

CAS name CAS no.	Trade name(s)	Chemical name	Molecular formula	Chemical structure
9-Cyclohepta- decen-1-one 542-46-1	Civettone Civetone	<i>cis</i> -9-Cyclohepta- decenone, 10-Ketocyclo- heptadecene	C <sub>17</sub> H <sub>30</sub> O	
3-Methyl- cyclopenta- decanone 541-91-3	Muscone	3-Methylcyclo- pentadecanone	C <sub>16</sub> H <sub>30</sub> O	
Oxacyclo- heptadec- 8-en-2-one 123-69-3	Ambrettolide	7-Hexadecen- 16-olide, 16-Hydroxy- 7-hexadecenoic- acidlactone, Cyclohexade- cenolide	C <sub>16</sub> H <sub>28</sub> O <sub>2</sub>	
Oxacyclohexa- decan-2-one 106-02-5	Exaltolide, Muskalactone, Pentalide, Thibetolide	15-Pentade- canolide	C <sub>15</sub> H <sub>28</sub> O <sub>2</sub>	

**Table 5** (continued)

CAS name CAS no.	Trade name(s)	Chemical name	Molecular formula	Chemical structure
Cyclopenta- decanone 502-72-7	Exaltone, Normuscone	Cyclopenta- decanone	$C_{15}H_{28}O$	
Cyclohepta- decanone 3661-77-6	Dihydro- civetone, Dihydro- civetone	Cyclohepta- decanone	$C_{17}H_{32}O$	
Oxacyclohexa- decen-2-one 34902-57-3	Habanolide, Globalide	Oxacyclohexa- decen-2-one	$C_{15}H_{26}O_2$	
1,4-Dioxa- cyclohepta- decane- 5,17-dione 105-95-3	Musk T, Musk NN, Astratone, Musk MC-5	Ethylene brassylate, Ethylene-1, 13-tride- candioate	$C_{15}H_{26}O_4$	
1,4-Dioxacy- clohexadecane- 5,16-dione 54982-83-1	Musk MC-4, Musk C14	Ethylendode- candioate	$C_{14}H_{24}O_4$	
1,6-Dioxa- cycloheptadecan- 7-one 6707-60-4	Musk 781, Cervolide	12-Oxahexa- decanolide, 12-Oxa-1,16- hexadecanolide	$C_{15}H_{28}O_3$	

The synthesis of macrocyclic musk compounds is difficult and in many cases a multi-step procedure. Due to the relatively high production costs, their economical importance is still limited. In 1996 they comprised about 5% of the total amount (8000 tonnes) of musk compounds [5]. In contrast to the nitro musks and the polycyclic musk compounds which are offered for 10–30 DM kg<sup>-1</sup> and 20–60 DM kg<sup>-1</sup>, respectively, the price for the macrocyclic representatives ranges from 50 to 5000 DM kg<sup>-1</sup>. Macrocyclic musks are expected to be of increasing importance in the future, especially because many of them are naturally occurring and even the artificial representatives (e.g., ethylene brassylate) closely resemble the natural counterparts [5]. In addition, the progress in synthetic chemistry contributes to declining prices and will stimulate increased use of this type of musks [60].

## 5 Perspectives

Due to critical public debates on the use of nitro musks and polycyclic musk compounds and the resulting regulatory limitations, the fragrance industry has put increasing emphasis on the development of macrocyclic and other musk odorants. A promising new class are the so-called linear musks. The first representative, a cyclopentenyl ester, was synthesized in 1975 and is being marketed as Cyclomusk. In 1990 another example (Helvetolide) of this class of compounds was discovered [61]. The future will show to what degree these new compounds will replace the “traditional” synthetic musk substances used so far to supply the fragrance industry with the desired musk odor.

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