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Synthetic musk odorants in cosmetic products

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Abstract

Musk has its place among the most important classes of odorants used in the perfume industry as it imparts sensuality, volume and diffusion to fragrance compositions. Synthetic musk odorants have been in use for over 130 years and are found in almost all fragrant consumer products including cosmetics and laundry detergents. The first group of synthetic musks comprised nitro musks. These are nitro derivatives of alkylbenzenes which, however, have been banned or their use has been limited to a significant extent. They were replaced by polycyclic and macrocyclic musks. Among the polycyclic musks, galaxolide and fixolide, derivatives of benzopyran and tetrahydrophthalene, were on the leading edge, respectively. Macrocyclic musks are cyclic ketones or lactones derived from the fragrance components of natural musk. The last, rationally developed and synthesised group are alicyclic musks, among which helvetolide and romandolide, esters of propanoic acid, have primacy. Currently, the new generation musk with a diene motif is synthesized and designed using the knowledge of the molecular target and molecular modelling methods.

Key words: Musk odorants; fragrances

1. Introduction

Substances with a musky scent remain the primary class of perfumery ingredients which provide the scent of perfume with its volume, diffusion and sensuality [1]. Initially, natural musk was used, but over the years it was replaced with synthetic musk, belonging to chemically diverse classes of organic compounds [2].

Natural musk is the secretion of the musk deer - Moschus ssp. It inhabits the mountainous forests of eastern Russia and several countries in southern and eastern Asia. This odorous secretion is used both to delineate territorial boundaries and to attract partners, as the so-called pheromone. The musk pouches obtained after killing the deer were dried and then subjected to alcohol extraction. The alcohol solutions thus obtained were used in perfumery. Tonquin musk from Tibet or China was considered the best. Musk was an extremely expensive and luxurious commodity, and the price of Tonquin musk grains was about twice their weight in gold at the beginning of the 20th century [2, 3].

Natural musk was legally used until 1979 when musk deer was placed under the protection of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES). Natural musk is currently used only in traditional East Asian medicine in amounts regulated by CITES or is alternatively obtained illegally [2].

This specific smell, similar in nature to natural musk, was also found in the compound called "Musk Bauer" accidentally obtained by Albert Bauer in 1888 (1, Fig. 1) [2, 4]. When used in the form of a 10% solution in acetanilide, it was half the cost of an ethanolic natural musk solution. From that moment the era of synthetic musk began.

Over approximately 130 years of synthetic musks being used, musks from the following four groups have been of significant importance: nitro, polycyclic, macrocyclic and alicyclic. Recently, a new group of musks with a diene motif - diene musks have been developed using molecular modeling methods for the receptor [5-7].

2. Nitro musks

The first group of synthetic musks were nitro derivatives of alkylbenzene. They were obtained unintentionally in 1888 by Albert Bauer, who was working on the synthesis of new explosives in the group of nitro derivatives of benzene. He received the following three essential types of musk: xylene musk (2) (1-*tert*-butyl-3,5-dimethyl-2,4,6-trinitrobenzene), ketone (3) (1-(4-*tert*-butyl-2,6-dimethyl-3,5-dinitrophenyl)ethenone) and ambrette (4) (1-*tert*-butyl-3-methoxy-5-methyl-2,4,6-trinitrobenzene) (Fig. 1). Nitro musk is most often the product of the nitration reaction of *t*-butyltoluene or *t*-butyloxylene [4]. It was the point of reference for musk for the next 50 years. For instance, Ernest Beaux's Chanel N° 5 (Chanel, 1921) perfume contained over 10% of nitro musk, mainly ketone, just as many other perfumes from that period. Musk ketone with an excellent odour threshold (0.1 ng/L of air) closely resembled the natural character of Tonquin musk, with a sweet, powdery, gentle, animal and warm character [8]. Xylene musk was commonly used in the production of soaps and powders because it had a slightly sharper odour. The unique feature of ambrette musk was the addition of a heavy floral side note to the persistent sweet tone of musk. Therefore, it was often used in floral perfumes and was difficult to replace when it began being withdrawn from the market in 1981 [9].

Research on further analogues from this chemical group has resulted in the production of a number of other types of musk, the most important being the Givaudan musk: musk tibetene (1-*tert*-butyl-3,4,5-trimethyl-2,6-dinitrobenzene) (5) and musk with a slightly different structure, an indene derivative, moskene musk (1,1,3,3,5-pentamethyl-4,6-dinitro-2*H*-indane) (6) (Fig. 1). It is believed to have an aroma similar to ketone musk [10].

Research on the relationship between the molecular structure and fragrance has shown that compounds with such a structure cannot have a molecular weight > 300 au to maintain their fragrance properties; they ought to have at least 2 nitro groups or one nitro one or alkoxy substituent; the t-alkyl substituent must be *ortho*- to the alkoxy group [11].

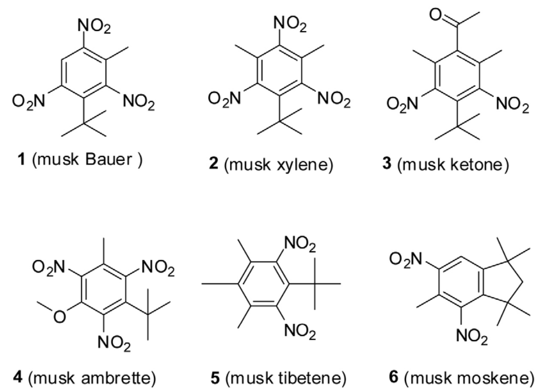

Fig. 1. Structure of the most popular types of nitro musks

The first generation of synthetic musks, nitro musks, constituted the basis in the perfumery business until the 1950s, when attention was paid to their instability and various side effects [9, 12, 13]. They include, amongst others, photosensitising and skin irritating factors [14, 15], and some of them are attributed with endocrine disorders and carcinogenic effects [9, 16, 17].

Currently, it is forbidden to use ambrette, tibetene and moskene musks in cosmetic products. Xylene and ketone musks can only be used in cosmetics with restrictions (Annex III, based on the recommendations of SCCNFP, SCCNFP / 0817/04). Therefore, they are being replaced with other chemical compounds, both of natural (plant) and synthetic origin, which have the so-called musky smell.

3. Polycyclic musks

3.1. Structure and characteristics

Polycyclic musks (PCM) were created between 1955 and 1970. This group includes, among others: galaxolide/pearlide (7), traseolide (8), celestolide/crysolide (9) with the indane system (Fig. 2) and fixolide/tonalide (10), versalide (11), vulcanolide (12), which are derivatives of tetrahydronaphthalene (Fig. 2). They are all aromatic condensed derivatives. Some of them: galaxolide (7), fixolide (10), vulcanolide (12) are in the form of stereoisomers [4]. These compounds have a characteristic intense, sweet, musky fragrance with dry tones of powder and amber. They are rich, round, base notes musk. Among the features which made them very popular there are a very high durability (250 to 400 hours on a blotter) and often low production costs.

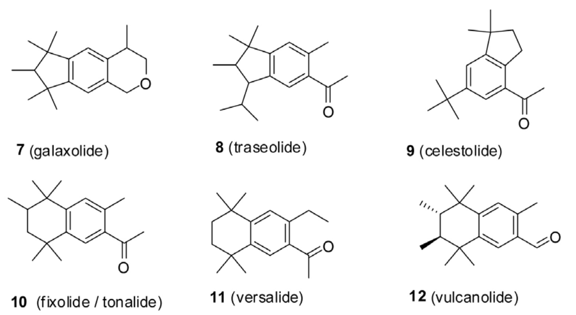

Fig. 2. The polycyclic musk fragrances

3.2. Galaxolide

IUPAC systematic name: 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[*g*]-2-benzopyran. Galaxolide (HHCB) was obtained for the first time in 1965 by Heering and Beets working in the laboratories of the IFF concern. The odour threshold for the commercial mixture of Galaxolide® isomers is 0.9 ng/L of air [18]. However, for other stereoisomers or a different mixture have this parameter may vary [4]. This compound is characterised by a musky fragrance with floral notes and can be sensed for 400 hours. It is used as a masking agent or aromatic substance in fragrance compositions. As it has high stability in an alkaline environment and is photostable, it is a commonly used component of fragrance compositions in soap, detergent and other cosmetic formulas [19]. Despite being on the market for over 50 years, this substance is still used in a wide range of cosmetic products, and its annual production is estimated at around several thousand tons. Amongst others, galaxolide had a share of 21.4% in Trésor perfumes created by Sophia Grojsman (Lancôme, 1990) [2].

3.3. Traseolide

IUPAC name: 1-[(2R,3R)-1,1,2,6-tetramethyl-3-propan-2-yl-2,3-dihydroinden-5-yl]ethenone (8) (Figure 2). Traseolide is a simple indane derivative where the basic bicyclic skeleton is modified with Me groups, isopropyl group and acetyl substituent. It is a compound from the group of aromatic ketones.

Traseolide has a musky, sweet, creamy fragrance with a hint of sandalwood. Gives a good fixing effect in fragrance compositions. Being a cheap compound, it is used in significant proportions. About 10% share in the fragrance concentrate provides a harmonising/mixing effect, as well as smooth richness of the fragrance and its preservation [20].

3.4. Tonalide (fixolide)

Tonalide, IUPAC name: 7-acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene (AHTN) (10) (Fig. 2). It was promoted by the IFF in 1967. It is an acetyl derivative of tetrahydrophthalene. It possesses a musky, sweet, dry, amber, powdery fragrance with elements of wood notes. It is one of the few types of musk which has stood the test of time. It is widely used in the recipes of many cosmetics. Fixolide gives beneficial combinations with coumarin, which is a very desirable ingredient in perfumes for men. It combines well with the following notes: powdery, sweet, woody, vanilla, incense, animal [21].

3.5. Safety of use of polycyclic musks

Polycyclic musks (PCM) at the end of the 20th century accounted for about 3/4 of all types of musks used in the chemical industry due to their remarkable durability and low cost of production. They appeared in perfumes and other categories of cosmetic products, but also on a mass scale in the production of soaps and washing powders. Among the seven polycyclic kinds of musk, galaxolide turned out to be unrivalled, while tonalide was ranked second. It is estimated that their total consumption was 3800 and 1500 tons in 1997 for Europe and the USA, respectively. These types of musk accounted for 95% of the total polycyclic musk production in 1996.

Initial studies on safety of using PCM did not imply any significant toxic and dermatological effects. The physicochemical properties and the octanol-water partition coefficient (log K_{ow}) of AHTN (5.7) and HHCB (5.9) suggest that these compounds will bioaccumulate. Moreover, their high level of consumption as well as extremely high chemical stability and low biodegradability indicated the need to reduce their use and replace them with other groups of compounds [22, 23]. Indeed, AHTN and HHCB have been detected in human breast milk and adipose tissue, fish, clams, shrimp and otters [24]. Very low biodegradability resulted in persistence in the water processed in sewage treatment facilities, accumulation in sediments and in adipose tissues of animals and humans [25-27]. Moreover, some studies suggest that they may have an ecotoxicological effect on certain organisms and cause endocrine disorders [23]. These compounds are forbidden for use in certain groups of perfume. They are not biodegradable and therefore their use is limited. Parallel to this, research into macrocyclic musk has made it more affordable and more diverse.

4. Macrocyclic musks

4.1. Structure

Macrocyclic musks, the third group, are derived from the ingredients of natural types of musk and are based on their structure. In 1926, Leopold Ruzicka isolated and chemically identified a molecule found in musk deer which primarily gave musk its characteristic smell and named it muscone ((R)-3-methylcyclopentadecanone) (13, Fig. 3). It was then discovered that removing the methyl group and leaving the initial cyclic system yields a compound with an acceptable musky odour profile. Thus, the first synthetic macrocyclic ketone, exaltone musk was formed (14, Fig. 3). Large carbon rings with a ketone group were difficult to synthesise, so attempts were made to replace the carbon atom with an oxygen atom or to introduce an additional oxygen atom. Compounds of this type were much easier to synthesise. In this way, a series of macrocyclic musks from the lactone group was obtained, such as exaltolide (17) or silvanone supra (18, Fig. 3) [28].

Macrocyclic musks are either naturally occurring compounds obtained by synthesis, or primarily they are new analogues based on the structure of natural compounds. Some are also obtained from plants. They were formed as a result of a simple modification of the lead molecule, consisting in changing the number of carbon atoms in the ring, introducing an oxygen atom, introducing a double bond or its different position. However, this translates into completely different methods of synthesis which in many cases are rather complicated.

Macrocyclic musks are C15-C17 ketones such as muscone (13), exaltone (14) or civetone (16) or C15-C16 lactones such as exaltolide (17) and silvanone supra (18) [4].

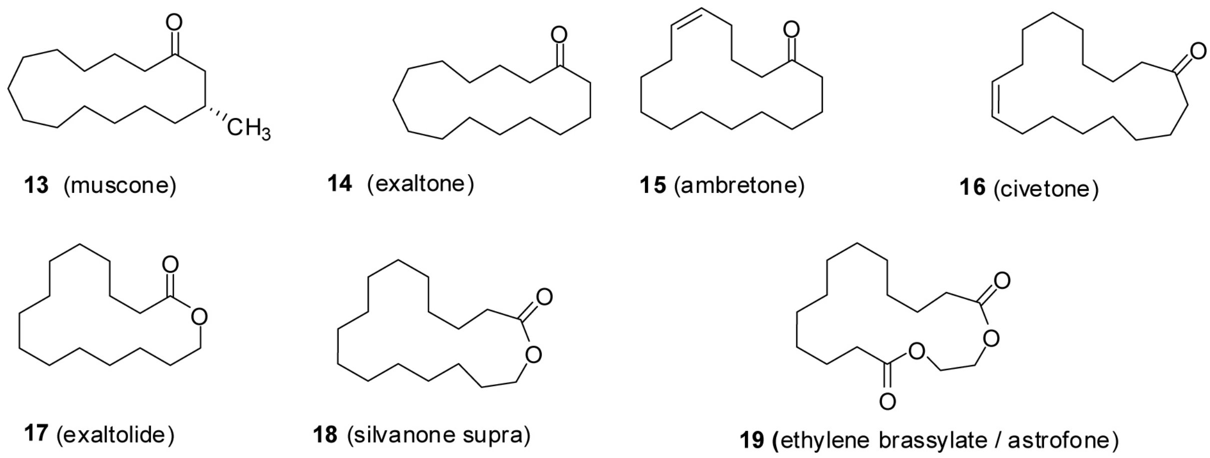

Fig. 3. The macrocyclic musk fragrances

4.2. Methods of synthesis

Obtaining macrocyclic musks often require complicated synthesis methods connected with high consumption of raw materials, generation of waste and pollution, and significant expenses [29]. One effort to reduce costs of synthesis has been the development of lactone systems instead of using cyclic ketones. Currently, scientists are working on the use of renewable sources for the synthesis of such systems. Particular attention is paid to the possibility of using biomass and enzymes for this purpose. With the development of the bio-industry, many researchers became involved in the chemo-enzymatic production of macrolactone musk. Lipase from *Psudomonas cepacia* having the ability to catalyse transesterification, esterification, aminolysis and oxymolysis reactions in organic solvents was used for the synthesis of hexadecanolide, exaltolide and ambrettolide. The cascade of enzymatic reactions involving cytochrome P450 hydroxylase and lipase was used for the biosynthesis of exaltolide lactone musk (17) with pentadecanoic acid and silvanone supra (18) (Fig. 3) [30].

4.3. Ambretone

Ambretone, IUPAC name: (5*E*)-cyclohexadec-5-en-1-one (15, Fig. 3). It is among the most popular macrocyclic unsaturated synthetic types of musk. This substance does not occur in nature. The compound is characterised by an intense musky scent with notes reminiscent of natural civet. It also has a smell similar to that of nitro musks. This substance maintains the fragrance for 400 hours after being applied to the blotter and has an intense and lasting fragrance, has high stability and is easily biodegradable. It is widely used both in the cosmetics industry, where it is, for instance, a component of parfume fragrances, and in household chemicals, e.g. in washing products. The recommended proportion of this component in the fragrance concentrate cannot exceed 4% [31].

4.4. Exaltolide

Exaltolide, IUPAC name: oxacyclohexadecan-2-one (17, Fig. 3), is a sixteen-carbon saturated hydroxypentadecanoic acid lactone. This compound was discovered in 1927 by Max Kerschbaum, working for Haarmann & Reimer, in the essential oil of Angelica root (Archangelica officinalis), a plant of the celery family. It is obtained mainly by various synthetic methods or from the essential oil acquired from the angelica root in which it occurs in small amounts. Biotechnological methods are also being developed. This compound has a light, buttery, waxy, sweet smell and is felt for 400 hours on the blotter. Exaltolide is used in the production of various types of cosmetic products as a valuable fragrance fixative and ingredient in fragrance compositions. According to the IFRA recommendations, it is used with restrictions - depending on the product category. The maximum quantity may not exceed 5% [2].

4.5. Ethylene brassylate

Ethylene brassylate, IUPAC name: 1,4-dioxacycloheptadecane-5,17-dione, also known as musk T and astrophone (19, Fig. 3). Chemically, it is a cyclic diester of ethylene glycol and 1,13-tridecanedioic acid (common name: brassylic acid). This substance has a characteristic powdery-musky scent with notes of wood and flowers. It also has notes associated with vanilla, the scent of ambretta seeds and talcum powder. It is characterised by medium intensity with a lasting bottom note. It is a universal fixative for all fragrances and a carrier of a musky note. Its shelf life is approximately 208 hours after blotter application. This musk is known commercially by several names. As ethylene brassylate it is offered by American companies such as: Berje, Vigon Penta International and Spanish Ernesto Ventos. It is marketed under the name Musk T by Takasago (Japan) and Prinova (United States), and under the name MC-5 by Soda Aromatic (Japan). Since it is a universal compound, it is also included in a wide range of products - both of floral character and those with natural musk notes [32].

5. Linear musks

5.1. Structure

Alicyclic musks, also referred to as linear, are the most recent group of synthetic musks. Their development followed the invention of helvetolide in 1990 (20) and - 10 years later - romandolide (21) (Fig. 4). The next, newer generation of linear musks are sylkolide (22) and serenolide (23), which are esters of cyclopropanecarboxylic acid, and appelide (24) - malonic acid diester (Fig. 24). Sylkolide is considered to be of the highest quality in this group. Combining alicyclic and macrocyclic musks is a very frequently used procedure, amongst others in order to obtain the so-called "white musk accord" [1].

5.2. Helvetolide

Helvetolide, IUPAC name: (1'*R*,4*S*)-4-(3',3'-dimethyl-1'-cyclohexyl)-2,2-dimethyl-3-oxapentyl propanoate (20, Fig. 4). It is also known as musk propanoate. This musk was obtained in 1990 by Giersch and Schulte-Elte working for the Firmenich. Helvetolide has an odour threshold of th=1.1 ng/L of air and activity 3.87 pM [1, 33]. It is the first synthetic linear musk to be used commercially with great success. Its predecessor, cyclomusk, in the 1970s, did not stand a chance against the commonly used galaxolide. Helvetolide is described as musk-ambrette, rich, having a fruity aroma with a pronounced pear accord. It works very well in combination with other musks [1].

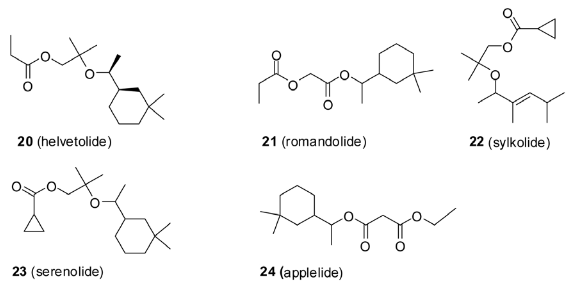

Fig. 4. The linear musk fragrances

It has a synergistic effect against substances such as exaltone, exaltolide and habanolide. As a result, the fragrance of these musk complexes, when used in very small doses, is clearly enhanced. This fragrance is classified between musk ambrettolide and ethylene-brassylate. Helvetolide works particularly well in liquid applications (shampoos, body washes, alcohol solutions) as well as in emulsions. It is very diffusive musk and one of the few musks with the highest notes [31]. Helvetolide was used by Alberto Morillas in the Emporio Armani White for Her perfumes with a share of 8.8% (Armani, 2001) and in Flower with a share of 3.8% (Kenzo, 2000).

5.3. Romandolide

Romandolide, IUPAC name: 2-[1-(3,3-dimethylcyclohexyl)ethoxy]-2-oxoethyl propanoate (21, Fig. 4). This musk was introduced by Firmenich. Romandolide has an odour threshold of th=0.4 ng/L of air and activity 1.48 pM. This compound was obtained by Alvin Williams by replacing the gem-dimethyl group present in helvetolide with a carbonyl group, in search of a molecule which would be easier to synthesise. It allowed to maintain the musky and fruity fragrance, and the blackberry nuance of helvetolide turned into a camphor side note.

Romandolide has a subtle musky note, is less fruity and more camphorous, and less ambrette than helvetolide. It is characterised by greater durability and volume. It can be used as a replacement for PCM and is stable in most applications. Being a pure, heavy, long-lasting fragrance, it in many ways resembles Galaxolide® musk. Although it is more diffusive than macrocyclic and polycyclic musks, it behaves similar to this type of synthetic musk. Increasingly, it is a more expensive and greener alternative to Galaxolide® in modern perfumes [31]. Romandolide is located, among others in recipes of such perfumes as: Absolu in the share of 5% (de Rochas, 2002) or Murmure in the share of 1.0% (Van Cleef & Arples, 2002) [1].

5.4. Serenolide

Serenolide, IUPAC systematic name: 2-[1-(3,3-dimethylcyclohexyl)ethoxy]-2-methylpropylcyclopropanecarboxylate (23) (Fig. 4). This musk was promoted by the Givaudan. It has an odour threshold of 0.39 ng/L of air and is approximately 3 times lighter than helvetolide [33].

5.5. Sylkolide

Sylkolide, IUPAC name: (3’*E*)-2-((3’,5’-dimethylhex-3’-en-2’-yl)oxy)-2-methylpropylcyclopropanecarboxylate (22) (Fig. 4). With its fruity and sweet fragrance, this musk was promoted by Givaudan. It can be found in the recipes of the following perfumes: Big Pony 4 for women by Ralph Lauren, My Pearls for women by The Merchant of Venice; Glory Musk by Arabesque Perfumes for women and men. Sylkolide has a radiant note of musk with accents of red fruit, which, due to the high volatility of the compound, are already visible in the top notes. It also contains some woody aspects as obtained in Ever Bloom perfumes (Shiseido, 2015) [1].

5.6. Applelide

Applelide, IUPAC name: 3-O-[1-(3,3-dimethylcyclohexyl)ethyl]-1-O-ethyl propanedioate. This musk was promoted by the IFF, has an odour threshold of th = 1.5 ng/L of air and is relatively easy to synthesise [1]. It is a powdery, creamy, warm, sensual-relaxing white musk containing fresh fruity notes and soft, soothing textures. Musk is particularly unusual in the top note, with a fruity dry element. It is described by Arcadi Boix Camps as one of the most versatile floral and fruit substances, creating impressive accords with products such as undecavertol, coranol, lilial. Gives the connections unique characteristics which cannot be substituted with any others [31].

5. Summary

Although the first musks, nitro, were a matter of a coincidence, the next generations were created as a result of the knowledge of the structure of the molecule and more or less rational design of subsequent molecules. Others were created as a result of the analysis of the structure of essential components of natural musk and the rational design of further analogues with a slightly different range of fragrances or physicochemical properties.

Apart from, of course, the most important feature which is the characteristic fragrance, the musks had to be non-toxic to humans and animals as well as easily degradable. These factors left some musks no longer attractive due to the threat to animals and the environment, or banned from use as they turned out to be dangerous to humans. Others, instead, began to play a dominant role.

Manufacturing costs were another important factor [34]. Some molecules were difficult to obtain, required many synthesis steps, purification methods, high consumption of reagents, which determined the high price of the product and naturally limited the application. The emerging new possibilities in synthesis, such as selective and stereoselective catalysts or biotechnological methods, often lowered the price and increased the interest of cosmetic manufacturers in these musks [29].

For several years, intensive research has been carried out on another group of musk with a diene motif by Kraft and colleagues [5-7, 35]. These musks are already the result of rational design of compounds using the knowledge of the molecular target and molecular docking techniques [6]. Compounds which are easy to synthesise, and therefore relatively cheap and biodegradable, are expected.

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