

2019 High Impact
Aroma Molecules E-book

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- High-Impact Aroma Chemicals
- Synthetics and the Future
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2019 HIGH IMPACT AROMA MOLECULES E-BOOK

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Welcome to Your High Impact Aroma Molecules E-Book



Balancing out the volatility of the unpredictable raw material market, high impact aroma molecules offer perfumers and flavorists a wider palette to reach evolving consumer demands for wellness, clean label and enjoyment all over the world. With a low odor threshold, recognizable and desirable impact and stability, among others, molecules are a growing presence for the industry.

Along with establishing regulatory compliance and economic viability (both commercially and internally as captives,) a pressing issue behind the aroma chemicals market is how to reframe its presence in a “natural-is-better” world. It’s an issue worth exploring from the F&F industry through communication and education for both customers and consumers, who are concerned with the safety and aromatic authenticity of an aroma molecule.

But still, the aroma chemicals market is expected to boom, according to Market Watch, reaching projections of \$47 billion by 2023 with a CAGR of 8.5%. With this growth comes a myriad of ways to develop aroma chemicals for the future, and we’re thrilled to put this e-book together, brought to you by Bedoukian Research, from Perfumer & Flavorist’s expert authors to bring more insight to your work.

We hope you enjoy this e-book.

Warmly,

Deniz Ataman
Managing Editor, *Perfumer & Flavorist*

^a Market Watch Report: 8.5% CAGR | Aroma Chemicals Market Will Hit The Value By 2026

More Fizz for Your Buck: High-impact Aroma Chemicals

■ by David Rowe, Oxford Chemicals,
North Gare, Seaton Carew, Hartlepool, UK

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Developments in the flavor and fragrance industry have gone hand-in-hand with advances in the chemical sciences. From the 19th Century, in which saw the identification and synthesis of key materials such as cinnamaldehyde and vanillin, to more recent decades, advances such as 'hyphenated techniques', in particular GC-MS and GC-Olfactometry, have enabled flavor chemists to identify the compounds present in natural materials. Some of these compounds, though present at only trace levels, are key contributors to the odor and flavor of natural materials. This has been augmented recently by the use of solid phase microextraction (SPME) to capture the aroma chemicals at source, such as the IFF's 'Living Flower' and 'Living Flavor' technologies and Givaudan's 'Taste-Trek' studies on aroma chemicals emitted by plants in the rain

forest canopy. Many of the materials identified are high-impact aroma chemicals, which will be discussed in this article.

The term 'high-impact aroma chemical' is one that many of us can understand but for which there is no official definition. I will set four key criteria that, for the purpose of discussion, will define these chemicals:

- Low odor threshold. This is an obvious feature, but there is no absolute definition of low to which we can turn. For the purpose here, I have set low odor threshold at less than 10 parts per billion (10 ppb, or 10 in 10⁹). Some apparently odorous compounds fall out by this definition. For example, 2,3,5-trimethylpyrazine (**1**) has an odor threshold¹ of around 1000 ppb and cannot be considered high-impact. However, the

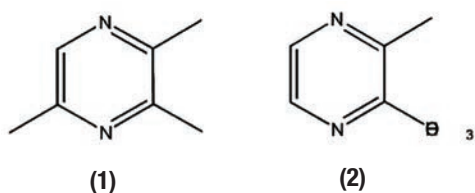
2-alkoxy-3-alkylpyrazines, such as 2-methoxy-3-methylpyrazine (2), which has an odor threshold of only five ppb, would constitute a high-impact material by our definition.

- Character impact. The material should have recognizable character, even at the low levels that such a material would be used at. This criterion eliminates many esters, such as ethyl 2-methylbutyrate (3), which has an odor threshold of only 0.1 ppb, but at low levels has only a vague fruitiness, which may be pleasant but not characteristic.
- Desirable character impact. Although many chemicals have a powerful odor, this characteristic is not always a desired one. For example, 2,4,6-trichloroanisole (4) is a highly odorous metabolite of a fungus that attacks paper. However, it is highly improbable that this can be considered a high-impact aroma chemical, because it is unlikely that a flavorist or perfumer will have a brief to recreate the aroma or taste of moldy books.

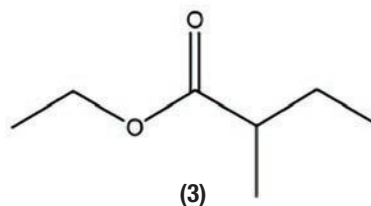
This is of course a matter of context, because many aroma chemicals are repellent when neat or in high concentration. In the correct context, however, they contribute to the desired effect. For example, the nature of 4-mercapto-4-methyl-2-pentanone (5) can be gleaned from its common name of Cat Ketone. However, it is also a key component of sauvignon grape.² Depending on the context, it can be used to recreate the bouquet of a fine cabernet sauvignon or the atmosphere of where the local alley cats have marked their territory.

- Availability to the flavorist. There are three aspects here: (i) Regulatory. The material should not be forbidden in the context in which it is to be used. For flavor use, the material should be nature identical, preferably FEMA GRAS. Natural status may be important, especially for the US where the nature identical category is lacking. (ii) Stability. Many materials can be manufactured but have insufficient shelf-life to be useful in a finished flavor. For example, *cis*-3-hexenal (6) is a key aroma chemical emitted by cut grass and other vegetation; it

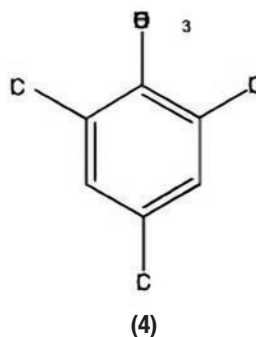
F-1. Contrasting pyrazines



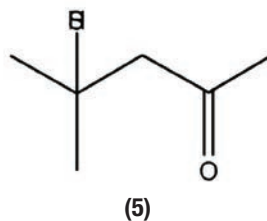
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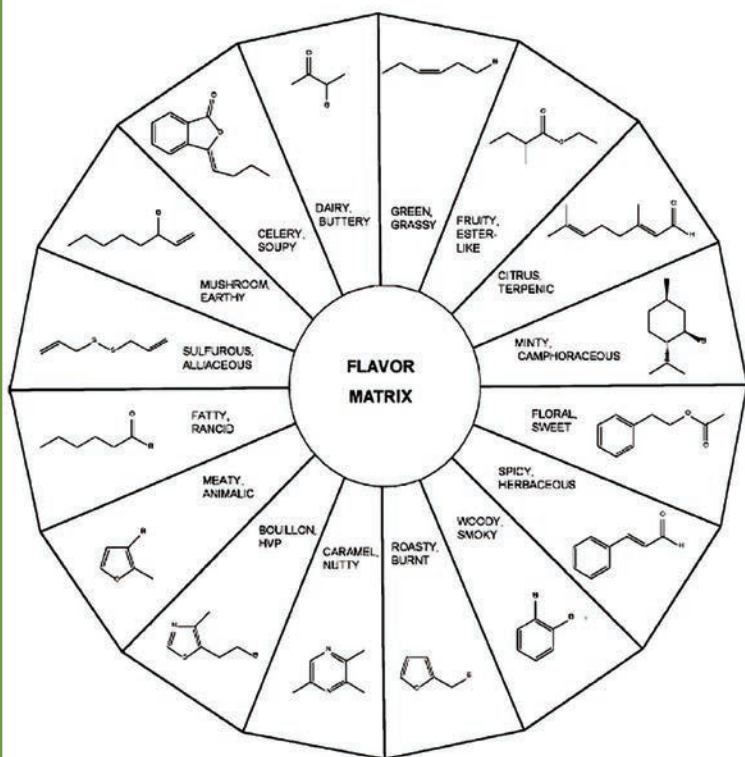
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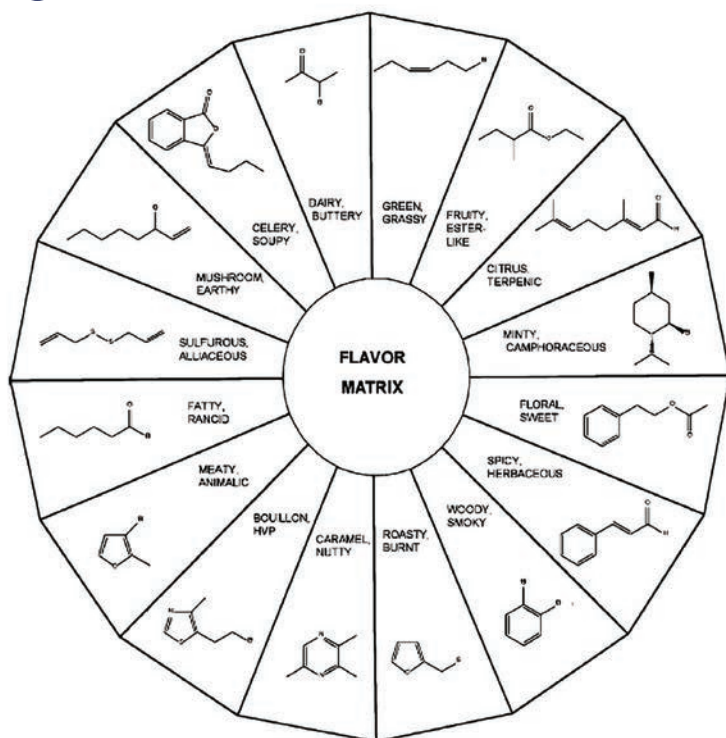
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F-7. A "Traditional Flavour Wheel"



F-8. A Flavor Wheel for High Impact Chemicals



has a low odor threshold (0.25 ppb) and a powerful, desirable green character. Unfortunately, it is chemically reactive, and readily rearranges to the more stable conjugated form, giving the more familiar *trans*-2-hexenal (7). Even the 'half-life' of the isolated material may not be enough to guarantee a useful level of stability. The rearrangement is 'prototropic' and hence catalysed by both acid and base; the rate will be increased by a factor of ten for each pH unit away from its 'optimum' stability point.

(iii) Economics. Many high-impact chemicals are relatively expensive, which reflects the small market volume and the difficulties associated with manufacturing and handling such materials. However, the material must be commercially available at a price that enables a flavorist or perfumer to add value to their formulation by its use. If the material is captive, the internal costs must not be prohibitive. In short, despite high prices, the high impact of these materials gives 'more fizz for your buck'. An example of this can be seen from garlic chemistry. The major component of garlic oil is allyl disulphide (8) (2-propenyl disulphide). The isomeric 1-propenyl disulphide (9) is also present (*cis*- and *trans*- forms), but whereas the former is readily synthesised, and hence cheap and readily available, no suitable route for large-scale preparation of the latter exists at present. Laboratory syntheses have been reported, but the costs of a material made in such a way means that any advantage in the flavor is outweighed by a vast increase in costs. The added value is therefore insufficient.

For the purpose of this discussion, high-impact chemicals are those which fulfil these criteria. Such compounds are powerful materials, highly active at low levels, the Viagra^a of the flavor and fragrance industry.

^aThis article is in part based on a presentation given at the ChemSources Association/Society of Flavor Chemists meeting in Cincinnati in April, 2000. At the same meeting, Carl Sheeley (Fontarome, St. Francis, WI) gave a presentation on how aroma chemicals related to the classifications generally used in the chemical industry. Commodity chemicals included solvents, and bulk chemicals, the widely used esters. Flavor and fragrance formulations included specialty chemicals and fine chemicals as active ingredients, whether pharmaceuticals (with Viagra as the example) or high-impact aroma chemicals. The author is very grateful to Carl for this uplifting imagery.

Uses

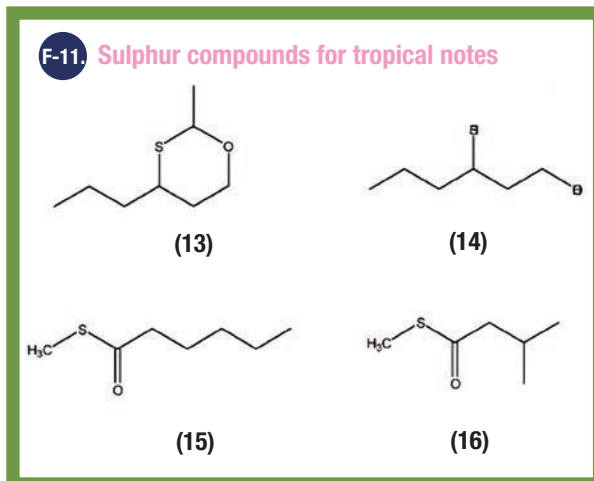
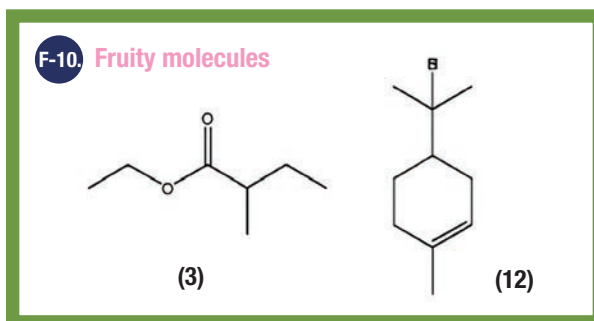
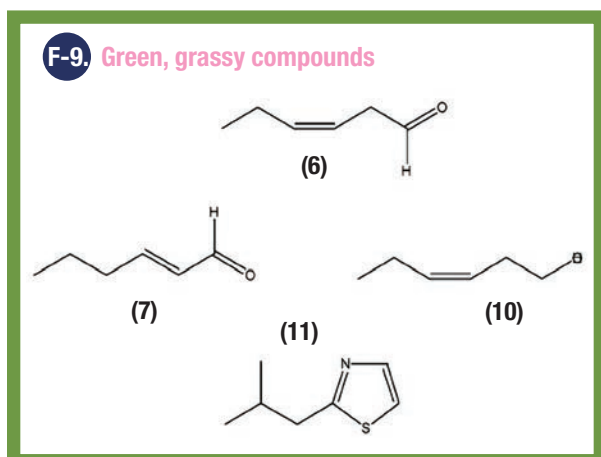
High-impact chemicals have been identified in many foodstuffs and have many applications, to the extent that a simple listing would make dull reading. At first thought it would seem appropriate to use the sixteen key notes of a flavor wheel to illustrate the applications. However, a traditional flavor wheel, as shown at left, is not very helpful. There is little to say for mint, camphoraceous that is not known from the menthol/camphor derivatives. There is nothing high-impact for dairy, buttery, and intensely floral, sweet character is best known in the synthetic materials of perfumery. Instead of the traditional wheel, an adapted flavor wheel can be used. The extra areas are extensions of the meaty notes, extensions of the fruity notes into tropical and blackcurrant, and division of the allium into both onion and garlic. Here we can illustrate the uses of high-impact chemicals in these sixteen segments.

Green, Grassy

In this category, the traditional molecules are the hexenyl compounds. As noted above, the true high-impact chemical in this group is the unstable *cis*-3-hexenal (6), the initial cleavage product of linoleic acid. The stable aroma chemicals *trans*-2-hexenal (7) (leaf aldehyde) and *cis*-3-hexenol (10) (leaf alcohol) are widely used. However, with odor thresholds of 17 and 70 ppb, respectively, they are borderline cases as high-impact chemicals. Despite this, their distinctive character is in their favor. A fresh greenness is also associated with the more odorous 2-isobutylthiazole (11) (odor threshold three ppb). This molecule is released by tomato vine and has both tomato and more general green (string bean, geranium leaf) character, especially on dilution.

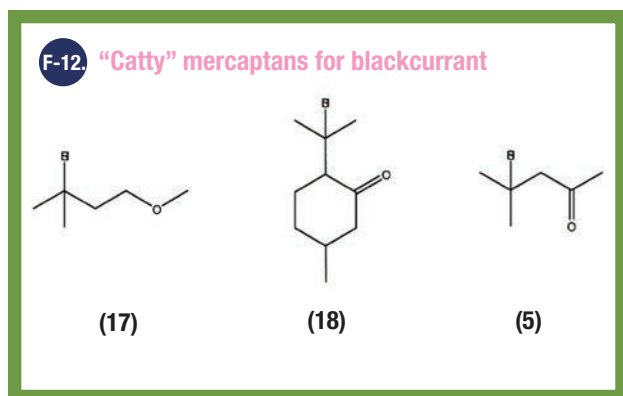
Fruity, Ester-Like

The esters are obvious candidates here. However, while many have low odor thresholds (ethyl butyrate one ppb, ethyl isobutyrate 0.1 ppb, ethyl 2-methylbutyrate (3) 0.1 ppb, ethyl hexanoate one-two ppb), they lack



the character which would make them truly high-impact. Instead, we may illustrate fruity notes with what may be the ultimate high-impact aroma chemical, *p*-1-menthen-8-thiol (12), the grapefruit mercaptan. This has the remarkably low threshold of $\sim 10^{-5}$ ppb, and retains its character even at low levels. At high concentrations, the molecule simply has a sulphurous, almost rubbery odor common to mercaptans, and requires dilution to at least 0.001% before the fresh grapefruit juice character can be recognized.



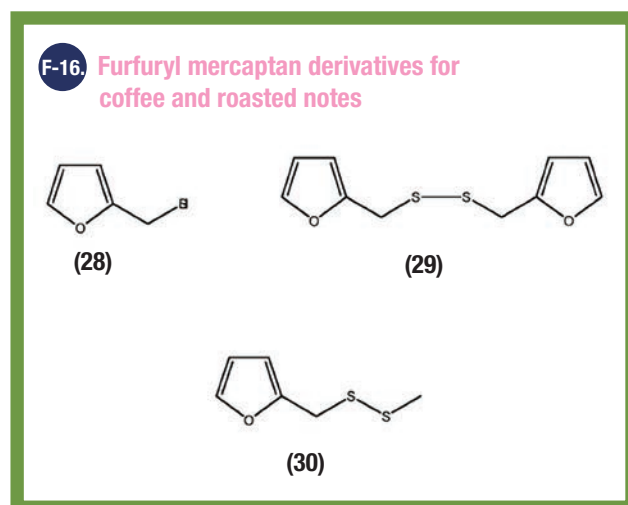
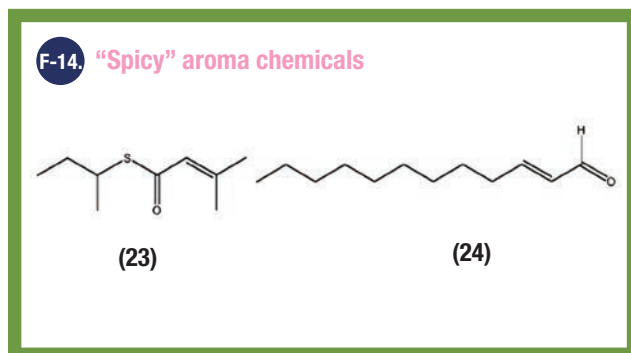
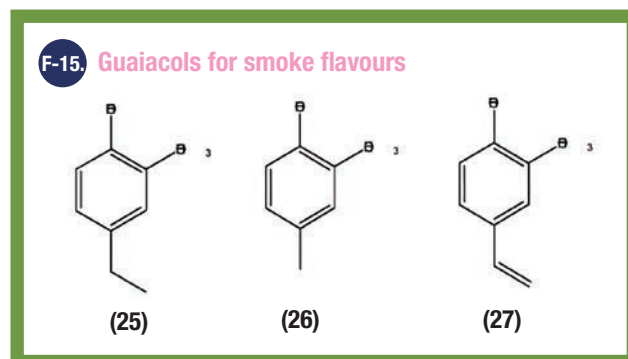
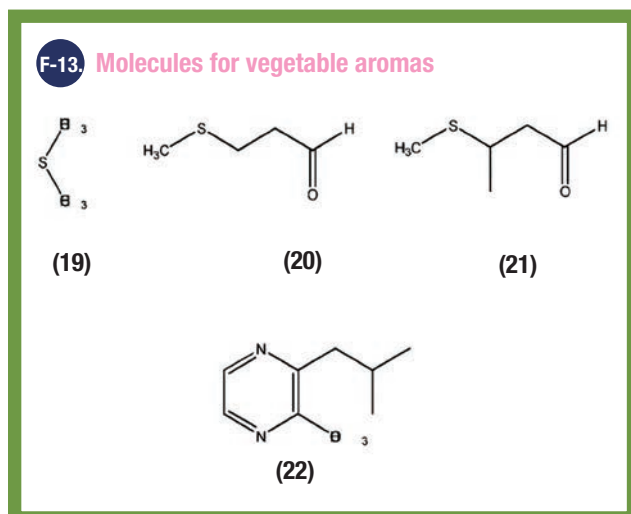


Tropical

This is one of the most important areas for high-impact aroma chemicals. Analysis of passionfruit and durian has shown the presence of many powerful sulphur compounds, a large number of which were included in FEMA's GRAS 18 list in 1998. Possibly the best known is trophathiane, 2-methyl-4-propyl-1,3-oxathiane (13), (odor threshold ~3 ppb); 3-mercapto-1-hexanol (14) and a number of acylated derivatives were included in FEMA's GRAS 18 list, as were thioesters, including thiohexanoate (15) and thioisovalerate (16).

Blackcurrant

This is a very popular flavor in Europe, associated with many health-related products (nutraceuticals or functional foods) and with alcoholic drinks (cassis liqueur, and added as a cordial to some spirits). The key material in blackcurrant is 2-methoxy-4-methyl-4-butanethiol (17); it is also a key component contributing a fruity flavor to olive oil.³ Two other materials have been used to recreate the rather catty note of blackcurrant; *p*-menthathiolone (18), the main odor-active ingredient of Buchu leaf oil, and



4-mercapto-4-methyl-2-pentanone (5), the cat ketone mentioned earlier.

Vegetable

This is obviously rather a large category. A compound of major importance is the ubiquitous dimethyl sulphide (19) (DMS, methyl sulphide, odor threshold ~3 ppb). When pure, this has a clean, crisp, sweet corn odor. Some material on the market lacks this note and has unpleasant, sulphurous, rotten cabbage odors. GCMS on such material has shown the presence of dimethyl disulphide and methyl ethyl sulphide. Other powerful compounds for vegetable notes are 3-methylthiopropenal (20) (methional, odor threshold 0.2 ppb) and its homologue, 3-methylthiobutanal (21). On a more specific note, we should mention 2-isobutyl-3-methoxypyrazine (22), the bell pepper pyrazine. It is the main character-impact compound found in green or bell peppers, with a very low odor threshold of 0.002 ppb.

Spicy, Herbaceous

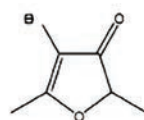
This is another very general category. Many essential oils used in flavors and fragrances are derived from herbs and spices, with a vast range of terpenoid components. From the perfumery sector, particular mention may be made of the thioester *sec*-butyl 3-methylbut-2-enthioate (23), a major contributor to the odor of galbanum oil. *Trans*-2-dodecenal (24), possessing a persistent fatty-citrus-herbaceous odor, is a character impact component of coriander.

Woody, Smoky

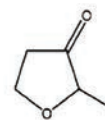
Guaiacols are very important in this area. 4-Ethyl- and 4-methylguaiacols, (25) and (26), have rather phenolic,



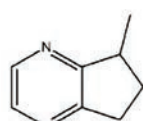
F-17. Molecules for "caramel" and "nutty" odours



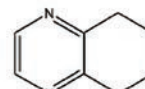
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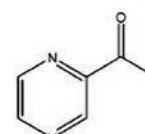
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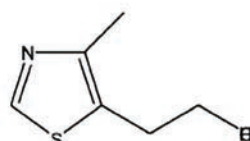


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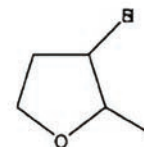


(35)

F-18. Savoury, bouillon compounds

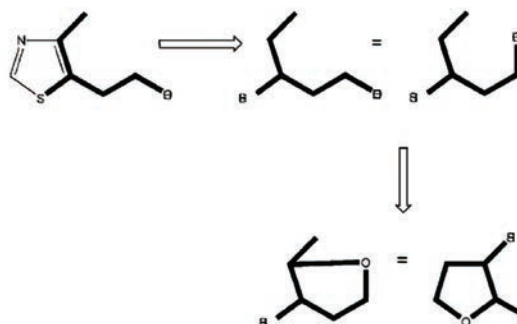


(36)



(37)

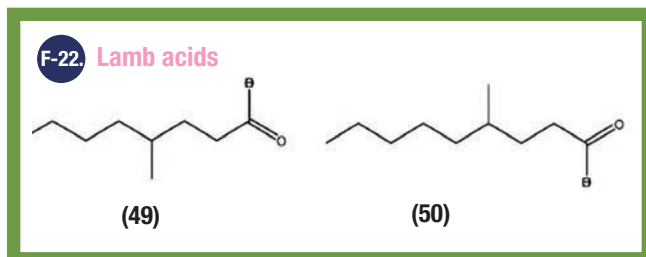
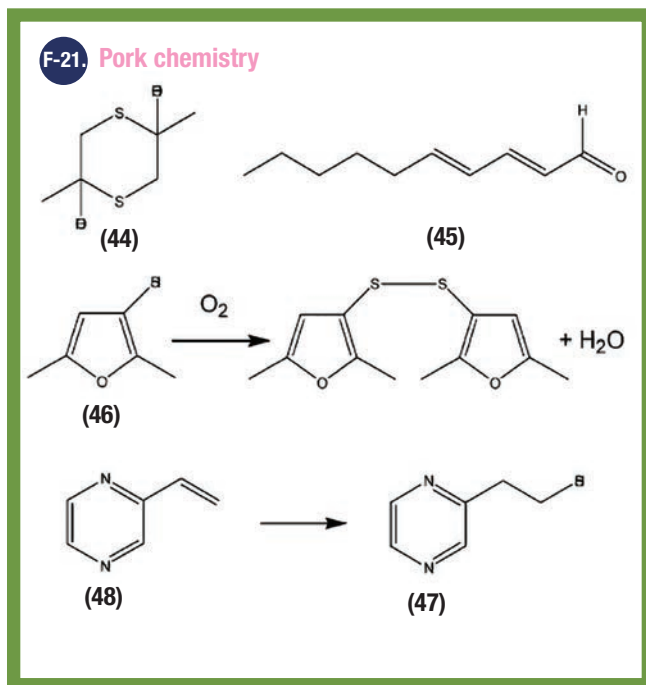
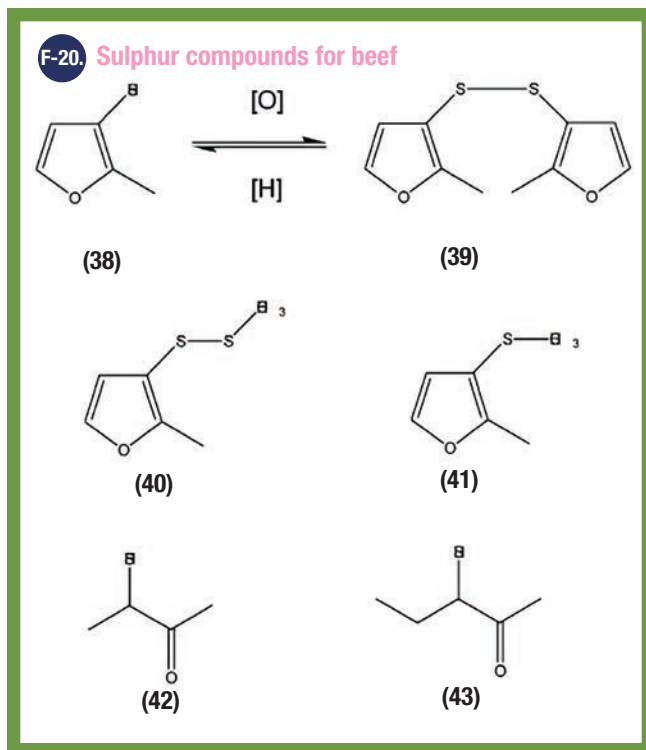
F-19. Structural relationship between sulphurol and 2-methyltetrahydrofuran-3-thiol



medicinal odors with thresholds of 90 and 50 ppb, respectively. However, more important is 4-vinylguaiacol (27) (2-methoxy-4-vinylphenol, MVP). This has a spicy, clove-like smokiness particularly associated with smoked ham, and a low odor threshold of only three ppb. It is available in a natural form.

Roasted, Burnt

This sector is the first associated with cooked food; in this and the following sectors the high-impact chemicals are those produced in the Maillard reaction. For roasted and burnt notes, derivatives of furfuryl mercaptan (28) are paramount. The mercaptan itself, with an odor

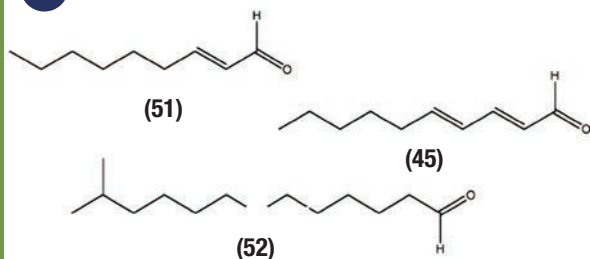
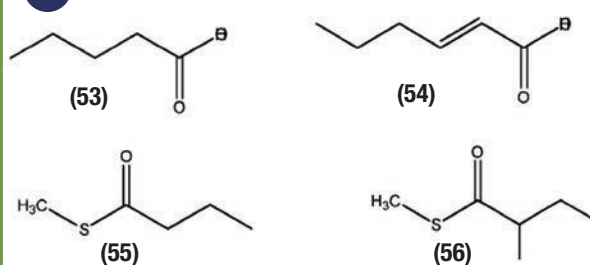


threshold of 0.005ppb, was the first high-impact aroma chemical to be identified. It exhibits one of the classic phenomena associated with high-impact chemicals, the change in the nature of the odor with concentration. At low concentrations (0.01-0.5ppb), the material has a roasted-coffee aroma, becoming burnt and sulphurous in the range 1-10ppb. The neat material has no coffee odor, only an unpleasant oily smell resembling gasoline. Derivatives of furfuryl mercaptan tend to be somewhat less odorous; the disulphide (29) (dithiodimethylenedifuran) is much less obnoxious, and the mixed disulphide furfuryl methyl disulphide (30) has a pleasant sweet coffee (mocha) aroma; the latter has an odor threshold of 0.04ppb.



Caramel, Nutty

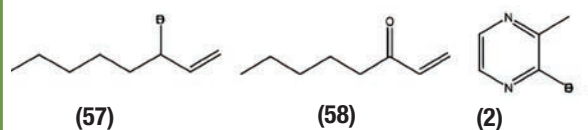
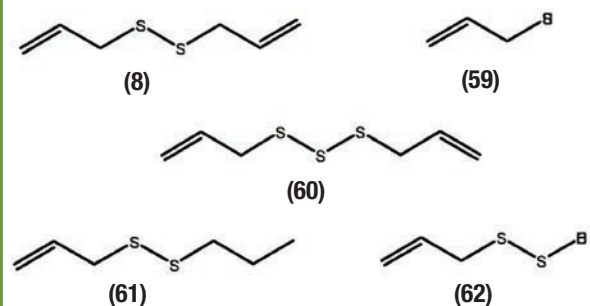
These two classifications are at first sight rather disparate, but are again linked by the Maillard reaction. The key materials in this group are pyrazines and furans formed from sugars and amino-acids. The ubiquitous hydroxydimethylfuranone (31) has a sweet, 'cotton-candy' aroma and a low odor threshold of 0.04ppb. 2-Methyltetrahydrofuran-3-one (32) (coffee furanone) is less odorous, but has a very pleasant, sweet-caramel character. Nuttiness is more associated with pyrazines. While it is part of the character of almost all pyrazines, it is particularly associated with the higher pyrazines, such as methyl-dihydrocyclopentapyrazine (33) (maple lactone pyrazine), and 5,6,7,8-tetrahydroquinoxaline (34) (THQ). 2-Acetylpyrazine (35) is very reminiscent of popcorn; while its odor threshold is rather high at 62ppb, its persistent character earns it membership of the high-impact club.

F-23. Fatty aldehydes and acids**F-24. Molecules for cheesy, rancid notes****Bouillon, HVP**

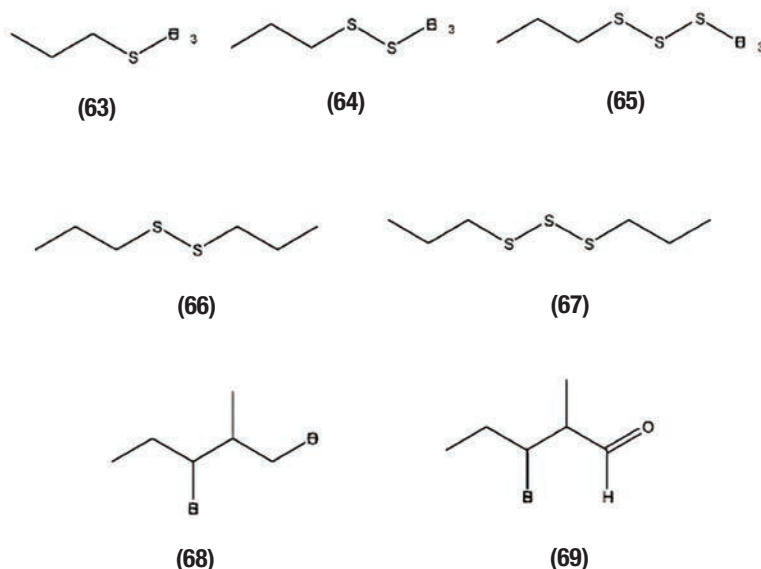
The aroma chemical associated with this group is 4-methylthiazole-5-ethanol (**36**) (sulfurol). However, it has a reported odor threshold of over 10,000 ppb, making this compound scarcely a high-impact chemical. It is also a well-known phenomenon that apparently identical batches of sulfurol have different odors, with the desirable meaty note not always present. A possible identity of this impurity is 2-methyltetrahydrofuran-3-thiol (**37**). This is an intensely savory molecule, with brothy, casserole, boiled-meat notes and allium overtones. Its carbon, oxygen, sulphur framework is actually the same as that in sulphurol; it may be a degradation product or a by-product formed during the synthesis of sulphurol.

Meaty, Beefy

This is the province of 2-methylfuran-3-thiol (**38**) (MFT) and its derivatives. The thiol, its disulphide (**39**), mixed disulphide (**40**) and thioether (**41**), have all been found in beef. The odor threshold of the disulphide has been reported as being as low as 2×10^{-5} ppb, but

F-25. Compounds for mushroom and earthy aromas**F-26. Aroma chemicals for garlic**

F-27. Old and new molecules from onion



our experience of working with these materials indicates that this odor threshold may be due to residual thiol. MFT itself has an initially rather chemical odor, becoming more meaty on dilution. The disulphide has more recognizable character, a rich aged-beef, prime-rib aroma. The GRAS 19 thioether has more roasted character.

Other mercaptans have beef character.

3-Mercapto-2-butanone (42) and 3-mercapto-2-pentanone (43) are commonly found in beef Maillard reactions; the latter has an odor threshold of 0.7ppb.

Other Meats

While 2-methyl-3-furanthiol is important in meats other than beef, in particular pork, other high-impact chemicals also occur. Mercaptopropanone dimer (44) has an intense chicken-broth odor, and the unsaturated aldehyde *trans*-2-*trans*-4-decadienal (45) is very reminiscent of chicken fat. The latter has been implicated in the following observation: while 2-methyl-3-furanthiol has been found in chicken, its intensely beefy disulphide is found in lower levels, if at all. It has been proposed that this is due to oxidants being scavenged by unsaturated aldehydes such as (45), and hence not being available for the oxidation of (38) to (39). 2,5-Dimethylfuranthiol (46) has been reported to be present in chicken, but other work has failed to confirm this. The author's experience with this material is that it is more prone to oxidation than 2-methyl-3-furanthiol.

This may be preventing its detection; when a sample of neat (46) is left in the laboratory exposed to the air, it rapidly becomes cloudy due to droplets of water formed as the by-product of aerial oxidation. A compound with excellent pork character is pyrazineethanethiol (47). This has not yet been reported in nature, but this again may be an analytical quirk. Because vinylpyrazine (48) has been found in pork (and other meats), and pork is rich in sulphur compounds, including hydrogen sulphide, it is difficult to see how it can't be formed.

Lamb character is associated with two acids, 4-methyloctanoic and 4-methylnonanoic acid. While these have the higher odor thresholds of other carboxylic acids, their sharp-fatty aromas give them at least honorary membership in the high-impact club.

Fatty, Rancid

This is not at first sight the most desirable of characters, but fattiness is a key character in foodstuffs (as those forced to eat low-fat or reduced-fat foodstuffs know to their cost), and a rancid odor is characteristic of cheese, especially hard and blue cheeses. Aldehydes have very fatty notes, in particular *trans*-2-nonenal (51) and *trans*-2-*trans*-4-decadienal (45). The latter is reminiscent of chicken fat and has an odor threshold of 0.07 ppb. A molecule with great potential in this area is 12-methyltridecanal (52). This tallowy material is found in beef fat and appears to originate from micro-organisms in the rumen of cattle.⁴ It is absorbed by the gut as plasmalogens, and released only when the beef is heated over a long period (e.g. stewing). Briefly roasting the meat does not release this chemical. Hence, with the use of this material, we have the potential to create a boiled or stewed beef flavors well-differentiated from roasted or fried beef.

Cheesiness, desirable or otherwise, is often associated with acids, but these have quite high odor thresholds (e.g. valeric acid (53)), which has a nauseating sweaty-cheesiness at high concentration. However, it also has the mercifully high odor threshold of 3000 ppb. Such is the character of these that the impact is greater than the odor threshold might imply. Unsaturated acids such as *trans*-2-hexenoic acid (54) have more powerful, acrid odors. Several *trans*-2-enoic acids (*trans*-2-hept, oct- and non-enoic acid) were included on the GRAS 19 list. Simple thioesters such as methyl thiobutyrate (55)



and methyl (2-methyl)thiobutyrate (**56**) also have an intense cheesy-sweet-fruity odor.

Mushroom, Earthy

Here we have a classical high-impact aroma chemical, 1-octen-3-ol (**57**), with an odor threshold of only one ppb, and very characteristic of mushroom. However, this is not the whole story, because the related 1-octen-3-one (**58**) has a threshold some two-hundred times lower, at only 0.05ppb. This has a very fresh wild-mushroom aroma. It has also been identified as a powerful odorant in materials as diverse as elder flower,⁵ raspberry and chocolate. Earthiness is also associated with some pyrazines, especially 2-methyl-3-methoxypyrazine (**2**).

Garlic

Garlic is rich in sulphur compounds, especially allyl compounds. Indeed, the commonly used term ‘allyl’ for prop-2-enyl derives from *allium sativum*, or garlic. The major component of garlic oil is allyl disulphide (**8**), with the mercaptan (**59**) and higher sulphides, such as the trisulphide (**60**), and mixed disulphides such as (**61**). Allyl methyl disulphide is particularly pungent, and has been detected at unexpectedly high concentrations in the breath of garlic eaters.

Onion

As with garlic, onion is high in sulphur compounds, but mostly these are saturated compounds such as the methyl and propyl sulphides (**63**) – (**67**). These have less harsh, ‘sweeter’ notes compared to the allyl compounds. Recently, two new highly odorous mercaptans were identified in onion⁶, 3-mercapto-2-methylpentan-1-ol (**68**), an onion- and leek-like material with an odor threshold of 0.15 ppb, and 3-mercapto-2-methylpentanal (**69**), more pungent and meaty, with an odor threshold of 0.95 ppb.

A Note on Associations

While the human nose is an unsophisticated instrument compared with that of some animals, it remains a more powerful organ than we sometimes realize. It appears to have a hotline to the brain; our ability to associate odors with people and with places is well known. The impact of some of the materials discussed above makes them very effective in this. Some of the associations that people have made when exposed to these materials are: greengrocers for 2-isobutylthiazole, presumably due to its tomato notes;

the cinema for 2-acetylpyrazine (via its popcorn odor); and fields at 6 am for 1-octen-3-one. Some twenty-five years ago, the commentator had a job starting early in the morning and would go out to pick mushrooms in an adjacent field. Some associations are very personal and depend on very individual circumstances. While most respondents commented on the blackcurrant, fruity aroma of 4-methoxy-2-methyl-2-butanethiol, a colleague with a six month old baby commented that it was reminiscent of wet diapers.

Conclusions

The demand for high-impact chemicals has been driven by the twin engines of increased consumer sophistication in the market for flavors and by improvements in the analytical techniques needed to identify character impact molecules. While much has already been done, the story is still being written with many chapters still to come. As the great 17th Century philosopher Rene Decartes might have said, “odorato ergo sum.”

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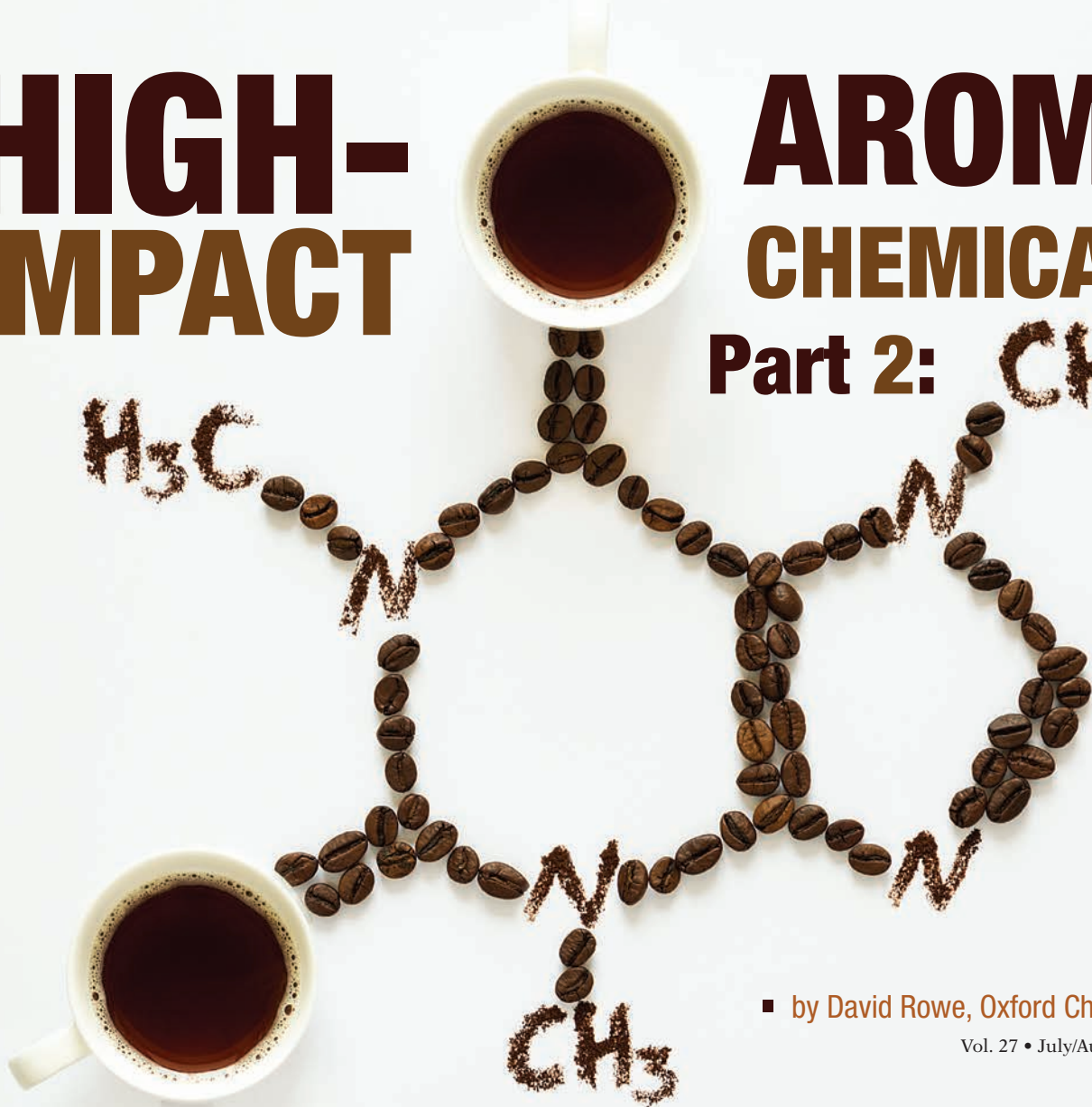
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HIGH-IMPACT

AROMA CHEMICALS

Part 2: CH₃



■ by David Rowe, Oxford Chemicals

Vol. 27 • July/August 2002

the Good, the Bad, and the Ugly

In Part 1, “More Fizz for your Buck”, the role of high impact aroma chemicals as character impact materials in foodstuffs was described.¹ In that article, a simple 16-segment flavor wheel was used as the theme to link the materials. Developing this idea further, I have produced a 20-segment wheel, shown in **F-1**.²

This expanded wheel enables us to see some broad groupings. The eastern sector is the “sweet” sector (pictured in **F-2**), with “savory” materials in the west (**F-3**); sweet and savory overlap in the southeast.

A second differentiator reflects the origins of the aroma chemicals, and, in turn, their applications. Clockwise from “mushroom” to “vegetable”, the materials are formed by biogenesis in plants, and so are of particular interest in creating the flavors of fresh fruits and vegetables (**F-4**). By contrast, most of

the others are commonly found as Maillard reaction products (the term “advanced” Maillard products has been used by Shieberle to differentiate them from the first formed Maillard products such as the Strecker aldehydes), and hence are of most interest in flavors for cooked foods (**F-5**).³

Whereas the first article emphasized the “separateness” of the flavor types, this article emphasizes how a more complex flavor uses the synergy between the aromas and the chemicals that create them. This can be illustrated by looking at three of the most popular flavors: coffee, roast beef and chocolate.

Coffee

The most obvious aroma associated with coffee (**F-6**) is the “burnt, roasted” note. Furfuryl mercaptan (**1**) (**F-7**) is the best-known contributor of this note, and in a study on reconstituting the flavor of coffee, it

was found to be the single most important aroma chemical. The derivatives of furfuryl mercaptan also have elements of this aroma; the disulfide (**2**) is rather milder, and the mixed disulfide (**3**) has sweet, mocha notes. The monosulfide (**4**) is also mild, and has earthy, mushroom notes, which may contribute to the “earthy” aroma character, one of the four key aroma qualities (earthy, sweet-caramel, sulfury-roasty and smoky) looked at in a reconstitution study.⁴ The headspace concentrations of these odorants is lowered by the addition of milk and cream, which may be due to a lipophilic interaction with fats.

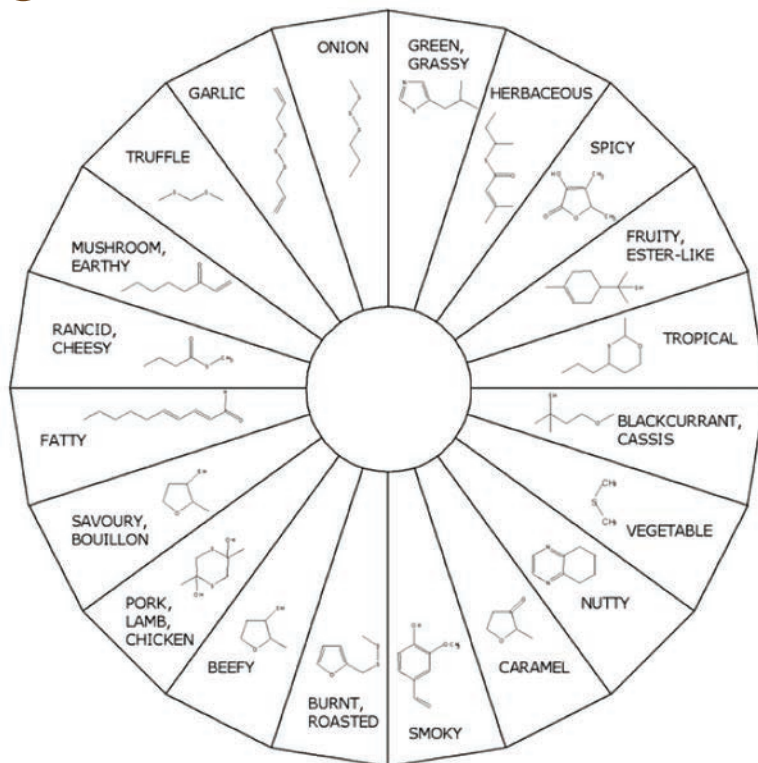
Another reconstitution study found that the second most important aroma chemical for coffee was 2-methoxy-4-vinylphenol (**5**) (**F-8**).⁵ This is a familiar material for smoke flavors, and is presumably formed from ferulic acid in the roasting process. Its saturated derivative, 4-ethylguaiacol (**6**), was also found. Alkylpyrazines, such as 2,3-diethyl-5-methylpyrazine (**7**), were found to influence the perceived strength of the coffee flavor.

The fourth group of powerful coffee volatiles, prenyl mercaptan (3-methyl-2-butene-1-thiol) (**8**), 3-mercapto-3-methylbutan-1-ol (**9**) and its formate (**10**), can be termed the “prenoids” in that they are in some way related to “prenal”, 3-methyl-2-butenal (**11**) (**F-9**).

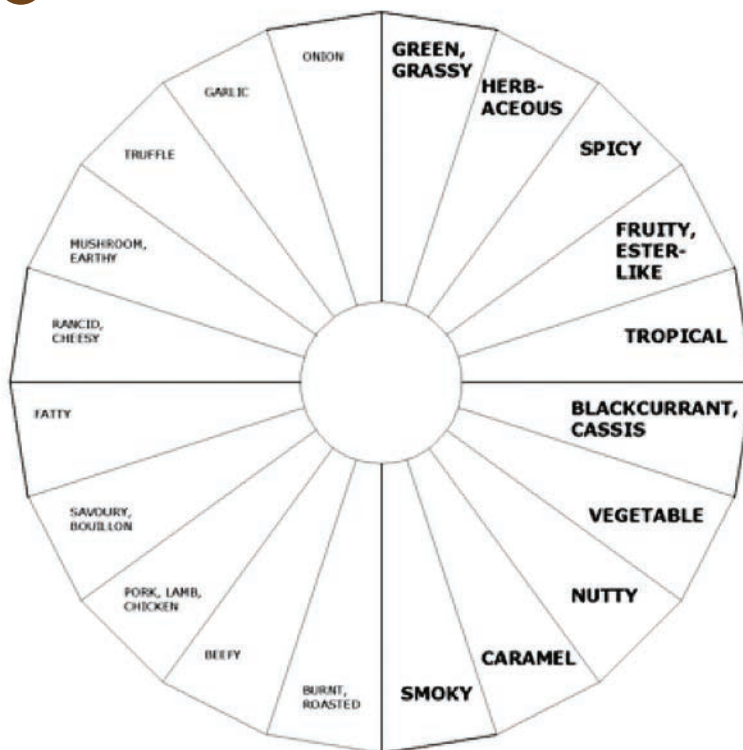
These are the more unusual volatiles in coffee. While they contribute less to the flavor than the more familiar materials, the greater volatility of these volatiles — in particular prenyl mercaptan (**8**) [b.p.130C, c.f. 155C for furfuryl mercaptan (**1**) and 230C for dithiodimethylenedifuran (**2**)] — may indicate that they are greater contributors to the “fresh roast” aroma than to the taste.

A second aspect of the prenyoids is that several are related to the

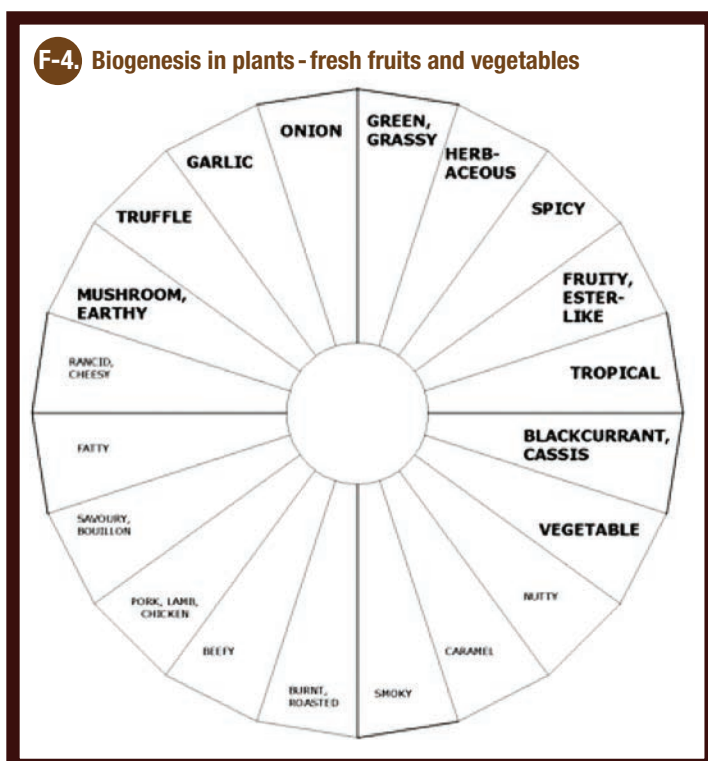
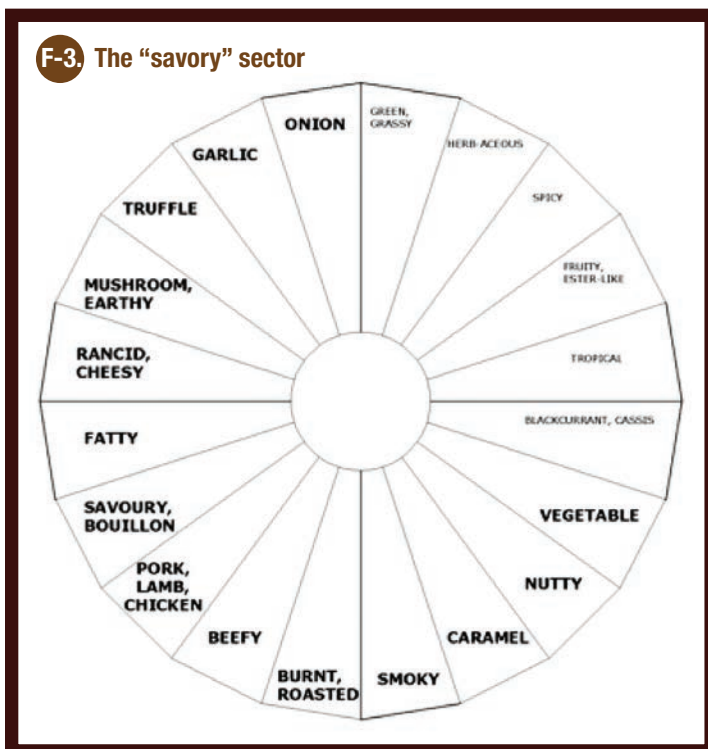
F-1. A Flavor wheel for high impact aroma chemicals



F-2. The “sweet” sector



aroma chemicals found in blackcurrants, cassis and wines, where they contribute the familiar catty note (F-10). Indeed, 3-mercapto-3-methylbutan-1-ol (9) is the simplest material having the catty olfactophore (F-11).



Roast Beef

This is both an important flavor in its own right and perhaps also the archetypal “meat” flavor (F-12). The single most important group of aroma chemicals in beef is derivatives of 2-methyl-3-furanthiol (MFT) (12) (F-13). While MFT is commonly formed in Maillard reactions and present in all meats, it is found at a much higher level in roast beef, up to 28 mg/kg, compared with 9 mg/kg in pork, 11 mg/kg in lamb and only 4.5 mg/kg in boiled chicken.⁶ Derivatives are of great importance in roast beef; the disulfide (13) is also very important; it has a strong meaty, roasted odor, and because MFT readily oxidizes to this material, it is characteristic of a more “aged beef” aroma. The odor of (12) and (13) can be described as “beef as it is roasting”, whereas (13) resembles a joint of beef when it has been cooked and allowed to stand. 2-Methyltetrahydrofuran-3-thiol (THMFT) (14) is also very powerful, with savory, brothy notes. The sulfide, 2-methyl-3-methylthiofuran (15), is milder with less “beef” character.

A second group of compounds of great importance is furfuryl mercaptan and its derivatives (F-14); essentially the same compounds are found in roast coffee and roast beef. It should also be noted that the levels of furfuryl mercaptan (1) found in meats parallel the pattern seen for MFT; up to 42 µg/kg in roast beef, 10 µg/kg in pork, 14 µg/kg in lamb and 2.4 µg/kg in boiled chicken.⁶ 3-Mercapto-2-pentanone (16) is also important, though at up to 73 µg/kg, this was at a lower level than in pork and chicken (117 µg/kg and 100 µg/kg, respectively).

All of these compounds have vicinal oxygen and sulfur, and this may be the “savory olfactophore” (F-15 and F-16).

Structure-odor relationships have been much less studied in the area of flavors than fragrances, in part because the usage of materials in the former is dominated less by activity and more by the issue of “nature-identical” (and/or natural). There is little value in designing the world’s most savory molecule if, in the end, it cannot be used. We might also comment that nature has done rather well in making high impact chemicals herself anyway. The concept can still be useful, however, in the possible identification of aroma chemicals. 4-Methylthiazole-5-ethanol (17) (sulfurol) (F-17) is widely used in savory flavors. Most thiazoles have green or fruity odors, and it is also a well known phenomenon that apparently identical batches of sulfurol have different odors, with the desirable “meaty” note not

always present. Because sulfurol has a reported odor threshold of over 10,000 ppb, a trace impurity will have a major effect. A strong candidate in the identity of this impurity is the disulfide (13); it has a very similar boiling point to (17) (both ca. 280C), and hence would be carried through the purification by distillation. As a derivative of 2-methylfuranthiol (12), its carbon, oxygen-sulfur framework is actually the same as that in sulfurol; it may be a degradation product or a by-product formed during the synthesis of sulfurol (F-18).

Perhaps the major difference between the aroma chemicals for roast beef and for coffee is the presence of fat-derived materials in the former. Fats and their derivatives influence both flavor and “mouth-feel”. Aldehydes typically contribute fatty notes, in particular *trans*-2-nonenal (18) and *trans*-2-*trans*-4-decadienal (19) (F-19); the latter is reminiscent of chicken fat and has an odor threshold of 0.07 ppb.



Chocolate

To the millions of “chocoholics”, this is “nature’s perfect food” (F-20). A look at the most important aroma chemicals perhaps gives some idea as to why this is. While chocolate is undeniably in the “sweet field”, it has both a savory (F-21) and sweet (F-22) character, the former deriving from Maillard reaction products formed in the roasting of cocoa beans. A study on the key odorants in milk chocolate and cocoa mass was able to identify the origin of most of the top 20 odorants in a milk chocolate (T-1).⁷ As expected, the cocoa mass provided most of the key odorants, especially those with “savory” aspects, such as the pyrazines and the MFT derivative (23). The sweet lactones probably

derived from milk powder, or, in the case of vanillin (24), as essentially an added flavoring. Surprisingly, the “beefy” MFT derivative methyl 2-methyl-3-furyl disulfide (23) has been detected in chocolate and

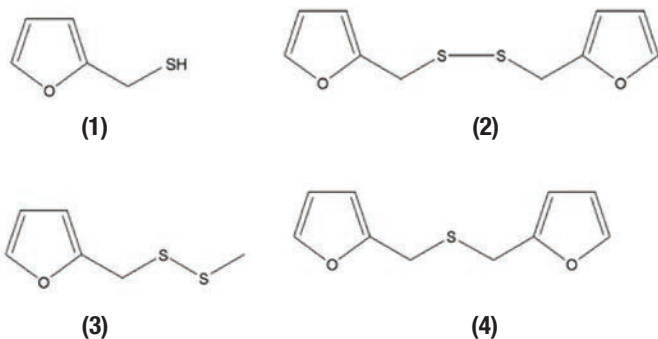
F-5. “Advanced” Maillard products - cooked foods



F-6. The coffee wheel



F-7. Furfuryl mercaptan derivatives



coffee, but not yet in roast beef; a closer look at the latter may well show its presence.

Summary

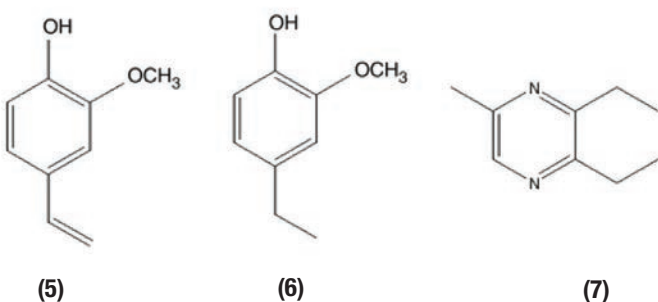
We can summarize the synergies and correspondences with the diagram presented in **F-23**, in which roast beef, chocolate and coffee are shown with their unique and overlapping characteristics.

Off-Notes

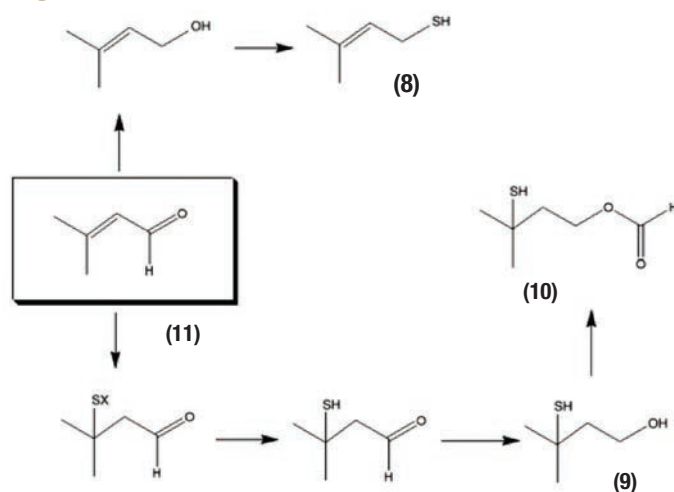
*“... I have smelt
Corruption in the dish, incense in the latrine,
the sewer in the incense, the smell of sweet soap
in the woodpath...”*

— T.S. Eliot, “Murder In The Cathedral”
(1934)

F-8. Guaiacols and pyrazines in coffee



F-9. “Prenoid” relationships

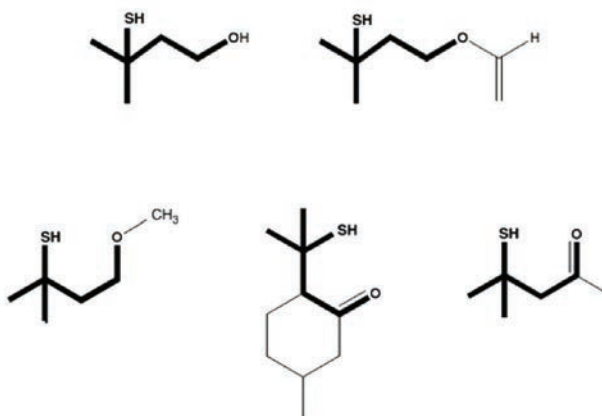


Eliot’s words, spoken to reflect the tension and mounting horror of the people of Canterbury as the murder of Archbishop Thomas Beckett approaches, convey the powerful sense of “wrongness” that our sense of smell can evoke. Some odors are inherently repulsive, while in other cases a sense of revulsion occurs when incompatible odors are mixed. At Oxford Chemicals, we put together a listing of “off-odors” that we are familiar with in the aroma chemicals business. While we are proud of the quality of our products, we occasionally have problems with off-notes that lead to the material going back for further purification. We take the view that if a supplier claims they never

detect any off-notes in their products, this means that the customer is doing their quality control for them. From these off-notes we devised the Devil's Flavor Wheel (F-24).

There are some terms used that one might not wish to use in polite society, but they are familiar from everyday experience. The wheel is not a random listing of horrors, in that while the off-notes on the eastern side are inherently bad (it is difficult to imagine anyone wanting a sickly, fecal flavor, or a burnt urine fragrance), the western side's odors can be both desirable and repellant. The context is critical; onion and garlic notes are undesirable in a pyrazine, but essential in allyl disulfide. This emphasizes the key notion that off-notes are themselves aroma chemicals, whether present as contaminants or as by-products of synthesis. The amount of contaminating material may be tiny, as many sulfur compounds have odor thresholds below 1 ppb, so a little goes a long way. Sometimes the off-notes are readily identified. For example, "gassy" off-notes may be due to methyl mercaptan, "ammoniacal" due to aliphatic amines or ammonia itself, and "biscuity" due to pyrazines. We have noticed that traces of pyrazines stand out against the fruity notes of esters, and that traces of sulfur compounds give an onion-garlic note that stands out against the earthy-nutty odor of pyrazines. More often, mixtures of trace impurities give the generic type of off-notes such as "dirty", "burnt" and "sulfurous". The same principles apply to foodstuffs, where a number of important aroma chemicals have also been identified as causing off-notes. Again, context is key; perhaps the phrase "one man's meat is another man's poison" is appropriate here.

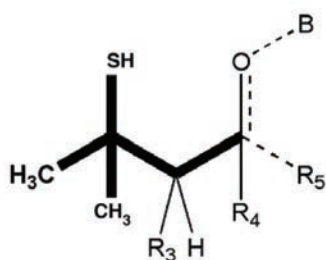
F-11. Molecules showing the catty olfactophore



F-12. The roast beef wheel

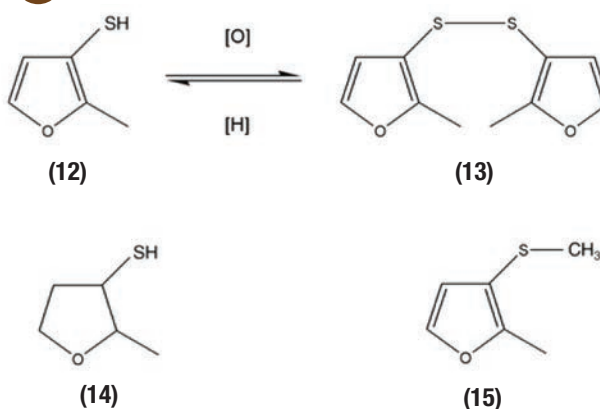


F-10. The catty olfactophore



B=H, CH₃, Acyl, absent if carbonyl
 R₃=H, alkyl, ring
 R₄=H, CH₃, ring, OR
 R₅=H, absent if carbonyl

F-13. MFT derivatives

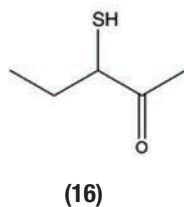
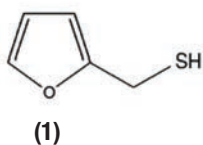


While some off-notes are well known in a number of foods — prenyl mercaptan (**8**) in “sun-struck” beer, 2-methoxy-4-vinylphenol (**5**) in orange juice, and lipid breakdown/oxidation products such as decadienal (**19**) — some are more surprising.⁸ Methional (**27**) and MFT (**12**) can cause problems in orange juice, sotolon (**28**) can cause unwanted burnt, spicy notes in citrus soft drinks, and methional (**27**) is a villain again in causing the “warty” note in alcohol-free beer (**T-2** and **F-25**).⁹⁻¹¹

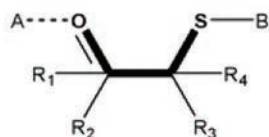
The Future(?)

There are three areas where developments are continuing. The first is in synthetic chemistry — materials that are interesting, but too expensive for use at present, may become available at an “accessible” price due to the discovery of a viable synthetic route. The cycle of discovery, synthesis, and manufacture with falling

F-14. More “beefy” mercaptans

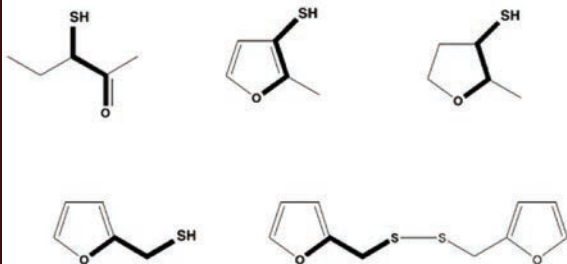


F-15. The savory olfactophore

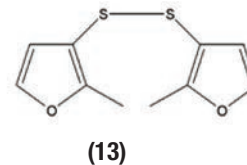
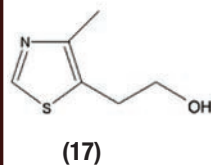


A=ring, absent if carbonyl
 B=H, CH₃, Acyl, SR
 R₁=ring, absent if carbonyl
 R₁, R₂, R₃=ring, H, alkyl

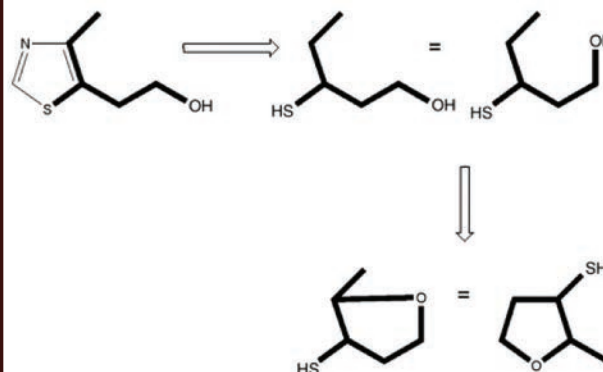
F-16. Molecules showing the savory olfactophore



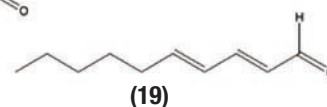
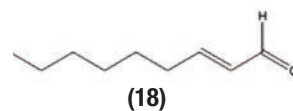
F-17. Savory compounds



F-18. Structural relationship between sulfurol and 2-methylfuran-3-thiol derivatives



F-19. Fatty notes for beef



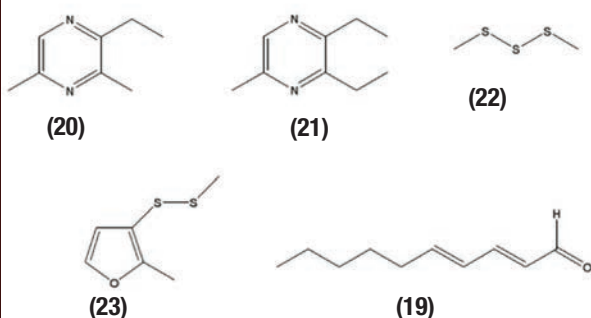
F-20. The chocolate wheel



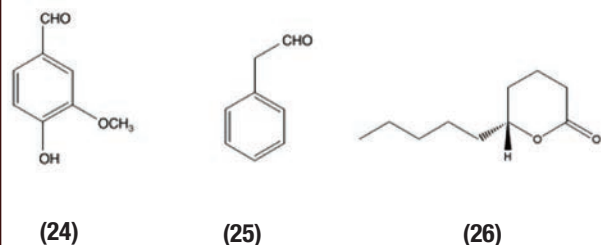
T-1. Key odorants in chocolate and their probably origins

Odorant	Probable source
vanillin (24)	Vanilla or synthetic
3-methylbutanal	Cocoa mass
2-ethyl-3,5-dimethylpyrazine (20)	Cocoa mass
5-methyl-2-hepten-4-one	Nut paste
2-ethyl-3,6-dimethylpyrazine	Cocoa mass
2,3-diethyl-5-methylpyrazine (21)	Cocoa mass
trans-2-cis-6-nonadienal	?
cis-2-nonenal	Cocoa mass
2- and 3-methylbutyric acids	Cocoa mass
methyl 2-methyl-3-furyl disulphide (23)	Cocoa mass
trans-2-trans-4-nonadienal	Cocoa mass
trans-2-trans-4-decadienal (19)	Cocoa mass?
R- δ -Decalactone (26)	Milk solids
1-octen-3-one	Milk solids or thermolysis?
dimethyl trisulphide (22)	Cocoa mass or thermolysis?
trans-2-nonenal	Cocoa mass
phenylacetaldehyde (25)	Cocoa mass
R- δ -octalactone	Milk solids?
ethyl cinnamate	Cocoa mass
γ -decalactone	Milk solids?

F-21. Chocolate's savory side



F-22. La dolce vita (the sweet side of chocolate)



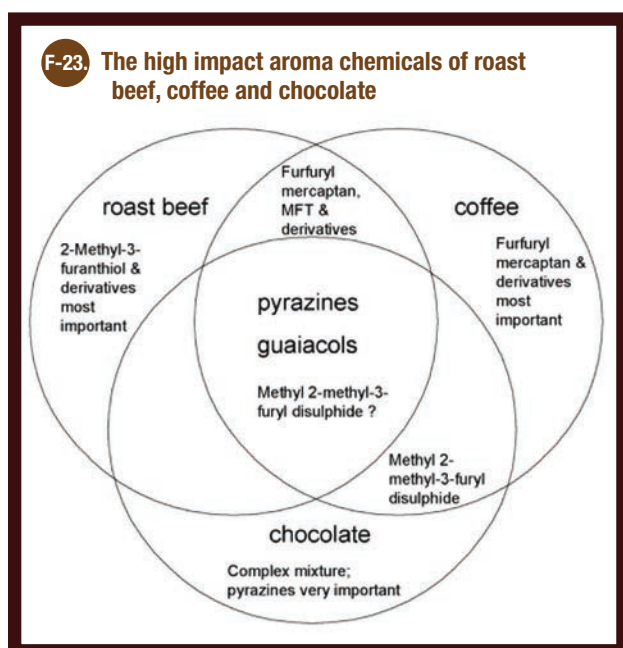
prices has continued since the work on cinnamaldehyde and vanillin in the 19th Century.

A second area involves further analytical work, which may be in the examination of new “exotic” foodstuffs, or reevaluation of familiar materials. For example, the cat ketone (29) (F-26) was recently found to be an unexpectedly important odorant in grapefruit.¹² We are also now able to go “further down in the noise” on gas chromatography and identify materials at lower levels and even lower odor thresholds; dimethyl selenide (30) has been detected in garlic and garlic breath.¹³ Handling and manufacture of such materials may require “glove-box” techniques more familiar from radiation chemistry.

The third area that may have an important effect on the usage of high impact aroma chemicals is work being carried out on delivery systems. A number of very interesting aroma chemicals are also highly reactive and have a short half-life in normal formulations. Systems that can trap and release such materials could enable their use for the first time; examples include the related 2-acetyl-1-pyrroline (31) (basmati rice) and 2-acetyltetrahydropyridine (32) (bread crust).¹⁴

T-2. Aroma chemicals in the wrong place at the wrong time

Aroma Chemical	As a Desirable Note	As an Off-Note
trans-2-trans-4-decadienal (19)	chicken meats	cooked potatoes
2-methoxy-4-vinylphenol (5)	coffee	orange juice
methional (27)	fried foods	orange juice
2-methyl-3-furanthiol (12)	beef	orange juice
prenyl mercaptan (8)	coffee	beer
methional (27)	fried foods	alcohol-free beer
sotolone (28)	fenugreek	citrus drinks



Why?

A final question that may be asked is, simply: “Why are we so sensitive to these aroma chemicals?”

The functions of our senses of smell and taste are threefold: 1. to find/attract a mate; 2. to find/identify food; and 3. to avoid toxins. It is actually quite difficult to really explain our responses in these simple terms.

1. To find/attract a mate: This is probably the least relevant here. While the extreme sensitivity of insects to sex pheromones is well studied, the fact that these aroma chemicals are found in foodstuffs is something of a complication; sexual attraction between an animal and its food is unlikely to be a successful evolutionary strategy.

2. To find/identify food: At first sight, this is the “obvious” explanation. However, most of the high impact aroma chemicals are formed only when food is cooked; because the cooking of food is of

very recent provenance in evolutionary terms, it is unlikely that we have evolved any physical features to respond to this. Some high impact materials are found in fruits, but again, the chemical may only be released when the fruit is actually being eaten; for example allyl disulfide and the other allium sulfides are only released only when the tissues of the garlic clove have been damaged, and a cow certainly doesn't smell of roast beef.

3. To avoid toxins: There are three main sources of toxins: those present in the environment, those produced as an organism's waste and those produced by the decomposition of food. It is this latter area that gives a clue that this may be the cause of the response to these high impact chemicals; the group of compounds to which we have the greatest sensitivity is mercaptans, and these are produced by the decay of cysteine and methionine in proteins. This may be the origin of our response to the

simple materials, such as hydrogen sulfide, methyl mercaptan and simple alkyl thiols; the cause of the enhanced response to mercaptans, such as 2-methyl-3-furanthiol and p-menthene-8-thiol, may simply be that these materials happen to trigger the receptors more easily. This is a coincidental response and not a specific “design”. To use an analogy from pharmaceutical chemistry, morphine happens to fit our endorphin receptors in the brain with great efficacy, but it is not suggested that we have evolved to develop morphine addiction. Evolution is conservative; a study on mouse olfactory receptor (OR) genes found that while humans have only two-thirds of the OR genes of mice, they occupied a similar receptor space — hence, we retain the ability to recognize a broad range of aroma chemicals.¹⁵ Furthermore, a large number of the OR genes were described as “fish-like”.

These phylogenetic links indicate that our response to these molecules appears to have a very “primitive” origin, and we have yet to meet an individual with specific anosmia to these materials. The ability to respond to chemicals in our surroundings is the primary sense. We now differentiate taste and smell, but to the simplest organisms it is as one. Even the simplest and most primitive organisms, the prokaryotic bacteria and archaea, have this sense, and this leads us to a fascinating possibility; there is much evidence that life evolved in a sulfur-rich environment, where a sulfur compound would be a nutrient or a toxin, depending on concentration. Does our love for roast beef, coffee and chocolate have its ultimate origins in the days when the only course on the menu was the primordial soup?

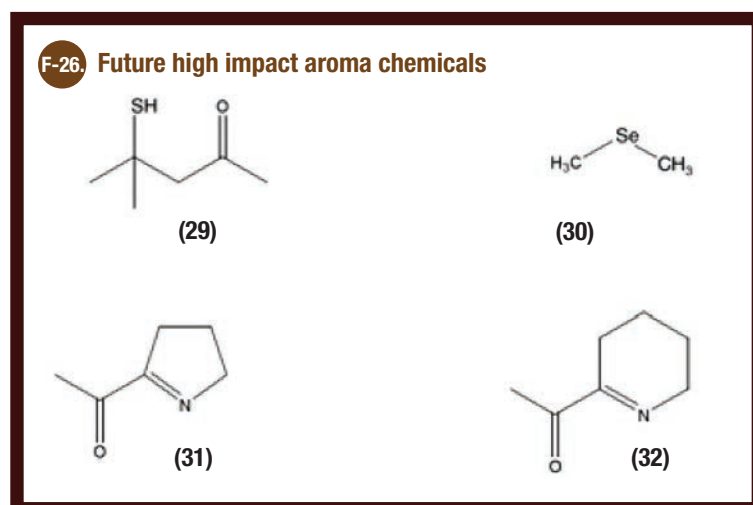
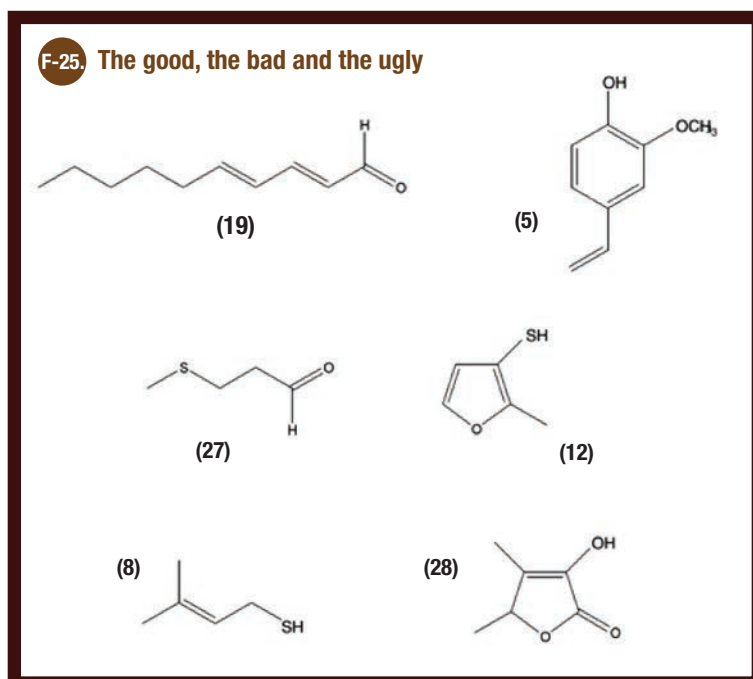
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SYNTHESIZING THE FUTURE

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How can brands, suppliers and the F&F industry as a whole create the message that synthetics are safe and effective to use for consumers, and for the planet?

■ BY STEVE PRINGLE

It's no surprise that a large and growing percentage of the population have a preference to the word "natural," as opposed to the word "artificial" when associated with their food, fragrance, medicine, cosmetics and other consumer goods. Even when the two are chemically identical and show no difference in their effectiveness, most people would choose the natural option than the artificial one.

Natural continues to be strongly linked with a positive effect. This preference is, in general, stronger in food and personal care products than in medicines, mainly because natural products are thought to be healthier, more appealing to the senses and kinder to the environment. There is also a comparatively strong moral reasoning that natural products are not only beneficial to the individual but to society at large. The preference doesn't change even when it is clear to the consumer that both the natural and artificial product are chemically identical.¹ There also appears to be a strong link to the "naturalness" of the product or ingredient in the consumer's mind with the way in which they were derived. Chemical transformations

reduce the "naturalness" of the material much more than physical transformations, and processes such as mixing materials have little effect on the consumer's perception. In addition, the history of ingredient processing is more important for the consumer's assessment of its naturalness than the nature of the ingredient's contents.²

In response to the consumer perception that natural is better, brands have pushed to remove ingredients from their products that give a negative image to the product to be perceived as being healthier (see F-1). However, as we can see from Panera Bread's "No No" list, there is little in the way of science behind this - synthetic vanillin is not allowed but natural vanillin is, despite both being chemically identical molecules.

There are significant challenges ahead for the F&F industry if it wishes to continue to use synthetic materials in its formulations. Some of these challenges can be combatted by educating the consumer, and to that effect the recent decisions by Proctor & Gamble, Unilever, SC Johnson, Clorox and Henkel to disclose the ingredients used in their fragrance formulations are positive moves to greater transparency

F-1. Brands that are removing negatively perceived materials from ingredient list

Company	Comments
Chipotle	"Just because food is served fast doesn't mean it has to be made with cheap raw ingredients, highly processed with preservatives and fillers and stabilizers and artificial colors and flavors" - Steve Eills, Co CEO Chipotle
Kraft	Removal from its iconic Macaroni & Cheese of artificial dyes Yellow 5 and Yellow 6 in 2016.
Taco Bell	Removed artificial flavors and colors as well as high fructose corn syrup and palm oil by the end of 2015, and "where possible" artificial preservatives by the end of 2017
Pizza Hut	Removed artificial flavors and colors from its US Pizzas by the end of 2015. "Today's consumer more than ever wants to understand the ingredients that make up the foods they enjoy" - David Gibbs, CEO
Subway	Committed to removing artificial colors, flavors and preservatives in North American stores by the end of 2017
Panera Bread	Released a "No No" list of ingredients it removed from its products by the end of 2016. These include Artificial Flavors, Artificial Colors, Parabens and Synthetic Vanillin
Nestle USA	Announced that some of its major brands such as Hot Pockets, Lean Pockets, DiGiorno, California Pizza Kitchen, Tombstone and Jacks would be artificial flavoring free by the end of 2015. "We know people want to feel good about the foods they eat, and they're seeking foods made with fewer artificial ingredients and less sodium" - John Carmichael, President Nestle Pizza & Snacking Div
General Mills	Committed to removing artificial flavors and colors by end 2017
Papa Johns	Committed to remove synthetic ingredients by the end of 2016 at a cost of \$100M, according to Bloomberg
Campbells Soup Company	Have pledged to stop using artificial ingredients by the end of 2017

and trust with the consumer. A 2016 study by Label Insight³ reports that 73% of consumers are willing to pay more for a product that communicates transparency, and 94% are likely to be loyal to a brand committed to full transparency. It seems, then, that consumers are willing to accept ingredients which have been synthesized, if there is some transparency around their inclusion in a product.

Chemicals are Evil?

We can conclude that consumers are wary of not only chemicals but also the process in which these chemicals are derived from. A series of experiments in the 1970s and 80s by Daniel Kahneman (Nobel Laureate in Economics) showed how people make judgements under conditions of uncertainty. These experiments demonstrated that we as humans prefer to avoid losses over acquiring gains.⁴ Apply this to the public's perception of the chemical industry and to the F&F segments in particular, and it becomes easy to understand why consumers put more weight on information that suggests something can harm us over information that suggests that there is no difference between two sources.

The vast majority of consumers have little understanding of chemicals and chemistry and simply get confused and concerned by chemical names. For example, tell someone that their green tea or blueberries are good for them because they contain anti-oxidants, then they have an increased level of confidence that their purchase of the product is giving them a health benefit. Tell them instead that they contain polyphenols, and they may be mildly confused, but as the benefits of polyphenols become more widely understood and

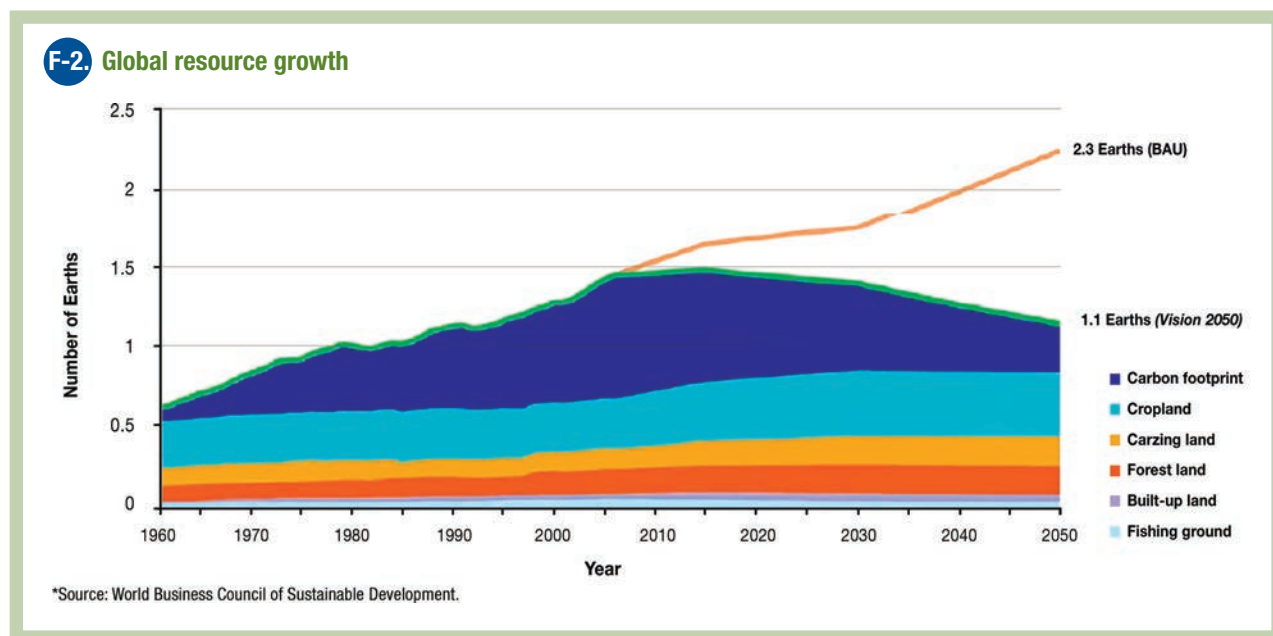
accepted, then they can overcome that confusion. One step further: simply tell them that a product has (2R,3S)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol and there is a good chance they will run a mile claiming that the government is trying to poison them.

Add this to some of the chemical and chemical industry-related incidents over the years, such as Bopal, Flint, Flixborough, Texas City and Toulouse or the more recent explosion at a fertilizer factory in West Texas (of which there are some interesting clips on Youtube), and we can see why consumers have such a fear of chemicals, and view the chemical industry as a major polluter and threat to society.

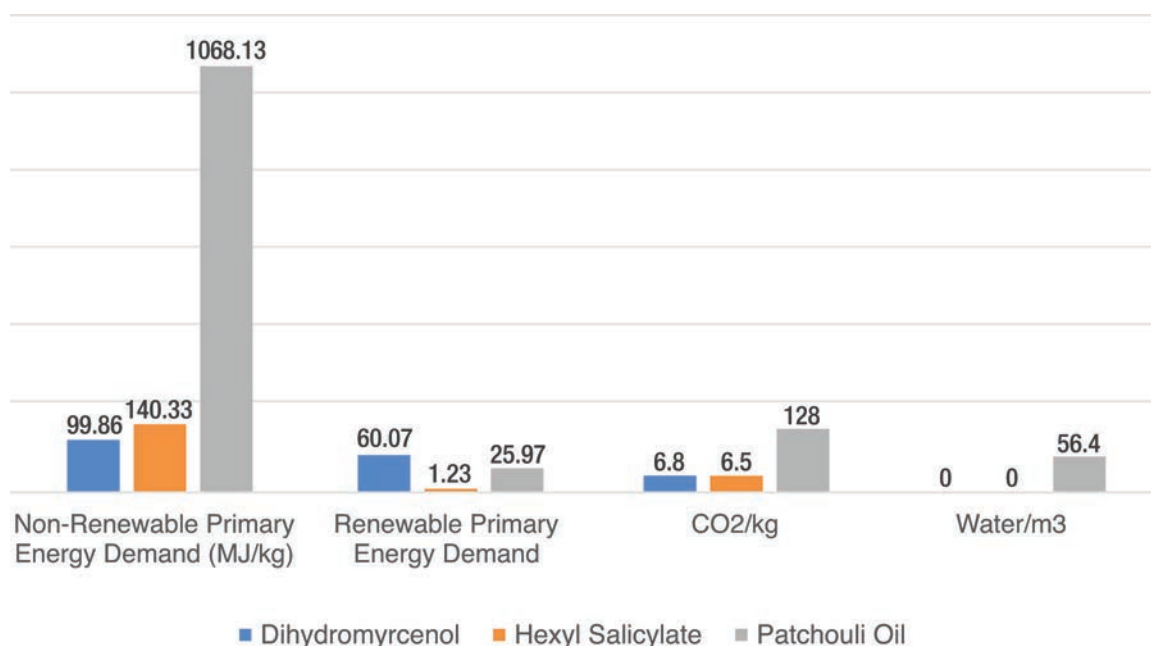
Despite these perceptions, the problem is that we need chemicals. There have already been numerous articles in this publication alone about the benefits that molecules bring to the creative process, so how do we get around this fear?

Can We Have Another Earth, Please?

While some sections of society think it would be nice to be able to source everything from a cultivated feedstock and remove synthesized chemicals completely, we must remember a couple of things. The consumer, I'm sure, would gladly accept fragrances and flavors created from extracts, distillates, absolutes and essences of plants that they can easily identify and connect with. However, if we were to cover the majority of notes and tastes the perfumer and flavorist would need, realistically this wouldn't be feasible. Firstly, not every material used in the creation of flavors and fragrances, whether it is a natural complex substance (NCS) or a distinct chemical molecule, occurs in nature. Some of the



F-3. Renewable and non-renewable emissions from dihydromyrcenol, hexyl salicylate and patchouli oil



key building blocks in fragrance creation in particular, such as dihydromyrcenol, Habanolide^a and delta damascene, are not naturally occurring, and to remove these from the perfumer’s palette would cause significant problems.

A wider issue, and one which will take on greater significance in the immediate future, is the question of resource. The global population has seen significant growth over the last century with the expectation that by 2048, it will reach nine billion people. We can determine that if we continue at this current rate, we will need 2.3 Earths to be able to satisfy the needs of nine billion people (F-2). Previously published fragrance industry data from *Perfumer and Flavorist*⁵ shows us that over 75% of the materials used (excluding solvents) in fragrance creation are synthetic ingredients from non-renewable feedstocks. Of the remaining 25%, only 7% stem from ingredients that the consumer would classify as “natural.”

We could expect that the industry should focus on the 7% of ingredients, which come from natural sources to help solve the conundrum. By focusing more on these cultivated sources, we could potentially make headway into the problems of resource. Unfortunately, this doesn’t appear to be possible. In a 2013 report, the Research Institute for Fragrance Materials (RIFM) examined a selection of fragrance

ingredients such as dihydromyrcenol, hexyl salicylate and patchouli oil.⁶ The results in terms of the CO² emissions, water consumption and energy used give interesting results (F-3).

So it seems even though the consumer prefers products made from ingredients more closely obtained from cultivated sources, and more recognizable as natural, doing so is considerably more resource-intensive than synthesizing chemicals. From all of this, two things are clear: our industry absolutely needs synthesized materials, and the consumer doesn’t understand or trust them.

Where Do You Get Your Carbons?

If 75% of the feedstocks used to create fragrances are from petrochemical sources, and 7% from natural sources, then where are the remaining 18% coming from? The answer is that these ingredients are synthesized from renewable feedstocks such as crude sulfate turpentine, gum turpentine and citrus by-products such as d-limonene.⁵ A quick review of the FEMA GRAS lists gives a similar picture, in that the overwhelming percentage of ingredients used in creation are distinct molecules that are synthesized. As much as the consumer would like it, we can’t get away from synthesized materials.

We have to remember that in the short term, we operate in a consumer driven market, but in the longer term we have the capability to shape consumers’ thoughts and preferences. At this time

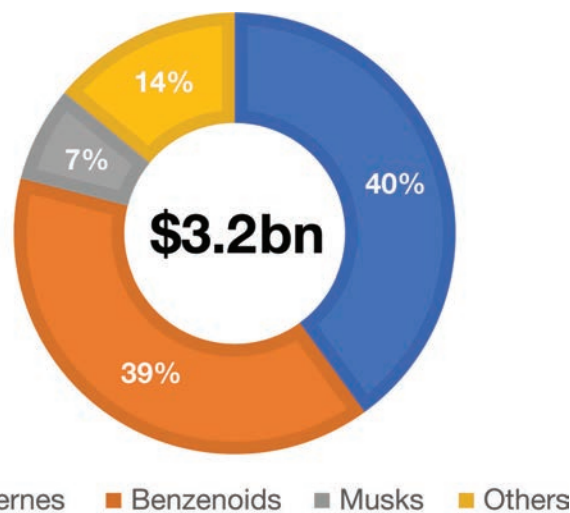
^a Habanolide is a registered trademark of Firmenich

consumers don't necessarily understand or trust chemicals but will be loyal to brands offering transparency. By offering greater transparency aligned with rigorous testing and supportive communication in the long term, we should be able to develop a level of confidence in the ingredients the F&F industry is using.

So should there be more focus and investment in producing synthetic ingredients from renewable feedstocks? Undoubtedly the answer has to be "yes," so we can not only solve the issue of resource and environmental impact, but also address the challenge of consumer confidence in synthetics. Unfortunately, as we stand, the only chemical class of ingredients where there are viable economical and synthetic routes from renewable feedstocks are towards terpene chemicals, which currently represent about 40% of the aroma chemicals used by value in F&F compounding (**F-4**), and not all of these are made from renewable feedstocks. There have been some moves towards more renewable feedstocks, with companies such as Takasago launching products like Biomuguet^b from their Sustainable Scent^c brand, which utilize renewable sources and green chemistry.

Over the past decade, a large proportion of the chemical industry has shifted its attention towards examining the potential to create value from food waste. Around 90 million tonnes of food waste are generated in the EU alone each year and the majority is a result from processes within the food industry rather than household or supermarket waste. Valorizing waste components could in fact lead to numerous possibilities for the production of valuable chemicals. Work has already been undertaken that shows that food biomass can be converted into various fuels⁷ or converting comparatively abundant waste streams such as spent coffee grounds.⁸ Additionally, biocollagenic materials with healing properties can be obtained from meat and leather waste by various extraction processes.⁹ These methods of conversion use traditional chemical routes. However, there are other ways in that waste streams can be converted into valuable intermediates. For example, bakery waste can be converted into succinic acid by selecting certain microbial strains in fermentation processes.¹⁰ By committing resource to creating value from what has been traditionally viewed as waste streams, other areas

F-4. Global aroma chemicals market



Source : Freedonia World Flavors & Fragrances Market Report, Sept 2013

of the chemical industry have discovered innovative solutions from currently available, renewable resources. The F&F industry has begun look in this area also, and I would anticipate in the medium term this approach will bring its rewards.

The biotech approach is becoming more common within the F&F world, as it shows how complex but desirable materials can be used in food production, such as various vitamins and essential fatty acids, can be produced.¹¹ There have also been successes in the biotech field, which have resulted in the direct production of aroma chemicals which are available today. For example, Firmenich's Clearwood^d is a patchouli-type material and is result of their white biotechnology platform. Biotechnology has also been able to produce versions of currently available molecules such as vanillin,¹² gamma decalactone¹³ and 2,4,6-tris(2-methylpropyl)-1,3,5-dithiazine (bacon dithiazine).¹⁴

This quite neatly brings me back to ingredients produced from natural sources. It has already been shown that the production of extracts, distillates, oils and absolutes is extremely carbon and water intensive. One of the areas where the biotech approach could bear fruit within the industry is the valorization of waste streams from the production of these products. Often these by-products are treated as waste, or sold for animal feed, which although this generates some value no doubt as technology evolves a number of other potential opportunities to create further solutions could

^{b, c} Biomuguet and Sustainable Scent are tradenames of Takasago

^d Clearwood is a registered trademark of Firmenich

arise. This could benefit the F&F industry in a number of ways. Farmers' livelihood relies on crops, which as we have seen with Vanilla and Citrus, are in a precarious position whether this is because of climate related events, pestilence or outdated farming methods. Having the potential diversify their income streams, and becoming less reliant on producing "perfect" crops can only benefit comparatively low income communities who rely heavily on farming. The F&F industry has the potential to pursue this route. We are already strongly connected to the farmers who cultivate these crops, and so by working alongside them to create further benefit the industry moves to be not only environmentally responsible, but also socially and economically responsible – something which strikes a chord with a growing segment of the population and which could be used further by food, beverage, personal care and consumer product manufacturers in their product positioning.

This raises a number of questions. Could we produce materials from naturally occurring sources which are chemically close to the cultivated feedstock? Could this offer the opportunity greater transparency? Would the consumer have greater confidence in flavor and fragrance ingredients that are produced from natural sources? Would the consumer see a greater connection of these materials to the natural world they desire? Can we shift the debate away from natural versus artificial to renewable versus non-renewable? Should we be promoting the production of materials from natural sources, rather than focusing on whether they are "natural" or "artificial?"

Tomorrow's Synthetics

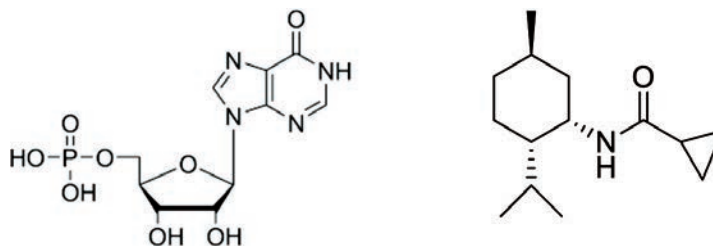
Whether produced through traditional chemical synthesis or through biochemical transformations, it is clear that the industry must continue to invest in the development of new synthetic molecules. The question is what type of molecule we need. We could argue that pretty much every odor profile is covered by materials that are currently available, and the creative energies of perfumers and flavorists should be able to use the current material palette to create just about every odor profile the consumer needs. This should not dampen our enthusiasm for discovery of new aroma molecules, whether driven by a need to improve on currently available odor profiles or concerns regarding safety (proven by sound science rather than public perception), or even by new discoveries from nature.

Beyond simply adding to our odor palette, there are other factors in determining synthetic use and their benefits. Areas such as sweetness enhancement, salt reduction, fat reduction and bitterness blocking, driven by consumers' greater understanding of the nutritional needs of the food they eat, has led to a growth in better-for-you products. We now have a far greater understanding of the interactions beyond odor at a receptor level, and how this contributes to our acceptance and enjoyment of the food we eat.

It has long been established that our sense of taste detects four basic sensations – sweet, salty, bitter, sour. The savory or umami effect is a more newly established effect and is known to be linked to chemicals with a glutamate structure in them. That human mother milk has high levels of glutamates indicates that we learn from an early age to appreciate this effect. The presence of glutamates in many other foods such as fish, cheese, tomatoes, peas and corn add to our liking for these foods. Other chemical structures have been found to exhibit umami character, such as the nucleotide inosinic acid, and the effect is unusually observed in the menthol derivative, N-isopropyl-5-methylcyclohexyl cyclopropanecarboxamide (**F-5**), where the structure is more associated with cooling.

While our understanding of these receptor mechanisms is clearly growing, there is much less reported data from research to enhance our understanding of the types of chemical structures that specifically trigger these receptors. There are, of course, naturally occurring materials currently available that can provide these effects. These materials often come with an odor which may not be desirable in the finished product and require additional work to formulate around. As the importance of providing these types of taste modulation effects grows, we should expect that the development of synthetic molecules to create these effects also grows. Additionally, we should expect to see the breadth of materials providing a gustatory effect, without imparting an increase in odor.

F-5. Non-glutamate chemical structures giving an umami effect



Ouch, That Hurts, But I Like It – Chemosensory Irritation

Chemosensory irritation (chemical “irritants” in the mouth, nose and skin) give rise to sensations such as pungency, warmth, cooling and tingling. These can often be desirable in food, beverage, cosmetic and personal care products. Such chemesthetic effects are often expected in naturally food ingredients. Alongside their obvious odor components, spices such as capsicum, cinnamon, cassia and ginger provide a warming in the oral cavity; other spices such as mustard, horseradish and wasabi provide a more nasal warming. Cooling spices such as mint and eucalyptus, numbing spices such as clove and wintergreen, as well as tingling spices such as jambu and Szechuan pepper.

These effects are activated when chemical stimuli excite the sensory neurons of the dorsal or trigeminal ganglia. These receptors belong to the class of transient receptor potential channels (TRP) of which seven subsets exist (TRPC, TRPV, TRPM, TRPA, TRPP, TRPML & TRPN). There are a relatively large number of known agonists, with some examples in **F-6**. However, the majority of these are present in botanical sources and come with an unwanted (sometimes) odor attached, which can limit where a perfumer or flavorist could potentially use them.

As with sweet, sour, bitter, salty and umami effects in some of the areas of chemesthesis, there is limited understanding of chemical structure and TRP channel effectiveness. In the majority of areas, the

agonists continue to be derived from natural sources. The notable exception in this is in the area of cooling where there has been a large amount of effort to synthesize more effective molecules than exist in nature resulting in a much wider array of materials, and a better understanding of structure/property correlation¹⁷. There still exists significant potential to create further molecules that target specific TRP channels, providing target sensory chemesthetic effects that may not have the handicap of an attached odor

The Final Frontier

While there is currently—and there probably will be for the immediate future—a considerable amount of noise around the synthetic ingredients used in flavor and fragrance, the reality is the future of F&F industry lies in how we use the resources around us more effectively and communicate to the consumer the safety and benefits of what the industry does.

Our ability to synthesize specific molecules, which target a specific gustatory or trigeminal function, along with potential solutions that biotechnology, green chemistry and waste valorization bring to the materials we currently use, or those we wish to create, mean that synthesized ingredients are the future of our industry. We must continue to focus on utilizing technology to bring benefits the consumer desires and recognizes. The challenge we face is how the food, beverage, personal care and consumer product companies create a message, with the support of their F&F partners, that synthetics

F-6. Popular chemical agonists

Chemical Agonist	Botanical Source	TRP Channel
Capsaicin	Chili peppers	TRPV1
Piperine	Black pepper	TRPV1
[6] & [8] Gingerol	Ginger	TRPV1
Alpha hydroxysanshool	Sichuan pepper	TRPV1, TRPA1
Allicin	Garlic	TRPV1, TRPA1
Camphor	Cinnamomum camphora	TRPV3, TRPV1
Cannabichromene	Cannabis sativa	TRPV2, TRPA1
(-) Menthol	Peppermint	TRPM8, TRPV3
1,8-Cineole	Eucalyptus	TRPM8
Carvacrol	Oregano oil	TRPV3,
WS-3	Synthetic	TRPM8
Cinnamaldehyde	Cinnamon, Cassia	TRPA1, TRPV3
Allyl isothiocyanate	Mustard, Horseradish	TRPA1



are not only good for you but good for the planet. The answer might be, to paraphrase Star Trek, “It’s synthetic Jim, just not as we know it.”

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Bedoukian Research— High Impact Aroma Chemicals

■ by Dr. Rahman Ansari, Ronnie McBurnie, and Dominic Morgenthaler



The demand for High Impact Flavor & Fragrance Chemicals continues to grow in the F&F Industry. The reasons for this are many. Firstly, constant pressure on cost reduction forces perfumers and flavorists to seek out ingredients for their creations that offer a “bigger bang for their buck”. Secondly, environmental (biodegradability) and toxicological concerns have led to regulations, self-imposed by the industry or otherwise, that either ban or restrict the use of many key aroma chemicals in fragrance and flavor creations. Consequently, perfumers and flavorists search for impactful ingredients that would impart the desired olfactive effects at an affordable cost and at greatly reduced

levels of use, levels well below the no observed adverse effect level toxicologically.

Further to the above, recent sophistication of analytical techniques have revealed the presence of truly trace quantities of chemicals in natural botanical products which are proven to be responsible for their intriguing odor and taste character. In other words, a touch of these impactful trace materials often defines the personality and beauty of these natural products.

The term “high impact aroma chemicals” can be subjective and is open to different interpretations. In other words, most of us can understand the term, but for which there is no specific dictionary definition or yardstick. We have learned that the primary aspects of odor and taste are “character” and “intensity” – both of which being required to define the value of a desirable and usable high impact material. To put it in the right context for this article and

for the Flavor & Fragrance Industry in general, D.J. Rowe, describes in his article in The Royal Society of Chemistry (R.S.C) 2002 publication “Advances in Flavors and fragrances – From the Sensation to the Synthesis – pp 202 - 226” edited by Karl A. D. Swift, some of the key criteria which will constitute a usable “high impact aroma chemical” from our industry point of view:

- Low odor and taste threshold of perception – less than 10 PPB.
- Have recognizable character – even at a low level where the material would be used. For example, just being fruity in general terms is not enough. It should either be recognizable as “apple” or “mango” or enhance or add a specific note, such as “green” notes to apple or “creamy” notes to coconut.
- Have desirable hedonics/character – just being powerful is not enough.

- Meet regulatory requirements.
- Commercially available and cost effective.
- From its inception, Bedoukian has been on a quest to offer clean, natural smelling and tasting, impactful aroma chemicals. Bedoukian has a portfolio of flavor and fragrance chemicals that when used, even in small quantities, can impart a distinct and unique “signature” to your flavor and fragrance creations. These materials deliver the promise of an inherently low environmental footprint, sustainability, a broad range of organoleptic properties, power and ultimate cost saving through the concept of “less is more”.

A select number of Bedoukian materials are presented here to demonstrate their uniqueness and natural overtones to help perfumers and flavorists to create innovative compositions for flavor and fragrance applications:

High Impact Fragrance Chemicals

- **Honeyflor** (Methyl-3-Hexenoate) – Green, Fruity, Honey, Hyacinth, Pineapple, Sweet, Apple
BRI 123 | CAS 13894-61-6

An impressive green character supported by natural, softly sweet and warm honey undertones. Working extremely well as a universal floralizer, Honeyflor imparts a harmonizing, delicate sparkling effect to green floral compositions, specifically hyacinth and muguet. Honeyflor is also useful in gourmand types – adding a raw, natural honey, full bodied effect to fragrances. This material occurs naturally in guava, pineapple, prickly pear, papaya and nectarines.



- **Aquaflor** (Methoxy Melonal) – Floral, Fruity, Watery, Ozonic, Muguet, Melon
BRI 280 | CAS 62439-41-2

A powerfully fresh character accompanied by a muguet floralcy and ozonic effect combined with fruity undertones of melon. Due to its strong and diffusive nature, Aquaflor works well in a variety of fragrances – adding a touch of freshness and elegance to fruity florals and white flower fragrances, as well as citrus and herbal compositions for air fresheners and personal care products. This material is not yet found in nature.

- **E,Z-2,6-Nonadienal** – Green, Cucumber, Fresh, Violet Leaf, Melon
BRI 332 | CAS 557-48-2

A robust green, characteristic odor of a freshly sliced cucumber reinforced by fresh notes of violet leaf with a hint of melon. A true powerhouse, E,Z-2,6-Nonadienal’s strength and diffusion make it a useful tool for adding green, leafy, watery and floral notes to all odor types while providing lift and an extremely fresh effect. This material occurs naturally in cucumber, melon, tea, mango and apricot.





► **Trans-2-Decenal** – Citrus, Aldehydic, Waxy, Coriander, Rose, Green
BRI 354 | CAS 3913-81-3

An impressively powerful and diffusive material, Trans-2-Decenal can be used in trace amounts to impart a desirable odor effect. Trans-2-Decenal offers an enticing green, citrus character with fresh orange peel notes supported by waxy, fruity, peach-like undertones. Due to its fresh, green, sweet aldehydic aroma, Trans-2-Decenal blends well with floral and citrus compositions, working particularly well alongside Aldehyde C10 in supporting orange, mandarin, kumquat and other various citrus notes. This material occurs naturally in orange, melon and coriander seed.

► **2-Dodecenal (High Trans)** – Citrus, Mandarin, Orange, Waxy, Aldehydic, Fatty
BRI 356 | CAS 20407-84-5

An aldehydic, waxy citrus character similar to mandarin orange accompanied by cilantro herbal-type nuances. In fragrances, effects can be seen as little as parts per thousand. Use 2-Dodecenal (High Trans) as a top note to achieve a fresh, clean mandarin effect. 2-Dodecenal (High Trans) is a natural component of Mandarin Oil and an essential component in a variety of reconstituted citrus oils, making it extremely useful for capturing authentic peel notes and boosting citrus types. This material occurs naturally in bitter orange peel oil, mandarin peel oil and coriander.



► **2-Tridecenal (High Trans)** – Citrus, Aldehydic, Waxy, Tangerine, Herbal, Green
BRI 357 | CAS 7774-82-5

An aldehydic, waxy citrus peel odor with strong herbal characteristics reminiscent of cilantro. Similar to 2-Dodecenal (High Trans), 2-Tridecenal (High Trans) is a great top note for adding lift and boosting freshness, particularly in green and herbal compositions. 2-Tridecenal (High Trans) is also useful for brightening citrus types – blending extremely well with bitter orange oil and lime oil. This material occurs naturally in coriander seed.

► **Cis-6-Nonenal** – Fruity, Fresh, Cantaloupe, Melon, Green, Cucumber
BRI 380 | CAS 2277-19-2

A powerful green, fruity character with the characteristic odor of a ripe cantaloupe melon supported by tropical juicy undertones reminiscent of mangosteen and jackfruit. Due to its captivating character, Cis-6-Nonenal is particularly useful for imparting a natural juicy effect from which almost all fragrance types will benefit. However, it may also be used to add soft, clean aldehydic notes to boost the dewy, floral character of a fragrance. With its powerhouse properties and outstanding performance, Cis-6-Nonenal makes for an excellent ingredient that works well in all applications, up to and including fine fragrance. This material occurs naturally in cucumber and melon.



► **Cardamom Aldehyde (Cis-4-Decenal)** – Citrus, Aldehydic, Orange, Spicy, Cardamom, Lemon
BRI 381 | CAS 21622-09-9

An impressively powerful, aldehydic, citrus aroma exhibiting an extremely clean, unique spicy note reminiscent of the exhilarating odor of freshly crushed cardamom pods with fresh accents of chamomile, mandarin and orange. Given its citrus and spicy aspects, it's not a surprise that Cardamom Aldehyde works incredibly well to complement and boost citrus and spice types. Its superior diffusion makes this material versatile in a wide



range of applications. Extremely powerful, Cardamom Aldehyde is a great top note for all types, bringing tremendous performance and freshness dosed at levels as low as 0.01%. Higher levels create the distinctive and captivating cardamom note without the eucalyptus-like side effects often associated with natural cardamom oil. This material occurs naturally in coriander leaf, caraway seed, cardamom, yuzu and mandarin orange.

► **Cis-4-Dodecenal** – Aldehydic, Citrus, Fruity, Mandarin, Orange Peel
BRI 387 | CAS 21944-98-9

A fresh, aldehydic, citrus character with mandarin and orange peel nuances. Long-lasting and diffusive, Cis-4-Dodecenal blends well and provides significant lift to citrus types. Less fatty and cilantro-like than 2-Dodecenal (High Trans), Cis-4-Dodecenal imparts an authentic, sweeter mandarin top note that brings a bright citrus aldehydic freshness to compositions. This material occurs naturally in mandarin and coriander.

► **Guavanate** (Methyl-Cis-5-Octenoate) – Fruity, Tropical, Guava, Sweet, Juicy, Woody, Creamy, Exotic
BRI 493 | CAS 41654-15-3

A sweet, exotic, juicy tropical fruit character combined with aromatic and slightly woody impressions reminiscent of the true essence of pink guava; finishing off with a comforting, creamy coconut on dry down. Breezy and bright like a tropical island, Guavanate exudes naturalness combined with crisp and clean fruit nuances. It is perfect for lifting top notes – contributing complexity and depth to fruity floral and tropical formulations. This material occurs naturally in mango, pineapple and snake fruit.



► **Cerezoate** (Ethyl-2-Methyl-Cis-3-Pentenoate – High Cis) – Fruity, Sweet, Black Cherry, Ethereal, Apple, Strawberry
BRI 512 | CAS 1617-23-8

A powerful, ethereal, natural black cherry character reinforced by a mélange of juicy fruit nuances similar to pineapple, apple and fresh berries. Cerezoate's multiple facets and performance allow for very interesting effects, boosting the fruity top notes of a fine fragrance. It also performs well in air care, shampoo and dish detergent. This material has not yet been reported in nature.

► **Vionil** (2E,6Z-Nonadienenitrile) – Floral, Violet, Green, Orris, Powerful, Powdery
BRI 640 | CAS 67019-89-0

An extremely powerful green floral character with distinct notes of orris and violet leaf supported by shades of fresh cucumber and a subtle hint of walnut. The stability and substantivity of this ingredient allows it to be used in all challenging base applications and in fragrances where long lasting, substantive violet green floralcy is desired. Vionil blends well with all green, floral and fruity notes, and its effect can be seen at levels as low as 0.01%. This material has not yet been found in nature.





► **Nuezate** (3-Methyl-2-Oxo-Ethyl-Pentanoate) – Gourmand, Nutty, Walnut, Hazelnut, Ethereal, Fruity, Woody

BRI 728 | CAS 26516-27-8

A fresh black walnut character combined with sophisticated woody nuances and a subtle fruity odor in the mix. A powerful ingredient, with effects seen at levels as low as 0.01%, Nuezate is excellent for emphasizing nutty notes and may also be used to reinforce spice notes. Nuezate also combines nicely with woody notes i.e. patchouli and fougere, chypre and oriental types – adding complexity, depth and a touch of elegance to all fragrances. This material has not yet been found in nature.

► **1,3,5-Undecatriene** – Green, Fresh, Galbanum, Bell Pepper, Cucumber, Vegetative
BRI 809 | CAS 16356-11-9

An extremely powerful galbanum odor with fresh, green bell pepper undertones. A strong and diffusive material, 1,3,5-Undecatriene imparts naturalness and great lift to a wide range of odor types. It is a key component in galbanum oil and works very well to support green notes in fragrances, particularly Cis-3-Hexenol and esters. This material occurs naturally in galbanum, hops and pineapple.

► **Terrasol** (2-Ethyl Fenchol) – Earthy, Patchouli, Mossy, Lime, Green, Camphoraceous

BRI 818 | CAS 18368-91-7

A diffusive and extremely powerful earthy, ambergris aroma combined with notes of patchouli and oakmoss. Terrasol can be compared with very expensive Geosmin due to its earthy character and incredible strength – making it a great choice for heavy oud and oriental types. Terrasol can also add richness and lift to floral and green notes, particularly in fine fragrance, but is suitable for other applications involving aggressive bases, such as bleach, where stability is needed. This material has not yet been found in nature.

► **Lavender Aldehyde** (2-Isopropyl-5-Methyl-2-Hexenal) – Natural, Herbaceous, Lavender, Sage, Cocoa, Fruity

BRI 857 | CAS 35158-25-9

A very powerful, natural, herbaceous character mixed with hints of cocoa, blueberry and lavender overtones. Powerful and diffusive, Lavender Aldehyde blends well with bergamot, clary sage, and citrus types, and may also be used to boost ozonic notes in fragrance formulations. It excels in floral and gourmand compositions, specifically lavender and chocolate, truly demonstrating its versatility of use. This material occurs naturally in cocoa.

► **Limediene** (Methyl Cyclohexadiene) – Citrus,
Lime, Lemon, Truffle, Tropical, Fresh
BRI 962 | CAS 30640-46-1

An extremely powerful lemon-lime top note with exquisite undertones of white truffle. This unique combination of highly desirable lemon-lime, tropical and watery notes make Limediene a great choice for imparting freshness and power to any application. Short-lived but highly impactful, Limediene makes its presence known as low as 0.01%. It adds an extraordinary bloom and spark to citrus, floral and cool water types – working extremely well in liquid dish detergent, shower gels, air care, and laundry detergent. This material occurs naturally in lemon.



High Impact Flavor Chemicals

High on the list of High Impact Flavor Chemicals, are the many sulfur containing chemicals which include strong, roasted, meaty and alliaceous types like mercaptans, thiols and sulfides, as well as nitrogen containing chemicals which include bready, roasted, nutty, chocolate and coffee types like pyrazines.

In addition to these, there are many non-sulfur and non-nitrogen containing chemicals that are high on the list of High Impact Aroma Chemicals. One of the strongest known to flavorists is Beta Damascenone, which is widely used for fresh, fruity, rosy notes for many fruit and berry flavors, especially raspberry. It has a flavor threshold in the 1-10 PPT (trillion) range, even stronger than most sulfur chemicals. This puts it in the same threshold range as the green bell pepper Pyrazine, 2-Isobutyl-3-Methoxy Pyrazine which has a flavor threshold of 2 PPT. Furfuryl Mercaptan, known for its skunky, roasted or burnt coffee, only has a threshold of 40 PPB, about 4000 times weaker than Beta Damascenone.

Unsaturated Aldehydes, Alcohols, Ketones, including dienals and dienols, contribute to many similar types of foods as mentioned above. For example, 2,4 Decadienal has a strong chicken fat character, but also works well to add fried notes to a variety of flavors. At lower levels it contributes to the sweet, oily notes found in roasted peanuts.

The following list contains some of Bedoukian's High Impact Aroma Chemicals for use in flavors:

► **Methyl-3-Hexenoate** (Honeyflor) – Flavor Threshold
Level in Water: < 50.0 PPB
BRI 123 | FEMA 3364

A very strong, sharp, honey character. It works well to enhance these types of notes in a variety of applications, on its own or, when used in combination with other types of flavors, such as lemon, orange, etc. for applications like Honey Lemon Tea or Citrus Honey throat lozenges. This material occurs naturally in guava, pineapple, prickly pear, papaya and nectarines.

► **Methoxy Melonal** (Aquaflor) – Flavor Threshold
Level in Water: < 20 PPB
BRI 280 | FEMA 4745

A natural juicy melon character, with dewy, watery notes that can add unique freshness to many other types of fruit and berry flavors especially apple, pear, raspberry. May also be used for the briny notes in shellfish type flavors. This material is not yet found in nature.



► **E,Z-2,6-Nonadienal** – Flavor Threshold in Water: < 0.02 PPB

BRI 332 | FEMA 3377

A strong cucumber, melon character on its own. In combination with Z-6-Nonenal, it changes from cucumber to a characteristic watermelon. It can also add freshness to a variety of fruit flavors, such as apple, raspberry and strawberry. This material occurs naturally in cucumber, melon, tea, apricot and mango.

► **2-Dodecenal (High Trans)** – Flavor Threshold in Water: <10 PPB

BRI 356 | FEMA 3402

A strong waxy, citrus peel, melon, and herbal character. It can add peely notes to many citrus type flavors, especially tangerine, mandarin and orange. It can contribute waxy notes to all types of melon flavors, especially watermelon. Because of its waxy, herbal character, it is very useful to add or enhance cilantro notes to a variety of applications. This material occurs naturally in orange, coriander seed, cooked beef, cooked chicken, cooked pork and roasted peanut.



► **2,4-Decadienal** – Flavor Threshold Level: < 0.3 PPB

BRI 364 | FEMA 3135

It is considered a key ingredient in chicken fat. So, to add this note to a vegan soup or gravy, it will simulate the chicken fat character. At lower levels it can add sweet fatty notes found in roasted peanuts and roasted sesame as well as contribute to peely notes in citrus. This material occurs naturally in cooked beef, cooked lamb/mutton, fish, potato chips, roasted almond, roasted peanut, roasted pecan, soybean, mandarin oil, orange and tomato.



► **Cis-3-Hexenal (50% in Triacetin)** – Threshold Level in Water: < 0.5 PPB

BRI 375 | FEMA 2561 (Neat Material)

A powerful green, fruity character that can add freshness to a variety of fruit flavors. At extremely low levels, it adds seediness to raspberry flavors. It is a very versatile flavor chemical contributing fresh green notes to a variety of flavor types, from fruits like apple, pear and grape to green vegetables like tomato to green tea. This material occurs naturally in apple, avocado, banana, guava, raspberry, strawberry, tea and tomato.



► **Cis-4-Heptenal** – Flavor Threshold Level: < 0.4 PPB

BRI 379 | FEMA 3289

At very low levels, it contributes the green, almost grassy notes found in fresh cream. It is a must to duplicate the complex makeup of fresh cream. Along with other dairy

ingredients, like lactones, acids and ketones, a non-dairy cream flavor is possible. Flavor can then be used alone or in combination with vanilla flavors, or wherever cream notes are needed. At higher levels, still in the PPB range, it works well for tomato and other green type vegetable flavors. Added to cooked tomato juice, it creates a freshness associated with “right-off -the-vine” tomato. This material occurs naturally in butter, milk, fish, krill, raw oyster, boiled potato, peppermint, spearmint oil, scotch and wheat bread.



► **Cis-6-Nonenal** – Flavor Threshold in Water:

< 0.01 PPB

BRI 380 | FEMA 3580

Another powerful, unsaturated aldehyde, which, by itself, is fresh cut watermelon. Like the dienal above, it also can be used for cucumber notes. At low levels it can add freshness to a variety of fruit flavors like apple, strawberry and some tropical fruits, as well as for green vegetables and herbal flavors. This material occurs naturally in cucumber and melon.



► **Cis-4-Decenal** (Cardamom Aldehyde) – Flavor Threshold Level in

Water: < 4.0 PPB

BRI 381 | FEMA 3264

Characteristic of fresh crushed cardamom pods, it is also a key component in orange juice flavors. It adds natural notes to several other citrus flavors including mandarin, tangerine and grapefruit. This material occurs naturally in cooked chicken, clam, cardamom, yuzu and mandarin orange.

► **Cis-4-Dodecenal** – Flavor Threshold in Water: <10 PPB

BRI 387 | FEMA 4036

A strong citrus peel, waxy, herbal character, specifically Tangerine or Mandarin. Used in combination with typical orange flavor ingredients and Dimethyl Anthranilate, a unique, natural tasting mandarin/tangerine flavor can be achieved. Can also be used to impart cilantro notes to a variety of applications. This material occurs naturally in mandarin and coriander.

► **1,3,5-Undecatriene** – Flavor Threshold in Water: <50 PPB

BRI 809 | FEMA 3795

A very characteristic galbanum, green bell pepper character. Because of its unique character, it can add these notes to a variety of applications, including, but not limited to, salad dressings, soups, casseroles or anywhere green bell pepper is used. At lower levels, it can add freshness to pineapple as well as enhancing herbal notes, especially cilantro in a variety of applications including infusions used for cocktails. This material occurs naturally in galbanum, hops and pineapple.



► **2-Ethyl Fenchol** (Terrasol) – Flavor Threshold Level: < 3.0 PPB

BRI 818 | FEMA 3491

Commercially used as an off-note marker by the beer industry to check for contaminated water used, Ethyl Fenchol, however, finds many uses for both flavors and fragrances. Since it is extremely earthy, it works well in many root-vegetable flavors, like potato, parsnip as well as beets. It can also be used to impart earthy, musty notes in mushroom flavors. At much lower levels it adds fresh-squeezed juiciness to both lemon and lime flavors. This material has not yet been found in nature.



PRODUCT LIST

A	2-Acetyl-5-Methyl Furan	853	G	Geranic Acid	520	
	Apritone	410		Geranyl Tiglate	422	
	Aquaflor	280		Guavanate	493	
B	Benzyl Tiglate	420	H	Habanene	965	
	Bisabolene	828		Hazelnut Furan FCC	858	
	Butyl Butyryl Lactate FCC	540		2,4-Heptadienal FCC	361	
	n-Butyl Hexanoate	548		gamma-Heptalactone FCC	450	
C	Capric Acid (Natural)	882		trans-2-Heptenal	351	
	Caproic Acid (Natural)	880		cis-4-Heptenal FCC	379	
	Caprylic Acid (Natural)	881		2,4-Hexadienal	360	
	Cardamom Aldehyde FCC	381		trans-2-Hexenal (Leaf Aldehyde) FCC	350	
	Cerezoate	512		cis-3-Hexenal (50% in Triacetin)	375	
	Citronellyl Acetate BRI FCC	706		3-Hexenal Mixture (50% in Triacetin)	376	
	Citronellyl Isobutyrate FCC	732		trans-2-Hexenoic Acid	441	
Cremeffleur	408	trans-3-Hexenoic Acid (Pure)		442		
D	2,4-Decadienal FCC	364		1-Hexenol	164	
	2,4-Decadienol	240		cis-2-Hexenol	166	
	delta-Decalactone	461		trans-2-Hexenol	140	
	gamma-Decalactone FCC	453		trans-3-Hexenol	138	
	trans-2-Decenal FCC	354		cis-4-Hexenol	135	
	trans-4-Decenal	382		trans-2-Hexenyl Acetate FCC	141	
	9-Decenal (98+%)	390		trans-3-Hexenyl Acetate	139	
	9-Decenoic Acid	891		cis-3-Hexenyl Benzoate	105	
	cis-4-Decenol	171		cis-3-Hexenyl Butyrate	106	
	3-Decen-2-One	613	cis-3-Hexenyl Caproate (Hexanoate)	108		
	Dehydroxy Linalool Oxide	820	cis-3-Hexenyl Formate	110		
	Dihydro Alpha Ionone	468	cis-3-Hexenyl Cis-3-Hexenoate	121		
	Dihydrojasmone	401	cis-3-Hexenyl Isobutyrate	107		
	2,6-Dimethyl-5-Heptenal FCC	383	cis-3-Hexenyl Isovalerate FCC	117		
	2,4-Dodecadienal	366	cis-3-Hexenyl Lactate	111		
	e,z-2,6-Dodecadienal	341	cis-3-Hexenyl Alpha Methyl Butyrate FCC	103		
	delta-Dodecalactone	463	cis-3-Hexenyl Methyl Carbonate	122		
	gamma-Dodecalactone FCC	455	cis-3-Hexenyl Propionate	113		
	2-Dodecenal (High Trans) FCC	356	cis-3-Hexenyl Pyruvate	114		
	cis-4-Dodecenal	387	cis-3-Hexenyl Tiglate	116		
	E	Ethyl Amyl Ketone	631	Hexyl 2-Methyl Butyrate FCC	130	
Ethyl Butyl Ketone FCC		630	Hexyl Tiglate	427		
Ethyl 2,4-Decadienoate		433	Honeyflor	123		
Ethyl 2-Decenoate (Trans)		517	Hydroxy Citronellal Diethyl Acetal	324		
Ethyl 4-Decenoate (Trans)		518	8-Hydroxy Para-Cymene	973		
2-Ethyl Furan		950	I	alpha-Ionol	260	
Ethyl 3(2-Furyl)Propanoate		852		beta-Ionol	265	
Ethyl 2-Hexenoate		445		alpha-Ionone BRI FCC	469	
Ethyl 3-Hexenoate		446		Isobornyl Isovalerate	977	
Ethyl 3-Hydroxy Hexanoate		434		Isojasmone3-Decen-2-One	415	
Ethyl Levulinate FCC		545		J	Jasmolactone Extra C	413
Ethyl 2-Methyl-3,4-Pentadienoate		510	cis-Jasmone		400	
Ethyl 2-Methyl Pentanoate		438	L		Lactone of Cis Jasmone	411
Ethyl 2-Methyl-3 & -4-Pentenoates		511			Lauric Acid (Natural)	883
Ethyl 2-Methyl-4-Pentenoate		436			Lavender Aldehyde FCC	857
Ethyl 2-Octenoate		515			Leaf Alcohol (Ethyl) Acetal	311
Ethyl Palmitate		894		Limediene	962	
Ethyl Tiglate		423		M	Maltol Isobutyrate	622
Ethyl Vanillin Propylene Glycol Acetal	831	12-Methyltridecanal	284MCT			
F	Farnesene	808	(10% in Medium Chain Triglycerides)			
	Farnesol FCC	719	Methyl Amyl Ketone		600	
	(e,e)-Farnesol 97+% FCC	7191-97	2-Methyl Butyraldehyde FCC		288	
	Farnesyl Acetate	718	gamma-Methyl Decalactone		456	
	Fruitaleur	9840	Methyl Dihydro Jasmonate Extra EPI (Cis)	398E		
	Furfuryl Acetate	845	5-Methyl Furfural	846		
	Furfuryl Propionate	861	Methyl 2-Furoate	867		

PRODUCT LIST

M	Methyl Heptine Carbonate	483	Prenyl Acetate	151
	Methyl Heptyl Ketone FCC	602	Pyruvic Acid BRI	890
	2-Methyl Hexanoic Acid	435		
	5-Methyl Hexanoic Acid	474	R	Rose Oxide BRI
	Methyl Jasmonate	399		480
	Methyl 3-Nonenoate (High Trans)	513	T	delta-Tetradecalactone
	Methyl Nonyl Ketone FCC	605		465
	Methyl Octine Carbonate	485		Terrasol FCC
	Methyl Octyl Ketone	603		818
	3-Methyl Pentanoic Acid	477		Tetrahydrocarvone
	2-Methyl Pentanoic Acid FCC	478		975
	4-Methyl Pentanoic Acid FCC	476		Tridecanal
	3-Methyl Pentanol	963		287
	2-Methyl-2-Pentenoic Acid BRI FCC	444		2-Tridecenal (High Trans) FCC
	4-Methyl-2-Pentyl-1,3-Dioxolane	860		357
	5-Methyl-2-Phenyl-2-Hexenal	856		Tropical Dienoate
	4-Methyl-2-Phenyl-2-Pentenal	855		536
	Methyl Propyl Ketone FCC	607	U	2,4-Undecadienal
	Methyl Undecyl Ketone	608		365
	Myristic Acid (Natural)	884		2,4-Undecadienal
				365-99
				delta-Undecalactone FCC
				462
				Undecatriene
				810
				1,3,5-Undecatriene FCC
				809
				2-Undecenal (High Trans)
				355
N	Nerolidol FCC	712	V	Valencene (Natural)
	Nerol Oxide	708		806
	Neryl Isobutyrate	703		Vanillin Propylene Glycol Acetal
	2,4-Nonadienal FCC	363		830
	e,e-2,6-Nonadienal	345		Vartol, Rhodinol Substitute
	e,z-2,6-Nonadienal FCC	332		715
	e,z-2,6-Nonadienal Diethyl Acetal	317		(Contains Geraniol, Citronellol)
	e,z-2,6-Nonadienol FCC	335		Vionil (10% in Dipropylene Glycol)
	3,6-Nonadienyl Acetate	338		640DPG
	delta-Nonalactone FCC	460		
	trans-2-Nonenal FCC	353		
	cis-6-Nonenal	380		
	cis-2-Nonenol	188		
	trans-2-Nonenol	190		
	cis-3-Nonenol	170		
	cis-6-Nonenol FCC	337		
	3-Nonen-2-One	612		
	cis-6-Nonenyl Acetate	9850		
	Nootkatone (Crystals 98+%)	801		
	Nuezate	728		
O	2,4-Octadienal	362		
	gamma-Octalactone FCC	451		
	trans-2-Octenal FCC	352		
	cis-5-Octenal	359		
	1-Octenol, (Amyl Vinyl Carbinol) FCC	160		
	trans-2-Octenol	185		
	cis-3-Octenol	162		
	cis-5-Octenol	168		
	2-Octen-4-One	614		
	3-Octen-2-One	611		
	1-Octen-3-One (50% in 1-Octenol)	628		
	1-Octenyl Acetate FCC	161		
	2-Octenyl Acetate (High Trans)	186		
	Orrisol	330		
P	Palmitic Acid (Natural)	885		
	Parmavert	310		
	Pear Acetate	179		
	Pearlate	1622		
	trans-2-Pentenal	349		
	4-Pentenoic Acid	448		
	1-Pentenol, (Ethyl Vinyl Carbinol)	159		
	cis-2-Pentenol	169		
	Phenyl Ethyl Tiglate	426		
	Pomelo Aldehyde	369		

For additional product information or to request a sample, contact Bedoukian at customerservice@bedoukian.com



Sustainability in Flavor and Fragrance Ingredients

Securing renewable natural ingredients and establishing sustainable synthetic chemicals are important for the future of F&F.

by Kaori Matsumura and Makoto Emura,
Takasago International Corp.

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Until the 19th century, all basic goods for human use were derived from plants and animals. In the 20th century, the rapid development of the petroleum industry changed people's lifestyles, enabling mass production, mass consumption and mass waste. Although producing goods in a sustainable way to meet 21st century demands is no easy feat, it is well known that the use of petroleum feedstock poses problems for humanity's collective future. Such products release CO₂ stored in fossil fuels and increase CO₂ levels in the environment, thereby exacerbating climate change (F-1).

Furthermore, the United Nations has announced that the world population will total more than 9.6 billion in 2050.^a It is quite feasible that this

population growth will cause a future shortage of water, food and energy. Similarly, it will have an impact on the flavor and fragrance (F&F) market, the size of which in 2013 was \$23.9 billion,^b which is estimated to expand about 6% annually over the next 10 years. Consequently, the F&F industry is exploring various ways to increase sustainability in the 21st century. From a raw material procurement point of view, this report describes two main streams, securing renewable natural ingredients and establishing sustainable synthetic chemicals in F&F (F-2).

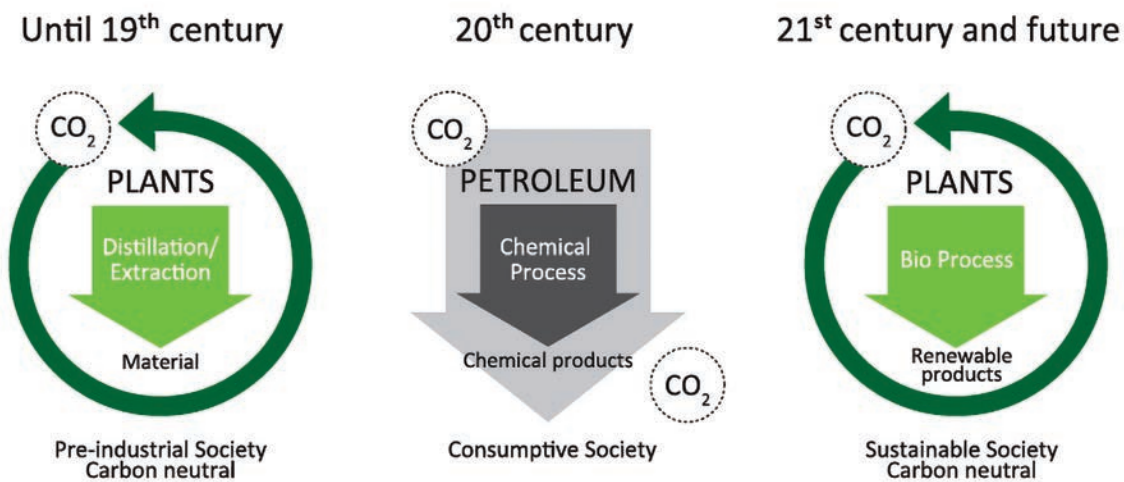
Secure Renewable Natural Ingredients

Much effort has been directed toward securing natural resources. At first, the F&F industry supported a range

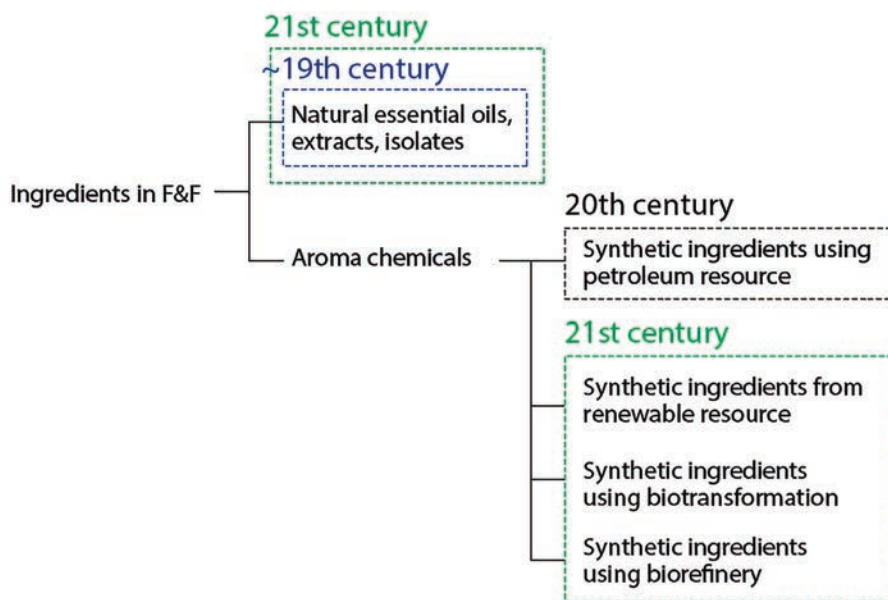
^aWorld Population Prospects: The 2012 Revision; http://esa.un.org/unpd/wpp/unpp/panel_populationw.htm

^bwww.leffingwell.com/top_10.htm

F-1. Paradigm shift in ingredient production



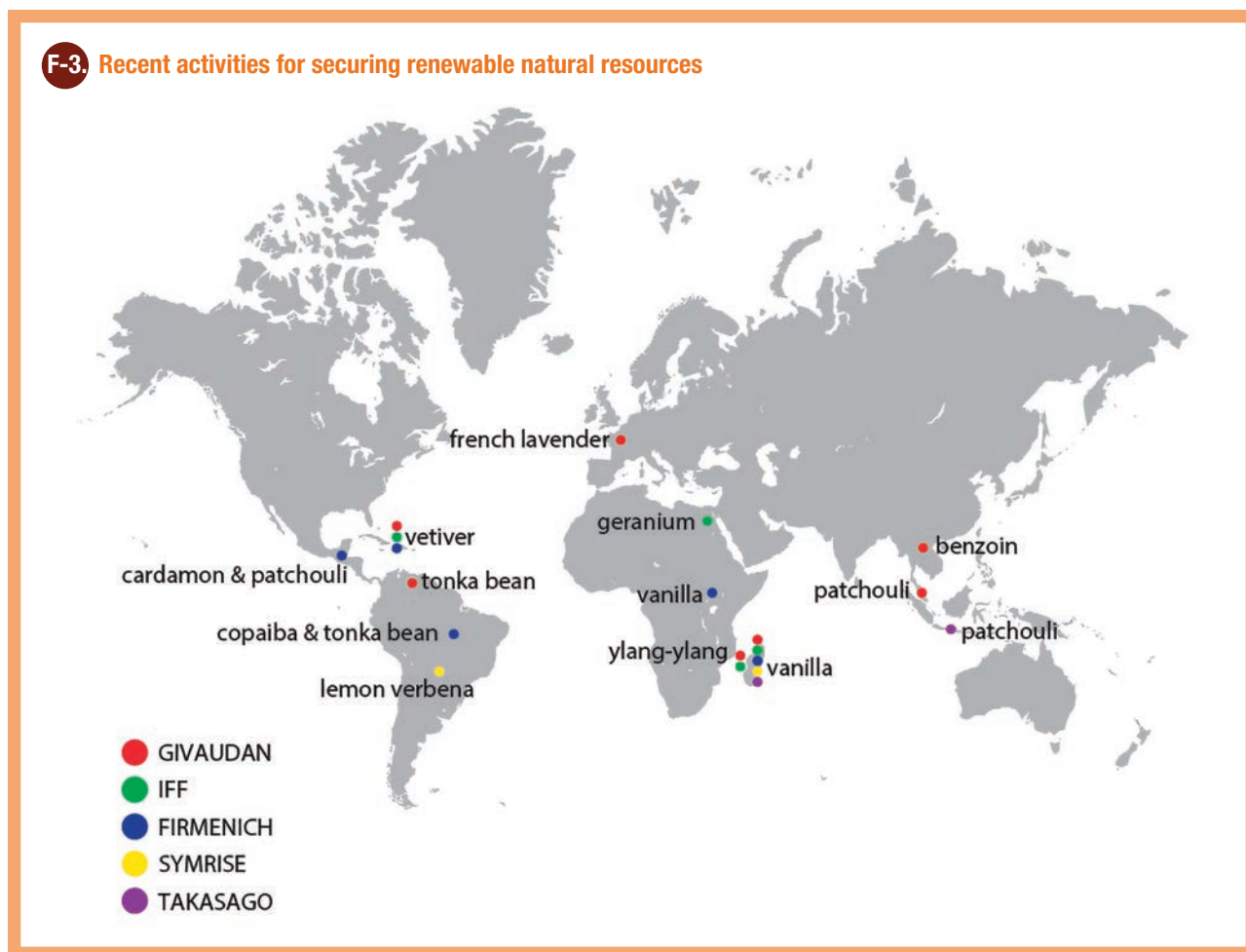
F-2. Categories of ingredients



of different approaches, which have been undertaken to enhance the quality of life for the communities concerned. Collaborating with an organization to preserve natural resources is one way to engage in sustainable activities. Some companies are not only teaching methods and skills to improve crop yields; they are also providing health services and

educational support for growing local communities (T-1). These activities show that industries are focusing on making long-term relationships with suppliers of natural ingredients. Consumers' strong demand for these natural ingredients is pushing industries to have a varied selection of natural ingredients, produced in a sustainable fashion (F-3).

F-3. Recent activities for securing renewable natural resources



Synthetic Ingredients Using Petroleum Resource

In the late 19th century, naturally identified coumarin and vanillin were chemically synthesized for the first time. Since then, with advances made in the petroleum industry, the advantages of synthetic ingredients began to outweigh the benefits of natural materials: synthetics were reasonably priced, of stable quality and available in substantial volumes. In the past, fragrances were only accessible to upper-class consumers and were applied to selected items, such as fine fragrances. The advantages of synthetic ingredients enabled fragrances to enrich consumers' lives in various daily products, ranging from household cleaners to cosmetic goods. In addition, novel synthetic ingredients contributed to the expansion of the perfumer's creativity beyond the scope of what nature alone would allow. For instance, about 2,000 synthetic ingredients are used in perfumery today.

Synthetic Ingredients from Renewable Resources

In their production of sustainable aroma ingredients, industries are looking to reduce their dependence on

fossil-derived petroleum raw materials. This, in turn, raises the demand for natural renewable resources. Recently, IFF reported that a synthetic musk ingredient was developed from a bio-based material.^c Symrise announced that Ambrocenide, Symroxane, Ysamber K and limonenal have been switched to a renewable raw material.^d Furthermore, Terranol^e was developed utilizing a renewable resource.^f Takasago has substituted bio-ethanol for the production of Thesaron^g for a 100% bio-based product. Switching feedstock from petroleum to renewable resources may seem like a recent trend, but there are several precedents. The drastic price increase of petroleum in the 1970s emboldened Takasago to alter the starting material of *l*-menthol from a petroleum-derived one to a renewable resource. Takasago celebrated the 30th anniversary of the asymmetric synthetic process using renewable myrcene in 2013.

^cSeeds of Growth; www.iff.com/custom/iff/books/sustainability_2011/files/inc/774950749.pdf

^dAmbrocenide, Symroxane and Ysamber K are trademarks of Symrise.

^eTerranol is a trademark of Symrise

^fPerspectives 2010; www.symrise.com/newsroom/article/perspectives-2010-symrise-publishes-csr-report/

^gThesaron is a trademark of Takasago.

T-1. Select sustainable ingredient activities among top F&F houses

Company	Material	Country	Activity	Source
Givaudan	Vanilla	Madagascar	Supported the community in education and infrastructure. Advised the local community how to improve the yield and quality of the vanilla crop.	Givaudan, 2010, "Translating Vision into Action"; www.givaudan.com/staticweb/StaticFiles/GivaudanCom/Publications/Sustainability/2010_sustainabilityReport.pdf
	Benzoin	Laos	Supported the community by building schools and introducing other fragrance ingredients to cultivate.	Givaudan, 2010, "Translating Vision into Action"; www.givaudan.com/staticweb/StaticFiles/GivaudanCom/Publications/Sustainability/2010_sustainabilityReport.pdf
	French lavender	France	Made an alliance with other organizations to combat a spread of a disease.	Givaudan, 2012, "Engaging the Senses"; www.givaudan.com/staticweb/StaticFiles/GivaudanCom/Publications/Sustainability/Giv_2012_SR.pdf
	Ylang-ylang	The Comoros	Installed new distillation stills. Expanded education supports for children.	Givaudan, 2010, "Translating Vision into Action"; www.givaudan.com/staticweb/StaticFiles/GivaudanCom/Publications/Sustainability/2010_sustainabilityReport.pdf
	Tonka bean	Venezuela	Provided technical and financial supports.	Givaudan, 2011, "Making Progress Together"; www.givaudan.com/staticweb/StaticFiles/GivaudanCom/Publications/Sustainability/2011_sustainabilityReport.pdf
	Patchouli	Malaysia	Signed an exclusive contact with GaiaOne and Kebun Rimau SDN BHD to develop sustainable plantations and local distillation.	Givaudan media release, January 24, 2014, "Givaudan Announces Exclusive Partnership for Sustainable Sourcing of Patchouli"; www.givaudan.com/Media/Media+Releases
	Vetiver	Haiti	Purchased an organic- and fairtrade-certified production stream.	Givaudan, 2012, "Engaging the Senses"; www.givaudan.com/staticweb/StaticFiles/GivaudanCom/Publications/Sustainability/Giv_2012_SR.pdf
Firmenich	Vanilla	Madagascar	Purchased Rainforest Alliance-certified vanilla. Supported community in healthcare field.	Firmenich, 2013, "Reflecting on Sustainability"; www.firmenich.com/filedownload.lbl%3Fuid%3D2adcf0ac-f8f8-3c5e-936b-78d859d7c01a
	Vanilla	Uganda	Supported community in education and healthcare fields. Provided technical trainings for farmers.	Firmenich, 2013, "Reflecting on Sustainability"; www.firmenich.com/filedownload.lbl%3Fuid%3D2adcf0ac-f8f8-3c5e-936b-78d859d7c01a
	Vetiver	Haiti	Supported the community "to enhance the value chain, increase farmers' incomes and crop diversification and strengthen community ecosystems."	Firmenich, 2013, "Reflecting on Sustainability"; www.firmenich.com/filedownload.lbl%3Fuid%3D2adcf0ac-f8f8-3c5e-936b-78d859d7c01a
	Patchouli	Guatemala	Free patchouli seedlings were distributed to local communities.	Firmenich, 2013, "Reflecting on Sustainability"; www.firmenich.com/filedownload.lbl%3Fuid%3D2adcf0ac-f8f8-3c5e-936b-78d859d7c01a

T-1. Select sustainable ingredient activities among top F&F houses (Cont.)

Company	Material	Country	Activity	Source
Firmenich	Cardamom	Guatemala	Guaranteed a stable income to farmers by direct purchasing.	Firmenich, 2013, "Reflecting on Sustainability"; www.firmenich.com/filedownload.lbi%3Fuid%3D2adcf0ac-f8f8-3c5e-936b-78d859d7c01a
	Copaiba/tonka bean	Brazil	Provided technical trainings and financial support.	Firmenich, 2013, "Reflecting on Sustainability"; www.firmenich.com/filedownload.lbi%3Fuid%3D2adcf0ac-f8f8-3c5e-936b-78d859d7c01a
IFF	Vanilla	Madagascar	Supported vanilla farmers since 2007. Guaranteed fair pricing for a steady income and created an educational environment for children. In 2012, set up a program for ethical vanilla production.	IFF, 2011, "Seeds of Growth"; http://www.iff.com/custom/IFF/images/IFF_Sustainability_Report_2012_small.pdf ; IFF, 2012, "Moving Forward"; www.iff.com/company/sustainability.aspx
	Geranium oil	Egypt	Concluded a long-term relationship with a local vendor. Established the best sustainable price level for the right quality. Supported community in health, education and infrastructure.	IFF, 2011, "Seeds of Growth"; http://www.iff.com/custom/IFF/images/IFF_Sustainability_Report_2012_small.pdf ; IFF, 2012, "Moving Forward"; www.iff.com/company/sustainability.aspx
	Vetiver	Haiti	With other key stakeholders from the industry, supported community to improve its living conditions.	IFF, 2012, "Moving Forward"; www.iff.com/company/sustainability.aspx
	Ylang-ylang	The Comoros	Company's supplier supported local community by providing not only technical training but also clean water and health services.	IFF, 2012, "Moving Forward"; www.iff.com/company/sustainability.aspx
Symrise	Vanilla	Madagascar	Provided technical support and invested in infrastructure and education for communities.	Symrise, "2011 Sustainable Solutions"; www.symrise.com/sustainability/article/sustainable-solutions-symrise-publishesits-2011-sustainability-report/
	Lemon verbena	Paraguay	Provided technical and financial support.	Symrise, "Perspectives 2010"; www.symrise.com/newsroom/article/perspectives-2010-symrise-publishes-csrreport/
Takasago	Vanilla	Madagascar	Signed a joint venture agreement with Ramanandraibe Export Co. Secured the material with stable price. Supported community environment.	Official press release, January 16, 2013; http://pdf.irpocket.com/C4914/JA1b/BJsv/Zzkr.pdf
	Myrrh	Namibia	Supported the indigenous community.	Company press release, April 3, 2013; www.takasago.com/en/sustainability/index.html
	Patchouli	Indonesia	Supported cultivation of patchouli and local living conditions.	Official R&D statement; www.takasago.com/en/rd/sustainability/index.html

Synthetic Ingredients Using Biotransformation

Biological processes play a major role in green and sustainable approaches by utilizing microorganisms or enzymes from a renewable resource. These starting materials require less organic solvent and generate less chemical waste from the process, compared to conventional means of production. In addition, some of these ingredients can be labeled as natural in accordance with CFR21 Sec. 101.22 and E.U. Flavor Regulation 1334/2008/ EC. Today, many biotransformed flavor ingredients have been developed and used in the market. It will be more important to the industry to uncover the potential of enzymes and microorganisms. However, developed products are currently limited since enzyme reactions for the substrate are highly specific.

Synthetic Ingredients Using Biorefinery Methods

The recent development of synthetic biology, which employs genetically engineered microorganisms intentionally designed with a desired synthase, is a powerful tool to address the aforementioned specificity of biotransformation capability. This biorefinery process uses abundantly available and inexpensive renewable biomass. This allows for the industry to develop structurally complex or highly functionalized ingredients that would never work in a practical way via chemical synthesis. As a result, synthetic biology can provide highly desirable natural products with the stable and steady supply benefit of synthetic products. For example, vanillin, which is labeled as natural when produced via synthetic biology, is one of the most popular flavors in the world; however, extraction from pods alone cannot fulfill the worldwide demand for it. Only 2% of vanillin can be obtained from a cured vanilla pod, while 33% of it can be acquired from a biorefinery technology.¹

Synthetic biology's potential has driven many companies to enter this field of research. In 2011, Firmenich partnered with Amyris to develop several sustainable materials. Their first product is patchouli oil, which will be launched in 2014.^h IFF and Evolva have been developing vanillin, which will be launched later this year.ⁱ Givaudan and IFF have also signed an agreement to produce new materials

with Amyris.^{j,k} It is obvious that the F&F industry is paying close attention to this area, and one should expect more materials to come.

Conclusion

Natural and synthetic ingredients must complement each other for future F&F. It is necessary to maintain natural ingredients and supply the sufficient amount of product in a renewable and sustainable way as the worldwide population increases. Synthetic ingredients have a short history compared to traditional natural ingredients; however, given technological advancement, world affairs and increasing consumer demand, the development of synthetic ingredients is burgeoning. The quest for more environmentally friendly products is one of the biggest requests from customers nowadays, and the industry is turning from the 20th century's petroleum-based practices toward the 21st century's sustainable alternatives. To answer these demands, the production of synthetic ingredients using renewable bio-based resources is already underway. Synthetic biology surely brings an unprecedented era of aroma ingredient development, which past technology never realized, and the possibility for perfumers and flavorists to broaden their creativity. The F&F industry is committed to collaborating with others outside of its industry, in order to pursue a sustainable society.

^j"Amyris Partners with Givaudan to Develop Key Fragrance Ingredient from Biofene"; www.amyris.com/News/137/Amyris-Partners-with-Givaudan-to-Develop-Key-Fragrance-Ingredient-from-Biofene

^k"IFF and Amyris Advance Innovative Collaboration to Develop Ingredients for the Flavors and Fragrances Market"; <http://phx.corporate-ir.net/phoenix.zhtml?c=65743&p=irol-newsArticle&ID=1903270&highlight=>

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References

1. R Shetty, *Cultured Ingredients Arrive*. *Perfum Flavor*, 38(11), 34–37 (2013)

^h"Amyris Enters into Collaboration and Joint Development Agreement with Firmenich"; www.amyris.com/News/141/Amyris-Enters-into-Collaboration-and-Joint-Development-Agreement-with-Firmenich

ⁱ"Evolva enters into collaboration with International Flavors & Fragrances Inc."; www.evolva.com/sites/default/files/press-releases/eve-iff-jan2011-en.pdf





Perfume and Flavor Synthetics

A model for research and academic-industrial cooperation

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Vol. 28 • September/October 2003

Cooperation between the Department of Organic Technology (DOT) at ICT Prague and Aroma Co. began in 1970 with research into problems with benzyl-acetate purity. The cooperative first consisted of an expert consultancy, which gradually grew into a systematic expert-research group focused on fields of basic research. The focus again moved to the field of the so-called creative-realization, before finally implicating new production processes of traditional and new perfumery substances. Original expert documents describing the obtained results were elaborated upon and today, together with about 50 authorizations, amount to approximately 80 papers.

The construction of the hydrogenation unit led to a breakthrough in the production assortment. This has occurred as a result of DOT's long scientific focus and because hydrogenation processes have particularly broad spectra of utilization in the synthesis of perfumery and flavor substances.¹ The so-called hydrocinnamic alcohol, 3-phenylpropane-1-ol was the first substance to be produced.²⁻⁶ Soon after this launch, the material founded a broad utilization in perfumery compositions, becoming an advantageous export item. 3-Phenylpropane-1-ol

was produced in two steps as shown by the two equations presented in **F-1**.

An analogous procedure was selected for the synthesis of 4-phenyl-4-methyl-1,3-dioxane, which was used for the production of 3-phenylbutane-1-ol by hydrogenolytic decomposition (**F-2**).^{2,3,5}

3-Cyclohexylpropane-1-ol and 3-cyclohexylbutane-1-ol were produced using hydrogenation of aromatic nuclei in both of the alcohols (**F-3**).⁷

All the four alcohols were used for the preparation of a number of esters; however, only esters

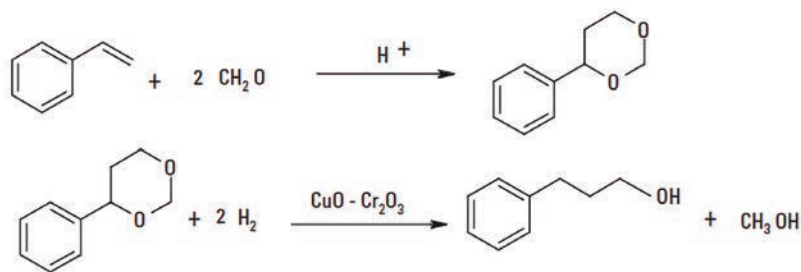
of 3-phenylpropane-1-ol and 3-phenylbutane-1-ol with acetic acid have reached the industrial utilization.⁸⁻¹¹ Similarly, dehydrogenations of all the mentioned alcohols to relevant perfumic aldehydes have been elaborated and consecutively used for the preparation of interesting acetals.¹² The fragrant properties of several of them, as well as fragrance properties of ethers, derived from 3-phenylpropane-1-ol have already been described.⁵

4-Phenyl-1,3-dioxane is a compound that is susceptible to a host of interesting transformations leading in some cases to compounds not yet described or substances with not yet described fragrance properties.⁵⁻¹⁴ Its acidolysis to 1-phenylpropane-1,3-diol-diacetate with the consequent re-esterification to 1-phenylpropane-1,3-diol, which is a very efficient repellent, has already been verified in a pilot system (F-4).

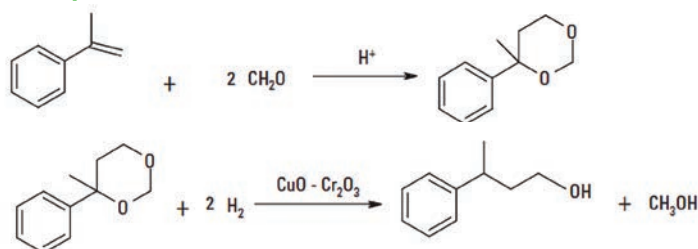
A number of new cyclic acetals with interesting fragrance properties, and naturally with excellent stability in alkaline environment, were prepared from 1-phenylpropane-1,3-diol.⁵ The transformations of 4-phenyl-1,3-dioxane on various catalysts are interesting. Besides the above-mentioned hydrogenolytic decomposition to 3-phenylpropane-1-ol, decomposition on palladium catalyst to 1-phenylpropane-1-one (propiophenone) and aluminosilicate catalyst to allylbenzene¹⁶ were discovered — both with high selectivity (F-5).^{3,15}

3-Phenylpropane-1-ol is a typical perfumery substance and an intermediate for other perfumery substances, whereas propiophenone and allylbenzene are semi-products with good opportunity for use in the synthesis of pharmaceuticals and herbicides. The decomposition of 4-phenyl-4-methyl-1,3-dioxane brings about more problems, and except the above-mentioned

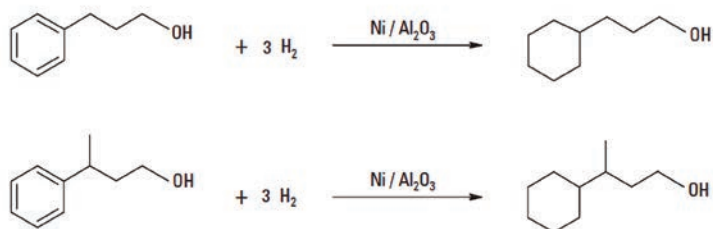
F-1. The two-step production of 3-phenylpropane-1-ol



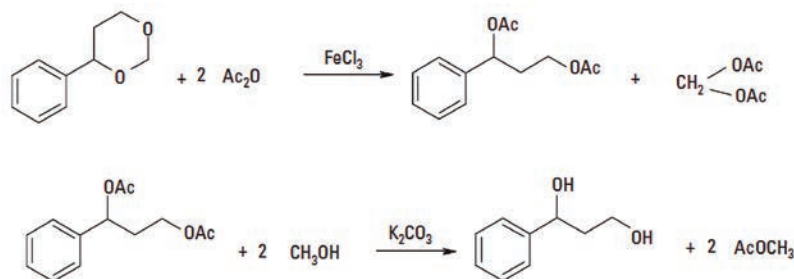
F-2. The synthesis of 4-phenyl-4-methyl-1,3-dioxane, which was used for the production of 3-phenylbutane-1-ol by hydrogenolytic decomposition



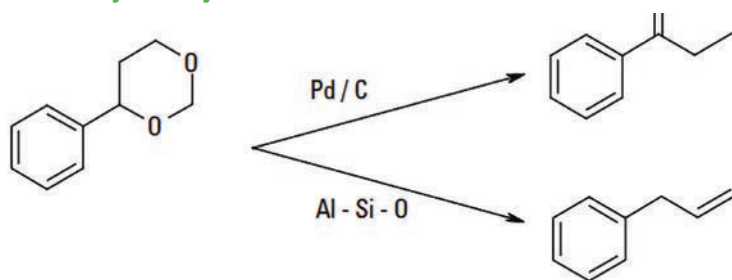
F-3. 3-Cyclohexylpropane-1-ol and 3-cyclohexylbutane-1-ol were produced using hydrogenation of aromatic nuclei in both of the alcohols



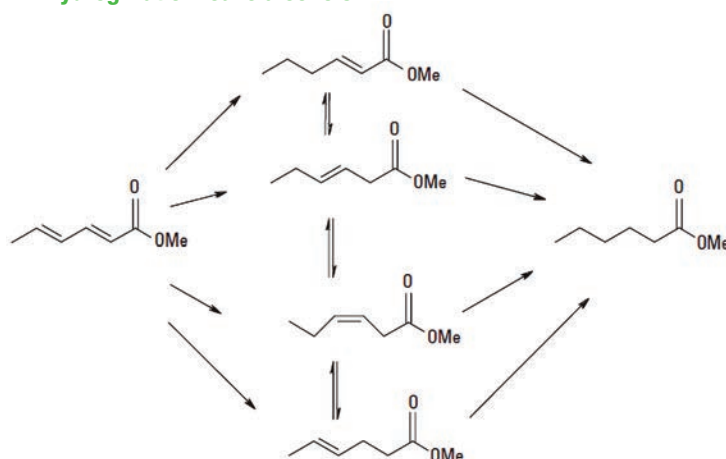
F-4. 4-Phenyl-1,3-dioxane's acidolysis to 1-2-phenylpropane-1,3-diol-diacetate with the consequent re-esterification to 1-phenylpropane-1,3-diol (which is a very efficient repellent) has been verified in a pilot system



F-5. Decomposition of 4-phenyl-1,3-dioxane on palladium catalyst to 1-phenylpropane-1-ol (propiophenone) and aluminosilicate catalyst to allylbenzene



F-6. The simplified reaction schema of the sorbic acid methylester hydrogenation leave alcohols



hydrogenolysis to 3-phenylbutane-1-ol, all attempts for analogous transformations were not successful.¹⁷

Following the above works, research on new substances based on 4-alkylstyrenes was initiated.¹⁸⁻²⁰ These materials were acquired using acylation of alkylbenzenes by acetic anhydride, followed by hydrogenation to relevant secondary alcohols and, finally, dehydration. Then, 4-alkylstyrenes were subjected to the Prins' reaction with formaldehyde; the resultant substituted 1,3-dioxanes were decomposed in the sense of transformations with 4-phenyl-1,3-dioxane. A number of new fragrance substances were acquired.^{18,19} New fragrance substances were also prepared from the above secondary alcohols.²⁰

Production technology of 1-phenylethanol by acetophenone hydrogenation²¹ was elaborated by DOT and materialized in the Zidovice plant; selective hydrogenation of 2-ethylhex-2-enal to 2-ethylhexanal has gone through a shorter production period. To the

contrary, selective hydrogenations of citral to citronellol and a mixture of citronellal, citronellol, geraniol and nerol have been solved on a laboratory scale but not yet materialized, especially for the reasons of price shifts on world markets. The resolved²² selective hydrogenations of dehydrolinalool and dehydrolinalylacetate to linalool and linalylacetate have so far experienced the same fate. Cyclization of citronellal to isopulegol and its subsequent hydrogenation to menthol is among the procedures verified in a large-scale plant.

Another scientific problem that has been solved is the chemoselective hydrogenation of C=C bonds located next to C=O bonds. It is the main benzylidene double bond in the products of condensation of benzaldehyde with acetone and the double bond in the products of condensation of cyclopentanone with aliphatic aldehydes. Common perfumery and flavor substances generally result from this, including Jasmamol, Frambinone, Zingerone and alkylcyclopentanones, which are used as intermediates for production of fragrant lactones.

The research was also focused on the opposite problem, i.e. the chemoselective hydrogenation of the carbonylic function next to the double bond C=C. This hydrogenation is more complicated because it requires specific catalytic systems;

in addition, the chemoselectivities are typically higher than in the previous case. Hydrogenation of cinnamic aldehyde to cinnamic alcohol was studied, and to a greater extent, the research on hydrogenation of methylester of sorbic acid (trans,trans-hexa-2,4-dienic) was initiated.²³⁻²⁵ This hydrogenation is very interesting in regards to the production of methylesters of cis-hex-3-enic and trans-hex-2-enic acids. These can be chemically reduced (LiAlH_4) to the relevant alcohols. These alcohols, the so-called leave alcohols, are very precious and difficult-to-synthesize substances. On the other hand, the reaction schema is rather complicated (kindly see its simplified form in **F-6**); the treatment of the reaction mixtures requires a very efficient rectification.

Alternatively, although it shows rather worse results, hydrogenation of trans,trans-hexa-2,4-diene-1-ol to relevant hexenols has been studied.²⁶ The

starting dienol is again prepared by chemical reduction of methylester of sorbic acid using LiAlH_4 . The quantity of side products in this case is higher than during hydrogenation of methylester of sorbic acid, since isomerization of unsaturated alcohols to aldehydes occurs in addition to alcohol hydrogenolysis, or its dehydration followed by hydrogenation of the double bond.

Increased attention was in the past paid to modern ways of introducing aldehyde group to aromatic nucleus, especially in regards to the production of ethyl-vanillin, but also to heliotropine and 4-hydroxybenzaldehyde.^{27,28} In the 1980s, an original procedure for the production of 2-ethoxyphenol, the intermediate of ethyl-vanillin, was worked out by DOT.²⁹⁻³⁴ The first two steps have already been verified using pilot system testing (F-7).

In the laboratory scale, utilization of 2-ethoxyphenol for synthesis of fragrant allylether was studied (F-8).

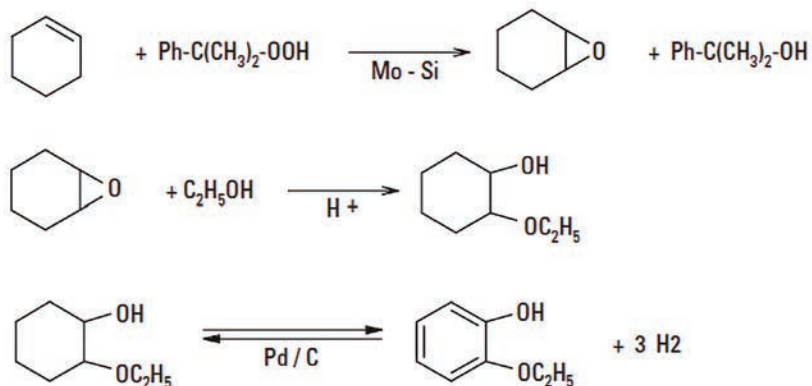
In the period of systematic research on opportunities for utilization of domestic resources and waste products for perfumery substance production, three technological procedures have been elaborated by DOT:

A: methyl-benzoate, the waste product from the production of dimethyl-terephthalate, was reesterified by some alcohols to higher esters

B: 4-methylpent-3-en-2-one (mesityloxide), the waste product from the production of vitamin C, was treated by alkaline condensation to the mixture of isoxylithones, i.e. substances with fragrant properties (F-9)

C: 2-phenylpropene, the waste product from the production of cumenic phenol, treated with formaldehyde in an environment of acetic anhydride and acetic

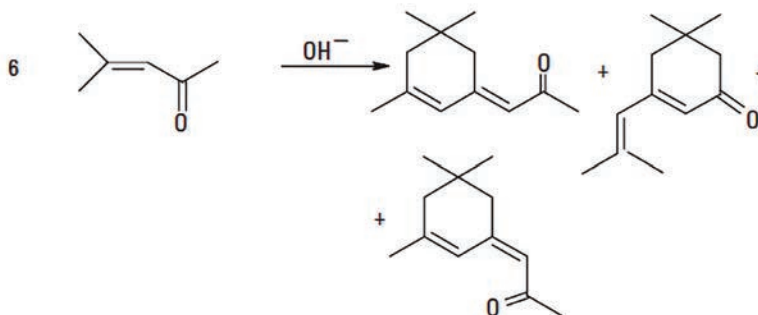
F-7. The three-step original procedure for the production of 2-ethoxyphenol, the intermediate of ethyl-vanillin



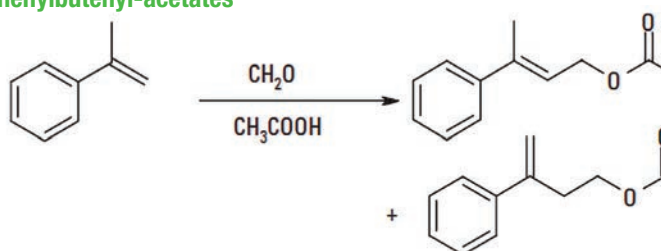
F-8. In the laboratory scale, utilization of 2-ethoxyphenol for synthesis of fragrant allylether was studied



F-9. 4-Methylpent-3-en-2-one (mesityloxide), the waste product from the production of vitamin C, was treated by alkaline condensation to the mixture of isoxylithones, i.e. substances with fragrant properties



F-10. 2-Phenylpropene, the waste product from the production of cumenic phenol, treated with formaldehyde in an environment of acetic anhydride and acetic acid, was transformed to a mixture of fragrant phenylbutenyl-acetates³⁵



acid, was transformed to a mixture³⁵ of fragrant phenylbutylacetates (**F-10**)³⁵

At present, Aroma Co.'s key materials are Arol and Arocet, which are mixtures of the stereoisomers of 2-*tert*-butylcyclohexanol and its acetate, respectively (**F-11**). These

are produced using catalytic hydrogenation of 2-*tert*-butylphenol, which was elaborated at DOT. From the commercial point of view, the ratio of *cis/trans* isomers has a fundamental significance, which, although

it can be influenced by rectification, is more economically enacted by conducting the hydrogenation so that the required representation is achieved directly. The reason for this is the difference in fragrance characteristics of the two isomers, which illustrates that demands are derived from product contents. The discovery of a possibility for modest adjustment of the above-mentioned ratio is an important key to this technology. The resultant product is a fundamentally important export item for Aroma Co.; the production has continually increased. At present, several hundred tons is produced annually.

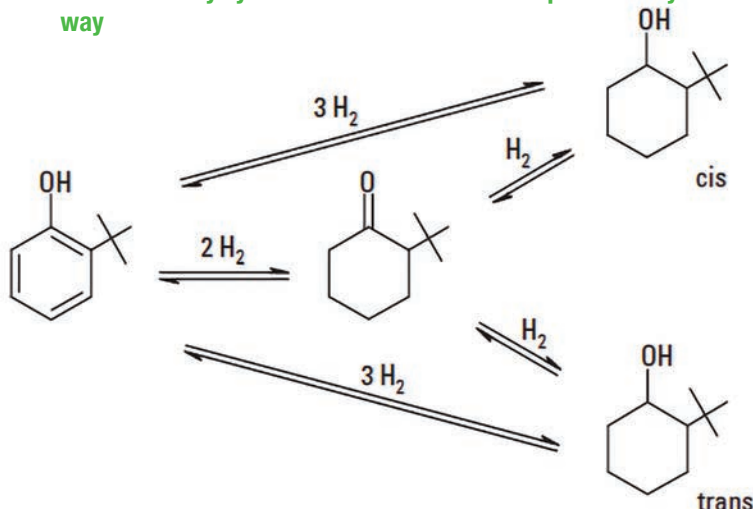
Although it is apparent that the dominant product will continue to be the mixture of stereoisomers of 2-*tert*-butylcyclohexyl-acetate, other possibilities of utilization of 2-*tert*-butylcyclohexanol are being sought. For instance, its derived carbonates have compelling possibilities.

The hydrogenation of 2-*tert*-butylphenol can be carried out so that 2-*tert*-butylcyclohexanone (**F-12**), which can be separated using rectification, is produced as well. Alternatively, this ketone can naturally be the main hydrogenation product. Its utilization in regards to preparation³⁶ of cyclic ketals is also interesting.

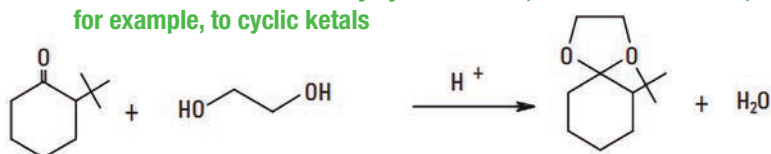
Several other alkylated phenols produced by Schenectady Co. were recently hydrogenated to alcohols or ketones (**F-13**).

Another scientifically resolved technology of production of allyl-3-cyclohexylpropanoate is prepared for testing in a large-scale plant. The pineapple scent of this substance makes it attractive. Its relatively simple production procedure elaborated in DOT was not found in the chemical literature. The starting compound is methylester of cinnamic acid; its C=C bond and aromatic ring are hydrogenated in

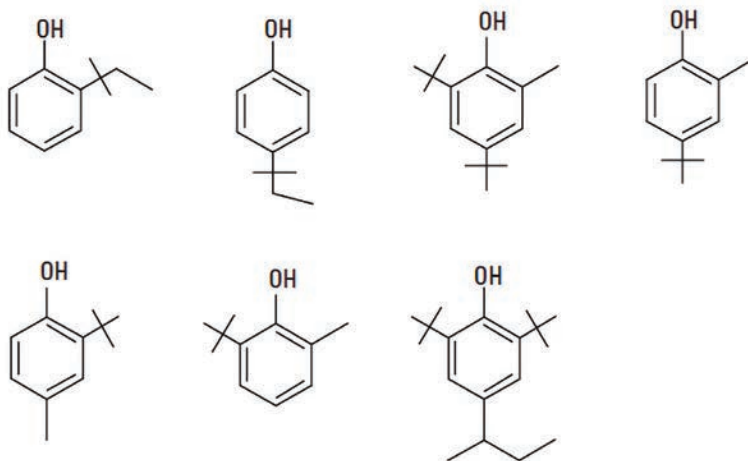
F-11. Reaction scheme of 2-*tert*-butylphenol hydrogenation; the main product is a mixture of *cis* and *trans* 2-*tert*-butylcyclohexanols, but 2-*tert*-butylcyclohexanone also should be produced by this way



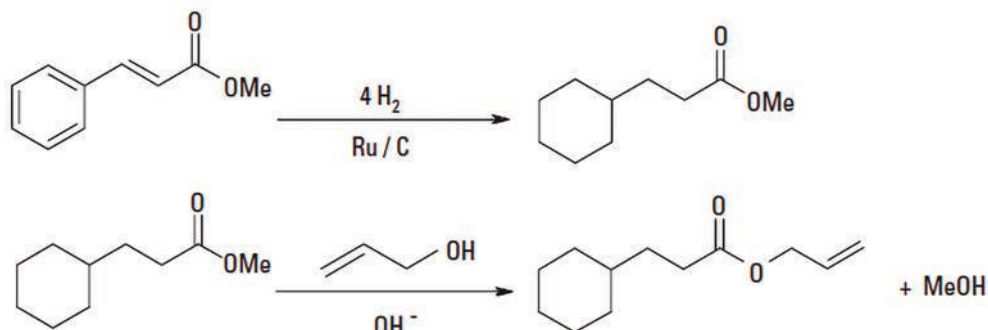
F-12. 2-*tert*-Butylcyclohexanone, separated using rectification from the mixture with 2-*tert*-butylcyclohexanols, can be transformed, for example, to cyclic ketals



F-13. Several alkylated phenols produced by Schenectady Co. were recently hydrogenated to alcohols or ketones



F-14. The production of allyl-3-cyclohexylpropanoate: the starting compound is methylester of cinnamic acid; its C=C bond and aromatic ring are hydrogenated in the first step; in the next, allyl-3-cyclohexylpropanoate is produced using re-esterification by allyl alcohol



the first step. In the next, allyl-3-cyclohexylpropanoate is produced using re-esterification by allyl alcohol (F-14).

The cooperation of COT with Aroma Co. and Aroco Co. is an example of mutual, long-term and systematic advantageous cooperation of an academic workplace with industrial companies. Three years ago, cooperation with Miltitz Aromatics GmbH began. A number of laboratory results have found use in industrial practice, especially due to targeted research. In addition, there has always been room for scholastic activities. Students of DOT have been broadly involved in the research; many of them not only remained loyal to the major they graduated from but also found use directly in the science, R&D or production of synthetic perfume and flavoring substances.

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To Synthesize or Not to Synthesize... that is the question

In the world of F&F formulation, synthetics are recognized for what they are: essential tools for creation; yet, how can we promote them to consumers without the stigma?





■ BY STEVE PRINGLE,

Vol. 42 • March 2017



The Food Babe, The Environmental Working Group, The Center for Public Integrity, Natural News, The Campaign for Safe Cosmetics and even Scientific American would all have us believe there is no substitute for natural. If we were to believe the websites, blogs and other communications from individuals or bodies such as these, we could believe anything that hasn't been immediately derived from a cultivated source is going to kill us – and anything that has been labeled artificial is toxic and will cause us serious harm.

This misinformation makes an impact on consumer perception. Over recent years, several large consumer product manufacturers—particularly in the food and beverage arenas—have made moves to eliminate anything artificial from a wide number of consumer products. At the same time, there is significant pressure on the natural sources of key ingredients in the flavor and fragrance supply chain.

A Natural Challenge

Not everything is simple in the world of naturals. For example, Huanglongbing (HLB; citrus greening), thought to be caused by the bacterium *Candidatus Liberibacter asiaticus*, has seriously affected citrus production in a number of countries in Asia, Africa, Brazil, USA, the Indian subcontinent and the Arabian Peninsula. Wherever the disease has appeared, citrus production has been compromised

with the loss of millions of trees. In August 2005, the disease was found in the south Florida region of Homestead and Florida City. Since that time, HLB was found in commercial and residential sites in all counties with commercial citrus.

In addition to citrus, there were recent challenges with vanilla, lavender, sandalwood and other materials derived from plants, flowers and other cultivated sources, which affected availability and cost. While some organizations in the F&F world have formed sustainable partnerships with growers and farmers in an attempt to combat supply volatility, this does not address the situation on a macro level – and the challenges around natural materials continue.

Moreover the safety of the oils, extracts and absolutes created from cultivated products has

been questioned. At the recent International Federation of Essential Oils and Aroma Trades (IFEAT) 2016 Conference in Dubai, Sean V. Taylor, scientific secretary to the Flavor Extracts and Manufacturers Association (FEMA) expert panel and the International Organization of the Flavor Industry (IOFI) scientific director, presented on the FEMA Generally Recognized as Safe (GRAS) evaluation and re-evaluation of flavoring complex mixtures. He indicated, “despite their incredible importance as food flavorings, there has not yet been significant scientifically based safety evaluations of essential oils.” He also continued to outline a rigorous and comprehensive evaluation and re-evaluation program to cover more than 250 natural complex substances (NCS).

Panel 1

21.CFR Chapter 1. Part 101.22(a).3

The term natural flavor or natural flavoring means the essential oil, oleoresin, essence or extractive, protein hydrolysate, distillate, or any product of roasting, heating, or enzymolysis, which contains the flavoring constituents derived from a spice, fruit or fruit juice, vegetable or vegetable juice, edible yeast, herb, bark, bud, root, leaf or similar plant material, meat, seafood, poultry, eggs, dairy products, or fermentation products thereof, whose significant function in food is flavoring rather than nutritional. Natural flavors include the natural essence or extractives obtained from plants listed in Secs. 182.10, 182.20, 182.40, 182.50 and part 184 of this chapter and the substances listed in Sec. 172.510 of this Chapter

21.CFR. Chapter 1. Part 101.22(a).1

The term artificial flavor or artificial flavoring means any substance, the function of which is to impart flavor, which is not derived from a spice, fruit or fruit juice, vegetable or vegetable juice, edible yeast, herb, bark, bud, root, leaf or similar plant material, meat, seafood, poultry, eggs, dairy products, or fermentation products thereof. Artificial flavor includes the substances listed in Secs. 172.515(b) and 182.60 of this chapter except where these are derived from natural sources.

Wading through this legalese, the conclusion is that if a material originated from a natural starting point, and as long as you use only materials which are derived from a natural starting point, you have a natural ingredient.

This leads to the plethora of natural aroma chemicals which appear in the US. It also theoretically could lead to the creation of “natural” aroma chemicals which haven’t been identified in nature, which is itself an interesting thought.

Can We Live Only in a Natural World?

Let’s start by seeing if we can actually define what natural is. This is something I’ve tried to cover previously in other articles – and while it should be relatively simple in reality, it isn’t because consumer perception of natural compared to the legislative definitions are widely different.

If we take the world of flavors for example, different regions of the world abide by different definitions of what would constitute a natural product. Take the U.S. definition outlined in 21 CFR. Chapter 1, Parts 101.22(a) .1 and .3 (see **Panel 1**) then this allows us to define anything which started its journey from a natural source can be labeled as natural in the consumer product.

The Europeans complicate matters further as the EEC Council Directive on Flavorings and source materials for their production (88/388/EEC) shows (see **Panel 2**). This legislation gives greater restrictions to what can be defined as natural, by restricting the processes which can be involved in creating a natural product.

What Makes an NCS?

Turning our attention to the world of fragrances, the International Fragrance Association (IFRA) only allows fragrances marked as “natural” if they contain fragrance ingredients corresponding to the terms and definitions laid down in the International Organization for Standardization’s (ISO) 9235:1997 (Aromatic natural raw materials – Vocabulary) or if substances are already present in them and isolated from them by purely physical means. For example, a substance such as menthol—which is naturally present in peppermint oil—can be called natural if it is isolated from the peppermint oil by physical methods only.

In general, ISO 9235 defines natural aromatic raw materials as being physically obtained from plants using distillation, expression and extraction.

Panel 2

Natural flavoring substance (Article 1.2(b)(i)) :

Means a defined chemical substance with flavoring properties, which is obtained by appropriate physical processes (including distillation and solvent extraction) or enzymatic or microbiological processes from material of vegetable or animal origin either in the raw state or after processing for human consumption by traditional food preparation processes (including drying, torrefaction and fermentation).

Flavoring preparation (Article 1.2(c))

Means a product, other than a defined chemical substance, whether concentrated or not, with flavoring properties, which is obtained by appropriate physical processes (including distillation and solvent extraction) or enzymatic or microbiological processes from material of vegetable or animal origin either in the raw state or after processing for human consumption by traditional food preparation processes (including drying, torrefaction and fermentation).

Natural flavorings labelling (Article 9.2)

The word 'natural' or any other word having substantially the same meaning may be used only for flavorings in which the flavoring component contains exclusively flavoring preparations and/or natural flavoring substances. If the sales description of the flavoring contains a reference to a foodstuff or flavoring source, the word 'natural' or any other word having substantially the same meaning, may not be used unless the flavoring component has been isolated by appropriate physical, enzymatic or microbiological processes or traditional food preparation processes solely or almost solely from the foodstuff or flavoring source concerned.

Natural flavoring substance (Chapter I Article 3.2 (c))

[This] shall mean a flavoring substance obtained by appropriate physical, enzymatic or microbiological processes

from material of vegetable, animal or microbiological origin either in the raw state or after processing for human consumption by one or more of the traditional food preparation processes listed in Annex II. Natural flavoring substances correspond to substances naturally present and identified in nature.

Flavoring preparation (Chapter I Article 3.2 (d))

[This] shall mean a product other than a flavoring substance obtained from:

(i) food, by appropriate physical, enzymatic or microbiological processes, either in the raw state of the material or after processing for human consumption by one or more of the traditional food preparation processes listed in Annex II.

and/or

(ii) Material of vegetable, animal or microbiological origin, other than food, by appropriate physical, enzymatic or microbiological processes, the material being taken as such or prepared by one or more of the traditional food preparation processes listed in Annex II.

Specific requirements for the use of the term "natural" (Chapter IV Labelling Article 16)

The term "natural" for the description of a flavoring may only be used if the flavoring component comprises only flavoring preparations and/or natural flavoring substances.

The term "natural" may only be used in combination with a reference to a food, food category or a vegetable or animal flavoring source if the flavoring component was obtained exclusively or by at least 95% by w/w from the source material referred to. The maximum of 5% (w/w) of the flavoring component derived from other source materials shall not reproduce the flavor of the source material referred to.

Natural fragrances are complex compositions of natural aromatic raw materials such as essential oils, fractions of essential oils, isolates, exudates such as resins, distillates, extracts and volatile concentrates. Synthetically reconstituted essential oils, synthetic nature-identical ingredients and intentionally chemically modified natural raw materials (e.g. chemical acetylation of essential oil) cannot be used in fragrance compounds described as natural. The Natural Products Association goes one step further to forbid the use of petrochemical solvents in the extraction process—so concretes and absolutes made using hexane are not permitted.

While I am certainly not a lawyer, it's my impression these guidelines are in place to protect the public from materials, which could cause them harm. However, do these guidelines make the assumption that everything immediately derived from a cultivated source is safe and therefore exempt from testing and regulation? There is also the added belief from the majority of consumers that, "natural = healthy or safe" and consequently, everything naturally derived must be better for you.

This kind of consumer pressure has led to companies such as General Mills and Nestle to commit to removing artificial flavors from its products. The one

clear thing that is when the majority of consumers refer to natural, they are thinking of an ingredient, which was immediately derived from the cultivated source, i.e. an NCS. This brings me back to the point: Do we really know and control with repeatable accuracy exactly what makes up an NCS?

From the perspective of the humble chemist, determining the safety of an NCS compared to an individual molecule seems to be a far more complicated and rigorous task. In addition, policing the chemicals, which are present in an NCS to ensure the dosage of chemicals in a consumer product are safe, is even more complicated. This would potentially require significant analysis and cost to ensure that should the required limits of each individual component be adhered to.

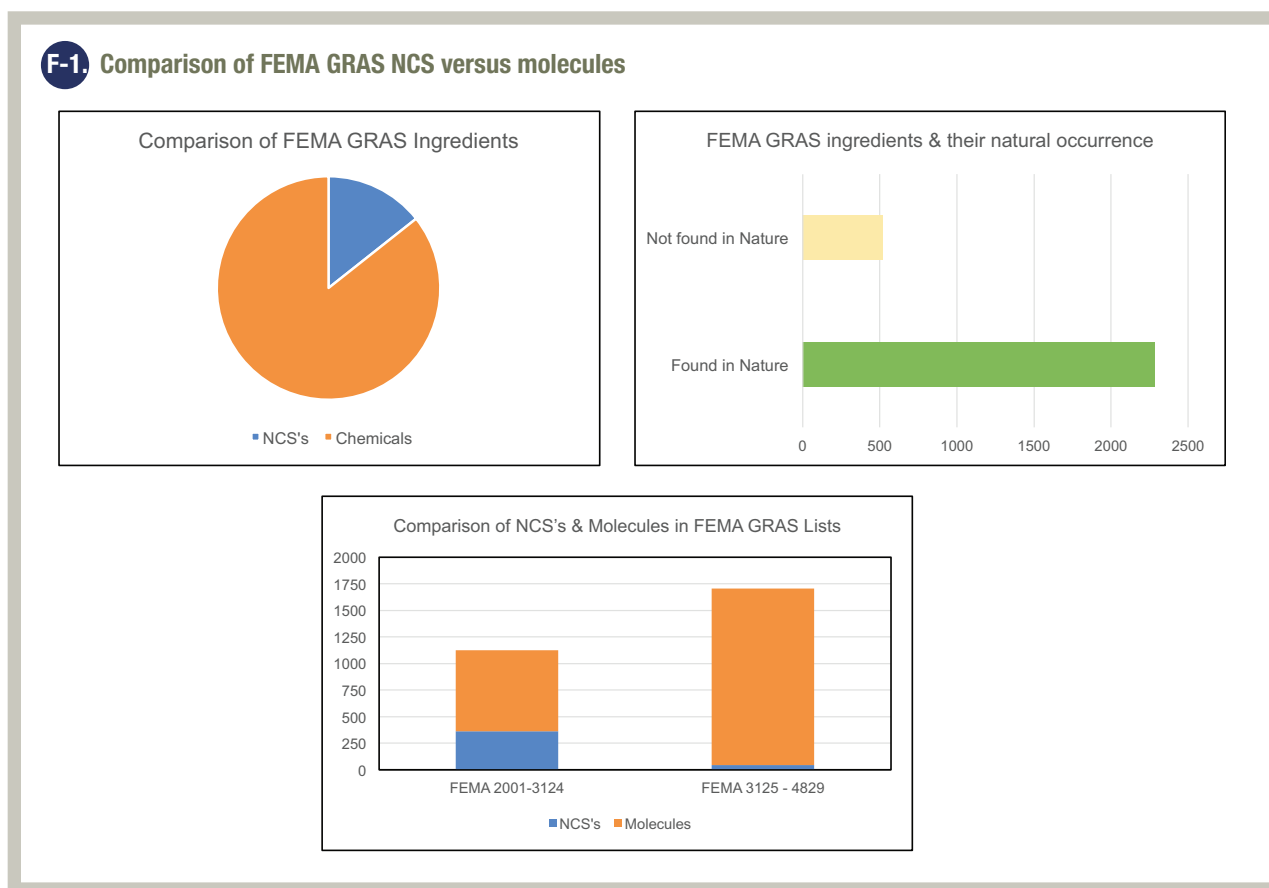
A World without Synthetics?

Looking at the FEMA GRAS list of ingredients, whether artificial or natural, gives us some surprising insights. Of the 2,809 GRAS ingredients, only 403 could be described as NCS (see **F-1**), while the remaining 2,406 are clearly defined molecules. Interestingly, of these 2,406 molecules, 522 are not actually found in nature, but could in theory be synthesized from a naturally occurring starting molecule using naturally occurring reagents to give

us a “natural” aroma chemical. Regardless of this, it is interesting for the flavorist adhering to the FEMA GRAS list, around 85% of the ingredients that could be used are distinct molecules, which need to be synthesized in some way.

Seeing the evolution of materials submitted to FEMA over time is also interesting. Looking at a complete FEMA GRAS list from 2001 up to 4838 (the highest number on the interim GRAS 28 list), it is clear from the alphabetical nature of the list that the first FEMA GRAS lists were populated by materials, which were currently in use: FEMA# 2001 being acacia gum and FEMA# 3124 being zingerone. Of these initial materials, 360 of the total 403 NCS are included in these early FEMA GRAS lists. In the subsequent 1704 additions, only 43 materials that could be considered NCS were added. Is this because the world has run out of natural materials to extract or distill? Highly unlikely, I would suggest.

A combination of other factors are the more likely contributors to this observation. Firstly, flavorists and perfumers have recognized while natural oils and extracts have complex and interesting notes, which add greatly to the products they create, the reproducibility of these materials can leave a lot to be desired. Year on year variations, regional variation and even local variation from farmer to farmer all have an



effect on the constituents of an oil or extract. Add the changes which occur to this as we move from botanical species to botanical species and we introduce a huge number of variables, all of which could have an effect on the odor and taste profile of the material being used.

Analytical techniques have also become much improved. The ability to analyze an oil, extract, distillate or even fruit, vegetables, meat and fish and subsequently, detect and identify the chemical constituents down to the ppb level has increased dramatically over the last few decades. This means some of the key odor constituents are the materials they were using—which were a mystery to flavorists and perfumers previously—which could be synthesized and utilized in formulations. This, along with other factors such as greater access and focus on molecular synthesis has led to an increase on the FEMA GRAS list. One example is materials with lower odor thresholds, which previously could not be characterized, but certainly could be identified by the trained nose.

Take a look at the more recently published GRAS lists and you will see them more highly populated with molecules containing sulfur, nitrogen and oxygen. Additionally, while the early GRAS lists contained a large number of esters and similarly, simple molecules to synthesize, the more recent GRAS lists saw a greater diversity in chemical structure. A greater focus on synthesis, rather than isolation, enabled greater access to not only research and development on a lab scale, but also greater access to more complex engineering solutions to producing these molecules on a large scale. These, and other molecules, which occur naturally at lower levels, are now recognized as being the key components in the creation of truly outstanding formulations.

Molecules are Important

The ability of synthetic chemistry to come up with either cost effective routes to molecules identified in nature or to novel molecules with interesting odor profiles has increased significantly in the last 20-30 years. This is one of the major factors behind the rapid increase in the number of molecules, which have found their way on to the flavorist or perfumer's palette. In just about all areas of flavor and fragrance creation the identification and production of synthetic molecules has

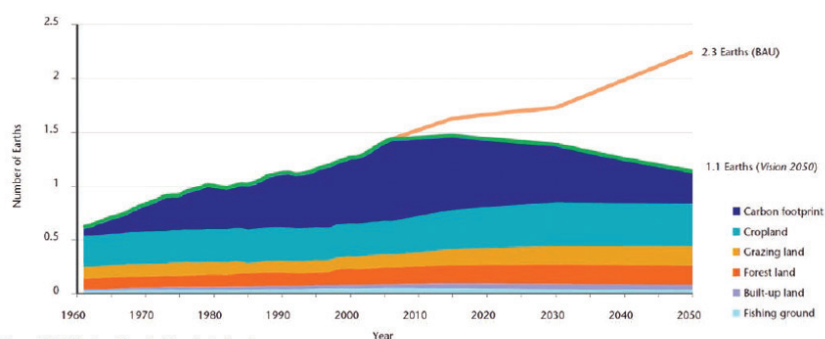
been a critical factor in the creation of more elaborate and pleasurable products.

While the consumer may be prejudiced against synthetics, the perfumer and flavorist certainly are not. Even in the world of fine fragrance, synthetics are recognized for what they are, namely the essential tools for creation. For example, the secret of Dior's Eau Sauvage is methyl dihydrojasmonate. Without hydroxycitronellal, the cult perfume *Quelque Fleurs* would be missing its heart and the more recent Calvin Klein fragrance, *CK One* would have a huge hole in it without dihydromyrcenol (see **F-2**). Synthetics are obviously not exclusively used in fine fragrance (see **F-3**). All three of the materials just mentioned, while being the key ingredients to some of the most successful fine fragrances are also the staples used in detergents, body wash and shampoo. This also does not mean synthetics are cheap either. Some materials cost over \$500-1000 per kilo.

Even though there was an increase in the range of synthetic molecules in more recent decades, this does not mean the use of synthetics is a recent phenomenon. The French perfume house, Guerlain could claim to have begun the synthetics revolution in 1889 in its fragrance, *Jicky*. The classic, *L'Heure Bleue* (1912) contains methyl anthranilate (yes, of the Concord grape flavor), *Mitsouko* (1919) uses the so called aldehyde C14 and the immortal *Shalimar* (1925) has a variety of synthetics, such as ethyl vanillin and a number of different quinolines.

The ability of chemistry to design and create synthetics it seems is essential to both the perfumer and the flavorist. So why do consumers have bad opinions of them?

F-2. Popular synthetics in fragrance formulations



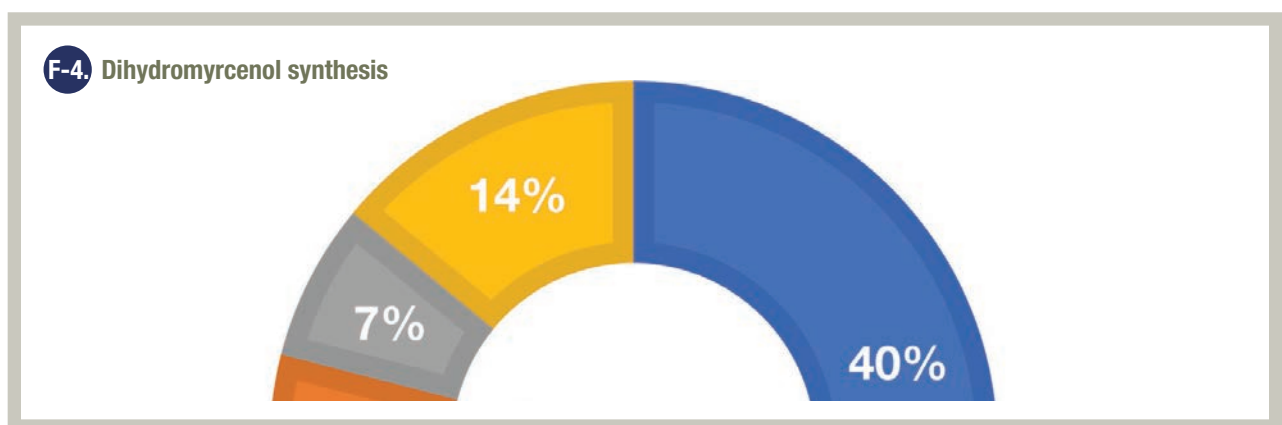
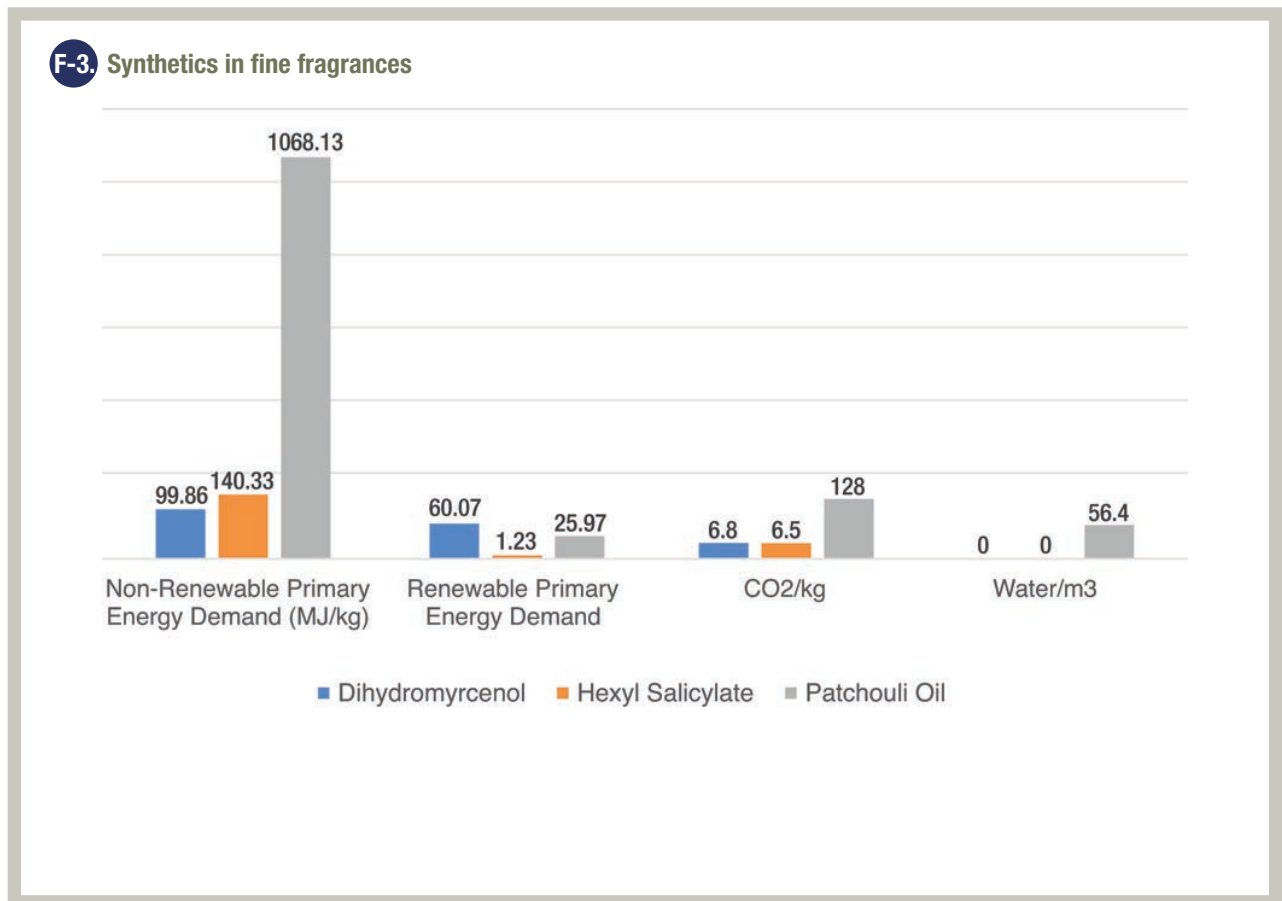
*Source: World Business Council of Sustainable Development.

Natural Carbon Source

Recently, there was a rise in articles and blogs, which refer to the starting point of the ingredients in our food. The disdain to which anything derived from petrochemicals is held and the leverage, which can be used in the mind of the consumer, is a clear link to the lack of understanding on just what a chemical is. Clearly petrochemicals link strongly to more industrial processes and application and for the average consumer, the thought of having a petrochemical in their food or their fragrance is a highly unappealing idea. From the point of view of

the chemist, however, the source of the material does not matter. For the flavorist or perfumer, if they have an interesting and cost effective molecule, which allows for the creation of something wonderful, then why should they care?

We should not however ignore the will of the consumer, regardless of how poorly or narrowly informed they are. This brings me to something, which in my view, is going to play an increasingly important role in the next few years in the fragrance and flavor world and that is ... just where do you get your carbons from?



The industry started to look at sustainability with increasing frequency in recent years. There are obvious reasons from both environmental and business continuity standpoints to do this. Business sustainability and environmental sustainability are heavily linked in the fragrance and flavor worlds – if even from the simple perspective there are a large number of critical ingredients, which are cultivated. If we acknowledge there is a limited amount of petrochemically derived feedstock available to us then at some point in the future we will have to face a different challenge. We should recognize formulating a flavor or fragrance using only NCS's is difficult and limiting and therefore the use of synthetics in flavor and fragrance creation is essential.

For example, dihydromyrcenol is one of those molecules the fragrance industry would find difficult to live without. Not only is it a staple detergent and, as previously mentioned, a key component of CK One, but it also appears in other fine fragrances such as Drakkar Noir (at 10%), Polo and Cool Water to name a few. The material does not appear in nature, but it could be said to be one of the most, “natural synthetics” available in the market currently. Natural synthetic seems to be something of an oxymoron, however what we need to consider is where our carbons have come from.

Let's take a look at the synthesis of dihydromyrcenol (see **F-4**). Produced by the pyrolysis of pinane to dihydromyrcene and subsequent hydration to dihydromyrcenol, the starting point for this is typically alpha pinene, which originally is sourced either directly or indirectly from pine trees. By sourcing the initial raw material from a natural, sustainable source we do two things: First, we start with “natural” carbons and second, we begin with a renewable source. Finally, through clever chemical synthesis, we create a molecule, which has a reproducible, interesting, useful and desirable odor profile.

There are other molecules, which can take their starting points from cultivated sources. Some are from the bottom end of the cost spectrum such as citronellol and geraniol and some from the top end. What most of these materials have in common is, in general, they belong to the same or similar groups of molecules. Terpenes are prevalent in the materials, which could claim, depending on their synthesis, “natural” carbons as their starting point. This particular family is an easy starting point due to the ease of availability of its precursors. It is not always easy to find accessible sources of raw materials from which to start, especially as there are a significant amount of crops, which do not already have demand.

There are two potential solutions to this. One is waste valorization, which is fast becoming an increasingly important area of R&D for academics and beyond. Chemists, such as Avtar Matharu, Ph.D. and Thomas Farmer, Ph.D. from the University of York's Green Chemistry department, are able to tap into a regional network of industries in their search for potential areas where the discarded materials from larger scale areas of the food and agricultural chains could be utilized. They then use their chemical expertise to isolate and synthesize materials of value, which could be useful to other areas of the chemical industry.

The second has received a lot of attention in the F&F world already. Biotechnology has for some time been seen as a potentially cost effective source of creating either existing molecules for the fragrance and flavor market, as well as a potentially novel way of coming up with intermediate molecules for further derivatization. Biotech also offers the potential to utilize natural carbons as its feedstock and has the advantages of comparatively low cost feedstocks such as sugar. The F&F world clearly sees biotech as being an important part of the production and creation of future synthetics. Firmenich, Givaudan, Mane, Robertet and Symrise have all invested in this area in recent years, and while the technology still has more areas to explore it is not the exclusive domain of the larger companies as the recent announcement of the REG Life Sciences and ACS International collaboration shows.

The fragrance and flavor world knows it cannot exist without synthetics, but perhaps it is time to shift our definitions of what is natural and what is not in order to help the conscience of the consumer. Instead of thinking about the nature of the material we are using, perhaps it is time to start thinking about the nature of the feedstock we are using and put the method of production to one side.



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THE SEARCH FOR NEW AROMA CHEMICALS

Although up to 10,000 natural and synthetic aroma chemicals exist, the search for new or improved products is ongoing in the flavor and fragrance industry (F-1). The search for new substances starts with the analysis of the possible benefits, the existing knowledge and the routes that can be followed. The hunt for new flavor and fragrance substances can, for example, be initiated by the following guidelines:

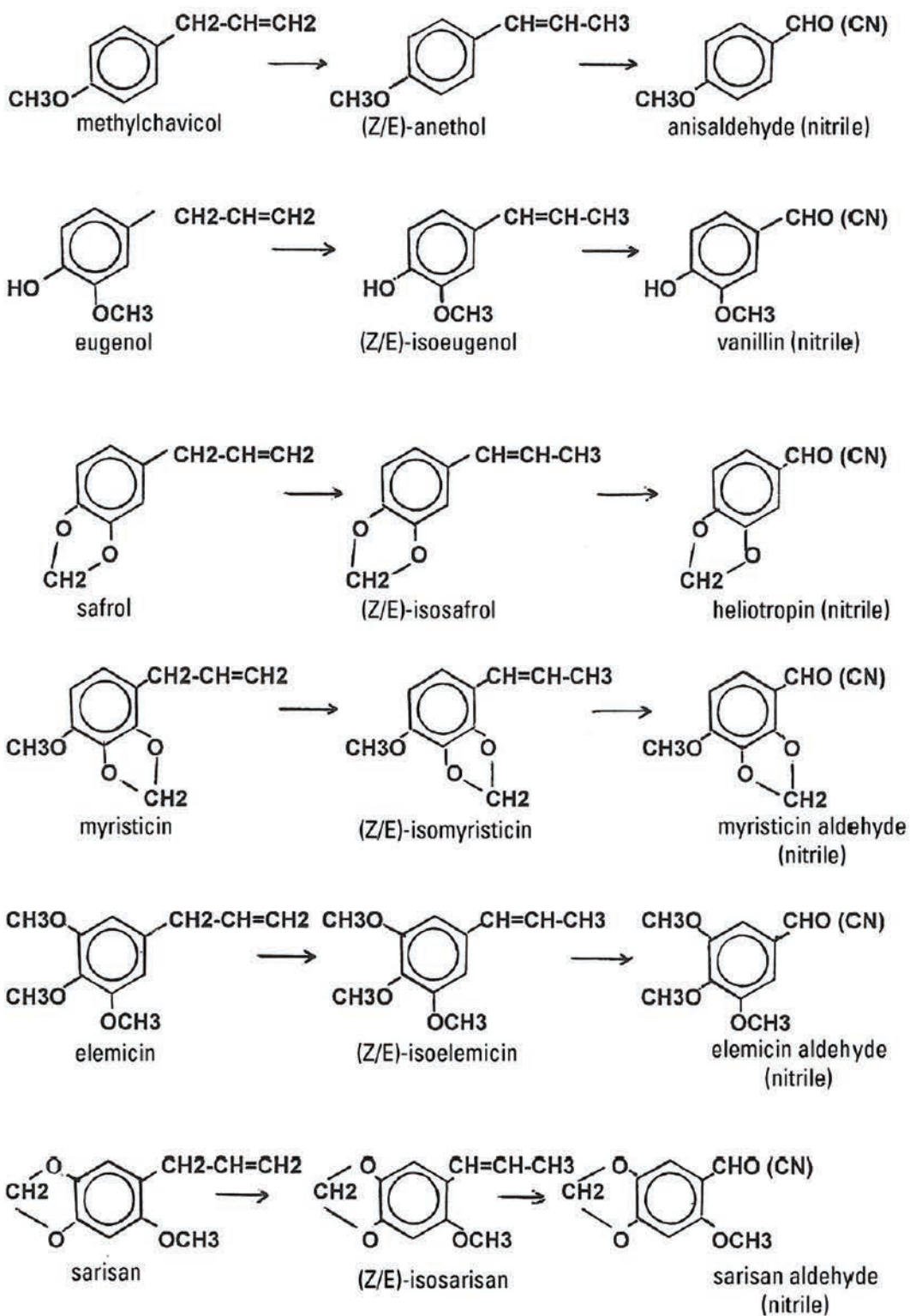
- Isolation of new natural products (mixtures or character-impact compounds).
- Searching for open spots in groups of existing natural compounds.
- Studying biogenesis (biochemical formation) of new volatile compounds.
- Investigation of reaction occurring during food processing (e.g. cooking, baking, frying).
- Predicting new groups of substances from structure-odor relationships.

Some recently published programs for the isolation of new products from nature will be discussed herein. In addition, a series of ideas for the development of new or improved flavor and fragrance substances will be presented. These ideas concern new mono- and sesquiterpenoids, substitution of sterical or electronical parts (functional groups) of molecules by more stable ones. New materials with greater organoleptic or olfactive value-for-money will be suggested.

General Introduction

One may question whether the search for new aroma chemicals is economic. In other words, are the costs for research in the flavor and fragrance industry a value for the money? Recent studies of the American Council for Chemical Research revealed that during the period of 1975 to 1998 every \$1 invested by 83 chemical industries produced a profit of \$2.6. The conclusion: research in the chemical industry does pay off. Recently some interesting publications appeared

F-1. Molecular structures of well-known and little known aromatic compounds



regarding the search for and the design of new flavor and fragrance materials.^{1c,2a,4a-b,6}

The initiation of a research program for new flavor and fragrance materials and improved preparation methods may have the following guiding thoughts:

- What is already known and what has been done in the past?
- How are the materials formed, what are the precursors and (bio)chemical routes to the end products?
- Are there reasonable reliable relationships between a designed molecular structure and expected olfactive and organoleptic qualities, and what is the target?

If one analyzes the search for new materials in the flavor and fragrance industry during the last half century, one may divide this work in different areas, as they are based on:

- **Natural Products:** new character-impact compounds, quantification of compounds emitting from new naturals, identification and quantification of existing compounds emitting from living natural products, and quantification in depth of natural isolates.
- **Chemical or Biogenesis Formation:** often used for the identification and preparation of new flavor materials: examples are the Strecker degradation of amino acids, the Maillard reaction of amino acids and sugars, followed by Amadori or Heinz rearrangements, the biochemical oxidation of unsaturated fatty acids and the biochemical formation of terpenoids and fatty acids.
- **Analogues of Existing Odorants:** the synthesis of analogues of ionones (ionones and methyl ionones), analogues of methyl jasmonates and damasc(en)ones, nitro-free benzenoid musk compounds.
- **Petrochemicals and Other Raw Materials:** fragrance materials derived from dicyclopentadiene and from substituted phenols.
- **Common Sense and Serendipity:** functionalization of monoterpenes and sesquiterpenes, C-10 derivatives.

Sometimes new aroma chemicals have been discovered by pure accident.^{1c,2a} It seems rather unscientific and uneconomic to carry out random organic synthetic research, to sit and wait until a valuable material comes out. However, even the unexpected discovery of a new aroma chemical as a certain reason for its preparation.

For the production of computerized databases we studied:^{5d}

- Forty-two hundred perfumery materials, e.g. aroma chemicals and natural isolates with their performance.
- Fifty-seven hundred fragrances with their qualitative composition.
- Fifty-five hundred flavor raw materials, e.g. natural, nature identical and artificial products.
- The quantitative analysis of 4,000 essential oils with 4,500 constituents.
- Over 7,000 volatile compounds in food products with their qualitative and quantitative occurrence.

Much know-how regarding the search of and the design for new materials was gathered from this study.

To develop a new aroma chemical, the investigation of structure-activity relationships is not just useful/helpful, but necessary. The reasons for studying odor-structure relationships can be, for instance, to produce an aroma chemical (flavor or fragrance material) with:

- Modified, new or unknown sensory properties, e.g. concerning odor quality and appreciation.
- More odor value-for-money, e.g. tenacity, persistence.
- Other improved physiological properties, e.g. better biodegradability, less toxicity.
- Better application properties, e.g. fiber, hair and skin substantivity.
- Improved physicochemical properties, e.g. chemical stability, desired volatility and solubility.

The purpose of the search for new flavor and fragrance materials or improved methods for their preparation has various facets:

- **Economics:** less raw material, lower variable, fixed and investment costs, for instance the synthesis of a macrocyclic musk compound.
- **Sensory Properties:** organoleptic and olfactive qualities, for instance character-impact compounds from natural isolates or (prepared) food products—preferred odor quality, higher intensity, longer tenacity.
- **Other Physiological Properties:** lower toxicity, less negative dermatological properties.
- **Application Properties:** better fiber, hair or skin substantivity.
- **Chemical:** good stability in functional perfume compounds, less vulnerable for (air) oxidation, hydrolysis, hydration.

- **Physical:** optimal volatility, evaporation, diffusion properties.

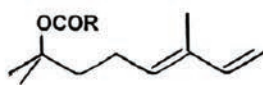
In the following sections we will discuss:

- Recently published programs for the isolation of new products from nature.
- Improved and new monoterpene alcohols, esters and aldehydes.
- New sesquiterpene derivatives.
- Substitution of isobutenyl by phenyl in monoterpenoids.
- Substitution of isopentyl by cyclohexyl in some aroma chemicals.
- Isobutyrate in place of acetate.
- Substitution of functional groups: aldehyde by nitrile, ester by ketone, *cis*-double bond by sulfur, chloro by methyl, allyl and geminal dimethyl by cyclopropyl.
- New natural sulfur compounds by addition of hydrogen sulfide and methylmercaptan to unsaturated natural flavor compounds.
- Volatile Schiff bases (**F-2**).

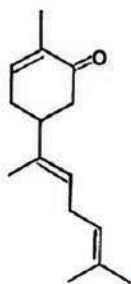
F-2. Proposal of molecular structures for new flavor and fragrance compounds



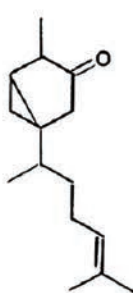
ocimenois and esters (fresh floral)



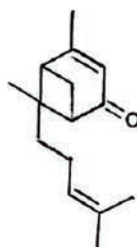
ocimenois (citrusy)



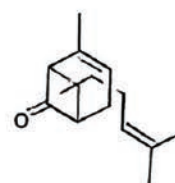
C-15 analogues of: carvone (woody)



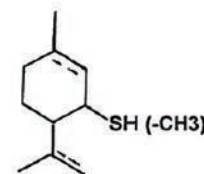
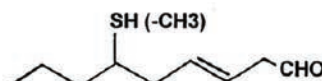
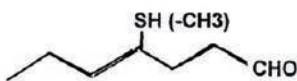
thujones



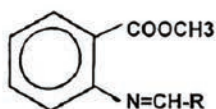
verbenone



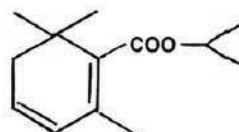
chrysanthenone



hydrogensulfide and methylmercaptan adducts to unsaturated compounds (fruity)



N-alkylidene methyl anthranilates (citrusy) (floral-rose)



cyclopropyl saffranate

Recent Research

In 1999, Givaudan carried out an innovative experimental program to discover new tastes, new molecules and new ingredients. A mission took their co-workers deep into the Gabonese rainforest to a place called Foret d'Abeille — one of the last unspoiled forests in Central Africa. In close cooperation with ProNatura, a non-profit rainforest preservation group, Givaudan accomplished a highly challenging expedition. Together with botanists and entomologists, the company's research teams from the United States and Switzerland explored the rainforest's incredible biodiversity, foraging on foot and hovering above the treetops on the world's largest hot air balloon.^{6a} Altogether, more than 250 samples were collected and evaluated. The following new fruit flavors were developed: Ginger Strawberry from *Aframomum giganteum*, Mangolino from *Dacryodes klaineana*, Gabonese Pineapple from *Diospyros mannii*, Rainforest Melon from a *Drypetes* species, Wild Garcinia from *Garcinia epunctata*, Bush Pearl from *Irvingia gabonensis*, jungle fruit from *Landolphia owariensis* and Paradise Fruit from *Pentadesma butyracca*.

In 1998 IFF sent, for the first time, a miniature rose into space to produce three alternatives to the hybrid rose plant under the influence of microgravity. A new rose fragrance was developed from the results of this experiment. IFF is now engaged in a second NASA project exploring new perfumery molecules.^{7b} This project will be continued in the coming years.

Recently, IFF (in the United States) has prepared ground for a new hydroponic greenhouse to complement an existing greenhouse facility. The hydroponics technique concerns the growing of plants in water with essential chemicals in solution, instead of in soil. The new facility will be used for the extraction of fruit and flower aromas from hydroponically grown plants. The addition will feature climate controls for each section, including underground heat. IFF states that there is a high interest in this method of growing plants to discover innovative natural products that will enhance the quality of life of consumers all over the world.^{6c}

Quest International, in conjunction with Oxford University and the Ecole Supérieur du Science Agronomique, has announced the results of open-air and underwater headspace sampling in Madagascar. The goal was to find new scent molecules, which could be created in vitro later on. Samples were taken from waterfalls, aquatic plants, forest mosses, tropical flowers, uncatalogued species of resinous plants and native woods and barks. New mono- and sesquiterpenoids were discovered in the process. Quest believes that new fragrance profiles will spur new fragrance trends.^{6b}

From these and earlier investigations, one may draw the preliminary conclusion that new character-impact compounds are seldom found. These studies often lead to new combinations and concentrations of already existing odoriferous materials as a consequence of new flavor and fragrance bases.



T-1. Odor tests with aliphatic compounds: how seven experienced test persons identified aliphatic methyl ketones and acetates based on their functional groups*

Compound		Number of Compounds	Number of Tests	Identified		Most Frequent Type of Mistake
				Correct	Incorrect	
methyl ketone	C-3 to C-63	3	21	76	24	spread
idem	C-7 to C-10	3	26	46	54	ester (50 percent)
idem	C-11 to C-15	3	21	0	100	alcohols (62 percent)
esters	C-3 to C-6	7	52	58	42	methyl ketones (25 percent)
idem	C-7 to C-10	8	51	80	20	spread
idem	C-11 to C-15	9	56	29	71	alcohols (29 percent)

*The methyl ketones C-7 to C-10 and the esters C-3 to C-10 were identified on their fruity odor character; the C-11 to C-15 compounds (methyl ketones, esters and alcohols) were often incorrectly identified because of their fatty odor characteristics.

Because much of this work is extremely expensive, one may question whether it is not more economic to investigate plant materials that are easily available and which possess unknown sensory properties (e.g. witch hazel, sweet pea, petunia, phlox).

Isolation Techniques and Chemistry

Nature and natural isolates have always stood as the models for the flavor and fragrance chemist. In former times these scientists used classical organic chemistry to synthesize new materials. This chemistry was in principle simple; the organic reactions were divided into ionogenic and radical. The ionogenic reactions could be either electrophile or nucleophile. As reaction types, one could, for instance, recognize additions, eliminations, substitutions and rearrangements. Ionogenic reactions often were carried out in polar solvents with a great deal of inorganic materials and wastewaters. Radical reactions were characterized by rather higher temperatures that allowed the formation of free radicals. Some catalytic processes were known as, for example, hydrogenations and oxidations. What has changed during the past decennium? For one thing, more and more knowledge about biochemical processes has been gained. Approximately 1,500 flavor raw materials are now prepared by these processes.^{5d} New techniques and spectroscopic methods have been developed to isolate and analyze constituents from nature down to parts per billion. Is this all old wine in new barrels or new wine in old barrels? No. New isolation techniques, such as the production of important organic compounds from natural products by specific membrane separation at room temperature, will allow progress. In addition, new membranes will be developed for these techniques. The biochemical (enzymatic) manufacture of flavor and fragrance materials will be improved and extended. These reactions will be carried out with greater specificity and in higher

concentrations. Scientists will increasingly realize what is happening in nature, as in the example of the plant exudate labdanum gum on *Cistus ladaniferus* in a subtropical climate at temperatures of up to 100°C in an acidic medium. Complete new reactions will be found as rearrangements (ring contractions) followed by photochemical oxidation (formation of amberoxide). In addition, many new homogenic catalytic enzymatic biological reactions will be discovered.

In flavor and fragrance chemistry it is normally accepted that natural isolates are mixtures of sometimes hundreds of chemical compounds, whereas in the search for new aroma chemicals, one often strives for chemically and olfactively pure compounds. It is far easier and more economic to make olfactively acceptable mixtures, as for instance with the addition of acetic acid to myrcene, acetylation cedarwood terpenes (thujopsene), or for the preparation of amber compounds. In another instance, a mixture of macrocyclic biomusk compounds could economically be prepared in a few reaction steps from 10-undecenoic acid and 1,4-butanediol or tetrahydrofuran.

Substitution of Functional Groups

More than 95 percent of the commercially available fragrance and flavor chemicals contain one or more functional groups. One may question, then, whether a functional group is necessary for the odor of a compound. No, it is not, because alkanes and benzenoid hydrocarbons sometimes have very pronounced odors. We wondered whether a trained observer would be able to recognize an odorant by its functional group. Therefore we tested 100 aliphatic (normal C-3 to C-15) compounds with and without functional groups. Seven odor-trained chemists were used. Each observer received known standards with eight carbon atoms and 13 different functional groups, e.g. octane, octanol,

T-2. Examples of substitution of functional groups with the same odor character

Original Functional Group	Example Aroma Chemical	Substituted Functional Group	Substituted Aroma Chemical	Odor Description
aldehyde	citral	nitrile	geranyl nitrile	citrusy, lemon-like
aldehyde	benzaldehyde	nitro	nitrobenzene	aromatic, spicy, bitter-almond-like
acetate	isopentyl acetate	methyl ketone	5-methyl-heptan-2-one	fruity, banana-like
(Z)-ethylene	(Z)-hex-3-en-1-ol (acetate)	sulfur	3-thiapentan-1-ol (acetate)	green, freshly mown grass, slightly sulfurous
chloro	(trichloromethyl)-benzyl acetate	methyl	trimethylmethyl-benzyl acetate	floral, rose-like
nitro	musk ambrette	acetyl	acetyl musk ambrette	musky, erogenic
gem.dimethyl	damasc(en)jone	cyclopropyl	damasc(en)one derivative	floral-fruity, rose and rum-like
allyl/propenyl	(methyl)ionones	cyclopropyl	(methyl)ionone derivatives	floral-fruity, orris- and strawberry-like

octanal, octanoic acid, hexyl acetate, octanethiol, octylamine, and so forth. The chemists received all samples under codes, and upon smelling and comparing with the standards, had to write the general chemical name, e.g. "This is an alkane, alcohol or thiol."

The results were:

- Seven hundred six tests were performed, from which 58 percent were correct and 42 percent wrong.
- For the C-3 to C-6 compounds, more than 80 percent were identified based on their functional groups.
- For the C-7 to C-10 compounds, over 80 percent of the aldehydes, alcohols and thiols were correctly recognized; from the other functional group compounds, more than 50 percent were wrong.
- For the C-11 to C-15 compounds, only the thiols could be identified correctly from the other functional groups; 50 to 100 percent were incorrectly identified.

The results with the methyl ketones and acetates are shown in **T-1**.

From this experiment it seems likely that experienced odor-perception observers can mistake certain functional groups (ketones) by others (esters), even with the use of odor standards. The same holds true for other functional groups, such as the case of the following substitutions:

- Aldehyde for nitrile in monoterpenoid and benzenoid compounds.
- Aldehyde for nitro in benzenoid compounds.

- *cis*-Olefine for sulfur in straightchain aliphatic compounds.
- Chloro by methyl in aliphatic and benzoid esters.
- Allyl and geminal dimethyl for cyclopropyl in damasc(en)ones and ionones (**F-2**).

Some examples of replacement functional groups in odorants with the maintenance of the more or less same odor character are shown in **T-2**. From this table it is clear that, at times, functional groups can be replaced by others without a big change in the odor character. Substitution of functional groups in molecules with more or less the same electronic charge distribution and similar odor characteristics are examples of "isoelectronic" molecules with similar olfactive properties.

The straight chain aliphatic aldehydes octanal and decanal are organoleptically character-impact compounds of orange peel oil and could have been used a lot more in perfume compounds. In fact, they are used in alcoholic perfumery in several luxury perfumes such as Chanel No. 5. The application of these aldehydes in functional perfumery (soap, detergents and other household products), however, has severe limitations because of the chemical stability of the aldehyde function (oxidation, condensation). Even in alcoholic perfumery, the aldehydes will form hemiacetals. The chemist working on odor-structure relationships will modify the functional aldehyde group.

There are several tools available to accomplish this:

- Substituting of the aldehyde function by a chemically more stable group such as nitrile, acetyl or oxim.

T-3. Commercially available acetates and isobutyrate of C-4 to C-10 alcohols*

No.	Alcohol Part	Acetate	Isobutyrate	No.	Alcohol Part	Acetate	Isobutyrate
1	butyl	+	+	18	citronellyl	+	+
2	sec.butyl	+	–	19	dihydromyrcenyl	+	–
3	isobutyl	+	+	20	tetrahydromyrcenyl	+	–
4	tert.butyl	+	–	21	tetrahydrolavandulyl	+	–
5	n-pentyl	+	–	22	neryl	+	+
6	2-methylbutyl	+	+	23	geranyl	+	+
7	3-methylbutyl	+	+	24	dimethyloctyl	+	–
8	hexyl	+	+	25	linalyl	+	+
9	2,4-hexadienyl	+	–	26	tetrahydrolinalyl	+	–
10	heptyl	+	–	27	myrcenyl	+	–
11	2-heptenyl	+	–	28	α -terpinyl	+	+
12	(Z)-3-heptenyl	+	–	29	dihydroterpinyl	+	–
13	octyl	+	–	30	benzyl	+	+
14	nonyl	+	–	31	phenethyl	+	+
15	decyl	+	–	32	α -methylbenzyl	+	–
16	2-decenyl	+	–	33	3-phenylpropyl	+	+
17	9-decenyl	+	–	34	cinnamyl	+	+
Total Number						34	16

*Source: 2002 Allured's Flavor and Fragrance Materials

T-4. Commercially available aroma chemicals with isobutenyl by phenyl substitution

Original Aroma Chemical (Chemical Identity)	Substituted Aroma Chemical	Commercial Name (Supplier)	Odor Description
6-methyl-5-hepten-2-ol	4-phenylbutan-2-ol	methyl phenethyl carbinol (F-3)	slightly floral, roselike, sweet aromatic
citronellol (3,7-dimethyloct-6-enol)	3-methyl-phenylpentan-1-ol	Mefrosol (Quest), Phenoxanol (IFF), Phenylhexanol (Firmenich)	diffusive, fresh floral, rose absolute type
citronellal	3-methyl-5-phenylpentanal	Mefranal (Quest)	green aldehydic
citronellylnitrile (3,7-dimethyloct-6-enenitrile)	3-methyl-5-phenyl-pentanenitrile	Hydrocitronitril (Haarmann & Reimer), <i>Citralis nitrile</i> (IFF)	citrusy, lime, fresh
geranyl nitrile	3-methyl-5-methyl-pent-2-enenitrile	Citronitrile (Haarmann & Reimer)	fresh citrusy, lemon-like, somewhat aromatic-balsamic notes

- Preparing a vinyl ether of the aldehyde to give the slow release of the aldehyde in acidic media.
- Making an acetal of a lower alcohol with the same target.
- Forming an equilibrium in a Schiff base with methyl anthranilate.

Isobutyrate in Place of Acetates

Esters of lower fatty acids, e.g. formic and acetic, have fruity-floral odor characters and occur in many food flavors and essential oils. Applications of these

esters in functional perfume compounds for alkaline media possess the disadvantage that they can saponify. In some cases, one may substitute the acetate function with an isobutyrate or even a pivalate one without great change in the olfactive character of the compounds. New aroma chemicals of this type are α -terpinyl isobutyrate, phenethyl pivalate and vanillyl isobutyrate. As can be seen from **T-3**, of the commercially available acetates and isobutyrate there is still room for a series of isobutyrate.

T-5. Commercially available aroma chemicals with isopentyl by cyclohexyl substitution

Original Aroma Chemical/ Chemical Identity (Commercial Name and Supplier)	Substituted Aroma Chemical	Commercial Name (Supplier)	Odor Description
isopentyl salicylate/3-methylbutyl 2-hydroxybenzoate (isoamyl salicylate)	cyclohexyl salicylate	Cyclohexylsalicylat (Cognis)	sweet aromatic- floral, somewhat medicinal- phenolic
allyl isopentoxyacetate/ prop-2-enyl-1 6-methyl-3-oxaheptanoate (A.I.A.A.-Inoue) (Allonate-Quest) (Allyfate-Quest) (Allyl amyl glycolate-IFF) (Galballynate-Bell Aromatics) (Isoamylx-Charabot) (Isogalbanate-Dragoco) (Pentyrate-Sensient)	allyl cyclohexoxyacetate	Allyvert (Quest) Cyclogalbanat (Dragoco) Cyclogabaniff (IFF) Hexylx (Charabot) Isoananat (Haarmann & Reimer)	green, fruity, herbal, reminiscent of galbanum, pineapple connotation
isopentyl phenylethyl ether/ 2-isopentoxy-1-phenylethane (Anther-Quest) (lphaneine-IFF) (phenylethyl isoamyl ether-Toyotama) (Treflon-Takasago)	cyclohexyl phenylethyl ether	Phenafleur (IFF)	floral note with hyacinth associations

T-6. Commercially available isoamyl and cyclohexyl esters*

No.	Ester/Acid Part	Ester/Alcohol Part		No.	Ester/Acid Part	Ester/Alcohol Part	
		Isoamyl	Cyclohexyl			Isoamyl	Cyclohexyl
1	acetate	+	+	19	isobutyrate	+	+
2	acetoacetate	+	-	20	isovalerate	+	+
3	angelate	+	-	21	lactate	+	-
4	anthranilate	-	+	22	laurate	+	-
5	benzoate	+	-	23	2-methylbutanoate	+	-
6	butyrate	+	+	24	nonanoate	+	-
7	cinnamate	+	+	25	octanoate	+	-
8	crotonate	+	+	26	phenylacetate	+	+
9	cyclopentenylacetate	-	+	27	3-phenylpropionate	+	-
10	decanoate	+	-	28	propionate	+	+
11	eugenyl	+	-	29	pyruvate	+	-
12	formate	+	+	30	salicylate	+	+
13	4-(2-furan)-butyrate	+	-	31	senecioate	+	-
14	3-(2-furan)-propionate	+	-	32	3-(methylthio)-propionate	+	-
15	geranate	+	-	33	tiglate	+	-
16	heptanoate	+	-	34	undecylenate	+	-
17	heptinecarbonate	+	-	35	valerate	+	-
18	hexanoate		+				
Total number						33	13

*Source: 2002 Allured's Flavor and Fragrance Materials

Substitution of Isobutenyl With Phenyl in Monoterpenoids

Various examples of the replacement of an isobutenyl group with a phenyl group are presented in the literature. Substitution of the butenyl group by a phenyl group causes little effect on the odor character of linalool, rose oxide and geranonitrile. Turin could predict with his method for spectrum calculation (inelastic electron tunneling spectroscopy) the similarities in odor character of these different structural classes.^{4b}

The isobutenyl part in the original molecules is more vulnerable to oxidation than the phenyl part in substituted molecules. And while the odor qualities of both molecules show a clear resemblance, the intensities of the phenyl substitutes will sometimes decrease. On the other hand, the odor tenacity of the phenyl derivatives is greater, and their substantivities better. Several of these phenyl substitutes are commercially available. There is room for many more monoterpeneoid substitutes, as for instance with: nerol/geraniol (esters), neryl/geranyl hemi-acetals, neric/geranic acid (esters), neryl/geranyl acetone, linalyl esters and hemi-acetals, and citronellyl

derivatives (see neryl/geranyl). Examples of commercially available aroma chemicals in which the isobutenyl part is substituted by a phenyl part are shown in **T-4**.

Examples of commercially available aroma chemicals in which the isopentyl part is substituted by a cyclohexyl part are shown in **T-5**. Substitution of certain groups in molecules with more or less the same profile (shape, volume) and similar odor characteristics are examples of “isosteric” molecules with reminiscent olfactive properties.

Substitution of Isoamyl by Cyclohexyl in Some Aroma Chemicals

The isoamyl group is a natural degradation product from leucine and often occurs in natural isolates, mostly as an ester. The lower aliphatic isoamyl esters may have strong fruity odors. A disadvantage of the application of these esters is that they are highly volatile and can easily saponify. One may substitute the isoamyl group with a cyclohexyl group without disturbing the odor character to any great extent. Some examples of this substitution can be found in the odors

T-7. Frequency of the occurrence and concentration of some mono- and sesquiterpenoids in 3,225 essential oils

Monoterpenoid	In Total Number of Oils	Concentration Range (Percent)	In Concentration Range (Percent)/Number of Oils	In Concentration Range (Percent)/Number of Oils
myrcene	2,180	0.01-95	1-95/1,063	10-95/81
myrcenol	20	0.01-8.2	-	-
myrcenyl acetate	2	0.01-6.0	-	-
myrcenal	0	-	-	-
(Z)-ocimene	880	0.01-43	1-43/228	10-43/41
(E)-ocimene	975	0.01-95	1-95/252	10-95/95
(Z)-ocimenol	3	0.01-1.5	-	-
(E)-ocimenol	4	0.01-1.5	-	-
ocimenals	0	-	-	-
menthol	195	0.01-85	1-85/123	10-85/101
menthyl acetate	126	0.01-52	1-52/102	10-52/101
menthone	262	0.01-60	1-60/171	10-54/18
thymol	405	0.01-90	1-90/180	10-90/91
carvone	364	0.01-80	1-80/87	10-80/46
carvomenthone	5	0.01-1	-	-
carvomenthol	0	-	-	-
carvomenthyl acetate	1	0.01-1	-	-
carvacrol	364	0.01-90	1-90/154	10-90/94
α -farnesenes	286	0.01-40	1-40/82	10-40/15
β -farnesenes	530	0.01-90	1-90/150	10-90/16
α -sinensal	71	0.01-3	-	-
β -sinensal	59	0.01-3	-	-

T-8. Commercially available citronellyl, geranyl and linalyl esters*

No.	Ester/Acid Part	Ester/Alcohol Part			No.	Ester/Acid Part	Ester/Alcohol Part		
		Citronellyl	Geranyl	Linalyl			Citronellyl	Geranyl	Linalyl
1	acetate	+	+	+	12	hexanoate	+	+	+
2	acetoacetate	–	+	–	13	isobutyrate	+	+	+
3	anthranilate	+	+	+	14	isovalerate	+	–	+
4	benzoate	+	+	–	15	2-methylbutanoate	+	–	–
5	butyrate	+	+	+	16	phenylacetate	+	–	+
6	cinnamate	–	–	+	17	octanoate	–	–	+
7	crotonate	+	+	–	18	propanoate	+	–	+
8	decanoate	+	+	–	19	tiglate	+	+	–
9	dodecanoate	+	+	–	20	undecylenate	–	–	–
10	ethyl oxalate	+	–	–	21	valerate	+	+	–
11	formate	+	+	+					
Total number							17	19	11

of cyclohexyl salicylate, cyclohexyl phenethyl ether and allyl cyclohexyloxyacetate (see **T-5**).

In **T-6** the commercially available isoamyl and cyclohexyl esters are shown; there is still room for more of the latter.

New Terpenoid Alcohols, Esters and Aldehydes in Natural Products

It is general knowledge that citrus oils contain farnesenes and the corresponding aldehydes α - and β -sinensal. Citrus oils also contain myrcene and ocimenes, but the corresponding aldehydes, myrcenal and ocimenals (see **F-2**), have not been detected up to now. During our studies of the composition of 3,225 quantitative analyses of essential oils it was noted that more than 50 percent of these oils contained either myrcene or ocimenes. However, less than 1 percent of these oils showed the presence of myrcenol or ocimenols (see **F-2**), and none of them contained the aldehydes. Synthesis of pure myrcenyl and ocimenyl acetate revealed that they possess excellent olfactive properties, and an extremely fresh floral character that improves those of linalool and its acetate. **T-7** shows the frequency of the occurrence and the concentration ranges of some monoterpenoids in essential oils. **T-8** shows the commercially available citronellyl, geranyl and linalyl esters. It is clear that more linalyl esters can be prepared; moreover, it is likely that new myrcenyl and ocimenyl esters will be found in nature and manufactured.

New Sesquiterpenoid Derivatives

The allylic oxidation of sesquiterpenes in analogy with that of limonene for the formation of C-15 will lead to analogues of carvone (**F-2**), perilla aldehyde and isopiperitenone. Sesquiterpene carbonyl analogues

should be developed from other olfactively interesting monoterpenoid ketones: thujones, verbenone and chrysanthenone (**F-2**). These sesquiterpene ketones could have useful odor qualities. **F-2** to **F-3** reveal the molecular structures of some of these sesquiterpenyl-carbonyls. There are interesting comparisons to be made between valencene and nootkatone, and α -cedrene and cedrenone.

Regarding the epoxidation of sesquiterpenes and the conversion of the epoxide to ketones (isolon-gifolanone, cedranone, caryophylla-none, etc.), epoxidation can easily be carried out with hydroperoxide and formic acid (or ester) to a mixture of epoxides, diols and formats, which in turn can be converted into simple sesquiterpene ketones. It should also be noted that methanol may be added to sesquiterpene hydrocarbons (such as IFF's cedryl methyl ether).

Studying the Biochemical Formation of New Volatile Compounds

The biogenesis of fatty acids and isoprenoids from acetyl-coenzym-A has been known for decennia. Fatty acids are linearly built up via aceto-acetyl-ScoA to higher β -oxo-acyl-ScoA derivatives, followed by reduction, dehydration and again by reduction into fatty acids with the general formula: $\text{CH}_3(\text{CH}_2)_n\text{COOH}$, where n is zero or an even number.

Isoprenoids are biochemically formed via aceto-acetyl-ScoA via β -hydroxy- β -methyl-glutaryl-ScoA and mevalonate to branchedchain $(\text{CH}_3)_2\text{C}=\text{CH}-[\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}=\text{CH}]_x-$ derivatives, where x is zero or a whole number. One could imagine that a combination of the two biogenetic pathways should lead to geminal-methylor 3-methyl-alk-2-enyl derivatives. If



this combination of the two routes is indeed possible, one could expect a series of these compounds in natural products, which contain the proper precursors and enzyme. We supposed that citrus fruits, containing fatty acid derivatives and isoprenoids, should present a fair chance of finding 3-methylalk-2-enyl derivatives. Therefore, we prepared a series of 3-methylalkenals and searched for their occurrence in different citrus oils. Indeed, it was possible to detect 3-methyloct-2-enal in lemon oil by a combined gaschromato-graphic/mass spectrometric technique. 3-Methyloct-2-enal has a distinct lemon flavor and improves the organoleptic quality of the natural oil. β -Methyl- γ -octanoic lactone has been found in alcoholic beverages. The compound has a coconut-like odor, but is indispensable for a good flavor of brandy, whiskey or rum. Geminaldimethyl-alkanoic acids have been found in various meat and in dairy products, e.g. 9-methyl-dodecanoic acid in mutton, and 11-methyldodecanoic acid in powdered milk. Hundreds of new substances can be designed and possibly found in nature following these biochemical guidelines.

So far, up to 70 volatile alcohols and about 60 fatty acids have been detected in food flavors, such as apple, banana, guava, grape, papaya, raspberry and strawberry.^{5d} A simple calculation makes it clear that $70 \times 60 = 4,200$ esters should occur. However, up to now less than 10 percent, or 420 esters in total, have been found in these fruits.

Investigation of Reactions During Food Processing

The most important chemical event during food processing is the Maillard reaction of amino acids and sugars, followed by Amadori or Heinz rearrangements. A European scientific committee was formed from universities and the flavor industry to study this reaction in detail. It was discovered that hydrogen sulfide (from cysteine) and methyl-mercaptan (from methylcysteine) can be added to (Z)-3-hexenol and limonene during flavor formation.

New flavor constituents can be formed by the addition of hydrogen sulfide or methylmercaptan to unsaturated compounds [e.g. (Z)-4-heptenal, (E,Z)-2,6-nonadienal, monoterpenes, sesquiterpenes, damasc(en)ones]. About 10 percent of all published volatile compounds are sulfur compounds. 7,10 An important group of these compounds are disulfides, of which (until now) about 60 have been found in food products. On the basis of all the ca. 50 (= n) thiols one could expect $n(n + 1)/2 = 1,275$ disulfides. Although not all the 50 thiols occur in the same foods or beverages, many more disulfides surely exist and will be found.

Volatile Schiff's Bases

A Schiff's base of methyl anthranilate with olfactively interesting aldehydes is well known in perfumery. However, this Schiff's base is a mixture of the starting materials in equilibrium with the end product. If one

purifies the end product, e.g. by high vacuum distillation, the resulting material is often odorless. One may produce volatile N-alkylidene methyl anthranilates (**F-2**) (from ethanal, propanal, butanal, isobutanol, pentanal, 2- and 3-methylbutanal, hexanal and hexenal) in pure form, which likely occur in natural products. Only one pure N-alkylidene methyl anthranilates (from 2-methylpentanal, mevanthral from Quest) is commercially available today.

Conclusion

New groups of aroma chemicals can be designed by the substitution of isosteric groups (e.g. isobutenyl by phenyl and isopentyl by cyclohexyl, gem-dimethyl by cyclopropyl) and of isoelectronic groups (e.g. aldehyde by nitrile, acetate by methyl ketone, allyl by cyclopropyl, chloro by methyl).

In closing, new flavor and fragrance materials can be developed by:

- Exploring new natural materials.
- Extending characteristic monoterpenoids to sesquiterpenoids.
- Developing new monoterpenoids from similar sesquiterpenoids.
- Functionalization of mono- and sesquiterpenes.
- New biochemical pathways.
- Volatile Schiff's bases.
- New biochemical pathways.
- New products formed during food processing.
- Extension of esters of naturally occurring alcohols and esters.
- Addition of hydrogen sulfide and methylmercaptan to natural and unsaturated compounds.
- Extension of sulfides and disulfides from existing thiols.

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