

New Perfumery Chemicals

Gyrane is an unsaturated aliphatic cyclic ether. It has a fresh green-floral odor with a touch of geranium. It can be used in all types of fragrance products (0.5-5% in the perfume compositions). The price is £15/kg.

Tachrysate is an ester of a hydroaromatic acid. It has a complex odor with aspects of tagetes, chrysanthemum, thujon and natural. It is especially applicable for shampoo and bath foam with use levels of 1-5% in the perfume compositions. The price is £14-50/kg.

PPF International Limited, UK, products were presented by Trevor Harding, assisted by Dr. Charles Sell. PPF has perhaps the most unique and highly professional presentation, with its visual material and samples all color coded. Three nitriles were presented. **Frescile**, the first, possesses a strong orange odor, which is suffused by a light, green, sea-fresh quality. When a distinct citrus/sea-fresh note is required, Frescile may be used to achieve this typical character. Because of its strength and impact, a concentration of only 2-4% is necessary. When used in conjunction with specific floral notes, the addition of 1-2% will subtly round out and expand the composition, giving it a bergamot character. Even at lower concentrations, Frescile will enhance the top note of a fragrance, adding lightness and a pleasant green freshness. It is priced at £30/kg.

Jascittle possesses an unusual floral odor consisting of a distinct waxy-jasmine character, combined with a pleasing argumen quality. It may be used with advantage, even at concentrations below 2% to develop and enhance the fresh natural character of jasmine, rose and muguet fragrances. The combination of floral and green notes renders it particularly valuable in the development of lilac compositions, and using it in conjunction with galbanum produces an accord of value in fougere and chypre fragrances. At concentrations greater than 2%, the agrumen quality becomes more forceful. It is priced at £45/kg.

Frutonile possesses a fine, light jasmine/floral odor with a soft peach undertone. Its floral nature and stability renders it useful in a wide range of traditional compositions. At concentrations of approximately 2%, Frutonile adds a soft sweetness to muguet and considerable depth to jasmine or rose. Its unusual floral/sweet-fruity character makes it a valuable addition to balsamic, amber and spice notes. It is priced at £40/kg.

Ronald Fenn closed the symposium with an excellent lecture on the development of new chemicals. Backed up with a slide presentation, the main thrust of his talk was the difficulties of selecting, screening and promoting new fragrance chemicals. The complete text of Mr. Fenn's presentation follows.

The Development and Introduction of a New Perfumery Chemical

By Ronald S. Fenn,
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The synthesis of new chemicals is one of the principal activities of the research and development program of International Flavors & Fragrances, Inc. (IFF). These new chemicals are extremely important tools which fuel the perfumer's creativity. Consequently, the majority of new IFF chemicals are first commercially used by our own perfumers in a fragrance or a specialty base.

Many of these new chemicals are possessed of extremely powerful odours and are synthesized for use as trace components in either natural product reconstitutions or "caricatures" of same. Thus specialty bases, Olifacs® and other

replacement products, will contain many such chemicals that are not marketed as separate entities. Nevertheless, a good percentage of these new products are eventually offered to the world's perfumers.

Sources of New Chemical Concepts

Ideas for new chemicals may emanate from the specialists involved in the many activities that support the R&D effort.

Perfumery—also Flavoring and Tobacco
Natural Products Investigation
Organic, Physical, Inorganic Chemistry
Microbiology, Biochemistry

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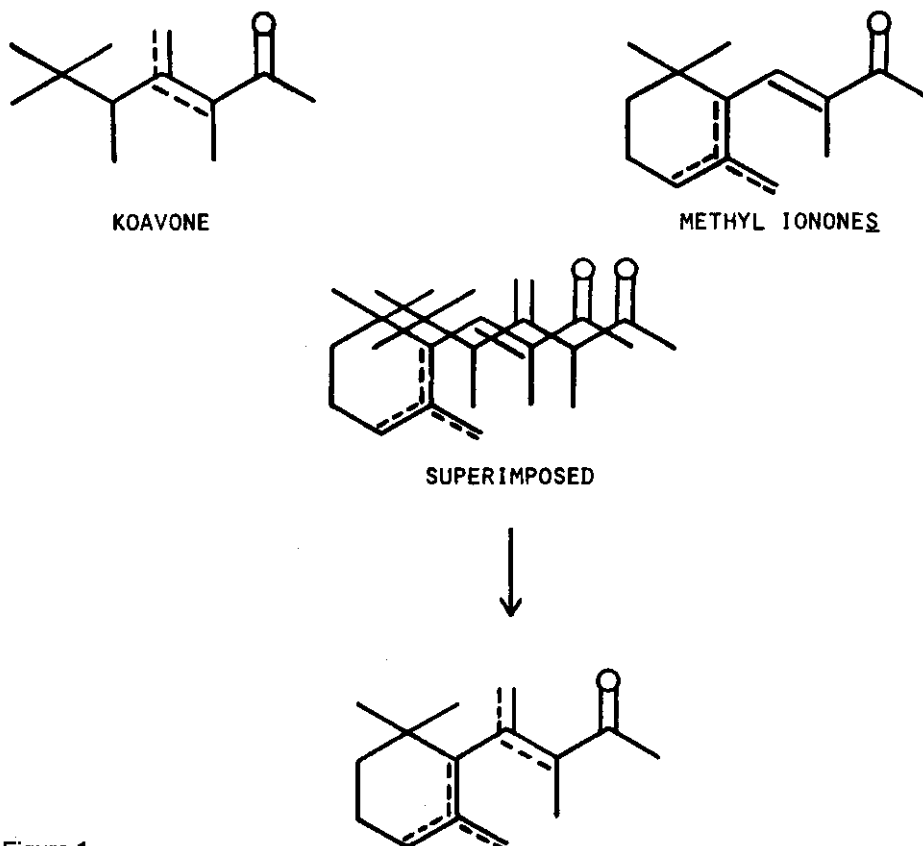


Figure 1

Computer and Literature Chemistry, Patent Law
Sensory Testing
Product Safety Assurance—Toxicology and Pathology; or Regulatory and Industrial Hygiene
Process Engineering
Analytical Techniques—NMR, GLC, MS, IR, etc.
Marketing and Sales

That contributions of new chemical concepts are made by some of the above is perhaps surprising. For instance, one expects an organic chemist working on natural products to be a source but two examples follow that are less than obvious. From the area of safety and industrial hygiene, adverse comments have prompted review of a certain process leading to experiments for the change of an undesirable solvent. This change introduced different impurities which, upon examination, proved to be new entities worthy of manufacture in their own right. Another less obvious source is a request from the patent attorney for certain chemicals to be synthesized in support of claims for another molecule. Such work has yielded products of considerable interest to the perfumer.

There is no magic formula that one can employ to give rise to a new chemical. One can only try to selectively manage the, fortunately, endless flow of such ideas. The specialists are prompted in their creative thinking more often than not by many activities including the investigation of natural products; analogy to, or suggested by, a known chemical structure; from new intermediates; by-product streams; application of a new reaction technique to a variety of feedstocks; the systematic preparation of a series of derivatives; from odour-structure relationships (computer aided); and the need for chemical stability in a demanding media.

Of course, finding an odour-important chemical in a natural product and then being able to develop a synthesis for same is traditionally more "glamorous" than developing a novel structure. However, in more recent years the majority of successful chemicals introduced have been generally of an entirely synthetic origin.

The petrochemical industry has, of course, been a most fruitful source of building blocks for the chemists specializing in synthesis. With the increasing emphasis on minimizing the amount of waste products to be treated and disposed of, much attention has been given to the use of by-

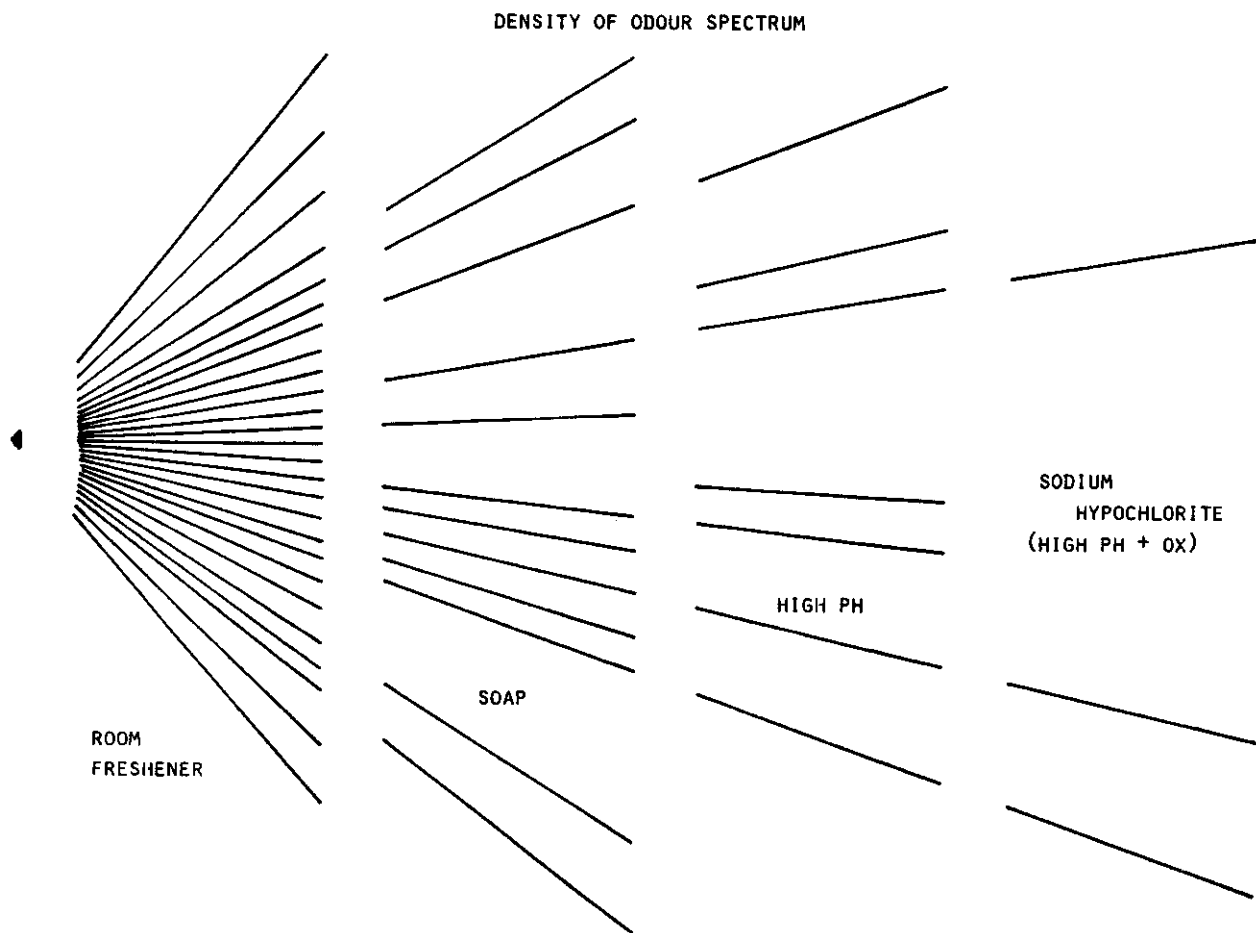


Figure 2

product streams. For example, a new IFF chemical, Koavone, was derived from such a by-product. The pinene family of chemicals provides a lengthy listing of the systematic preparation of derivatives of one starting raw material. These are too numerous to mention comprehensively but, for example, of IFF manufacture, tetrahydro muguol, dihydromyrcenol, lylal, ocimenol and myrcenyl acetate.

Odour and structural relationships have also led to several new molecules. Nowadays we have the computer expertise to thank for identifying certain structures that are likely to have a specific odour correlation (see fig. 1). Koavone's somewhat similar odour to the methyl ionones (at economically lower concentrations in view of its lesser molecular weight) would constitute a case in point.

Difficult media to fragrance, such as sodium hypochlorite solutions, that are themselves chemically very active and also in turn subject to decomposition, provide challenges to the synthesist. Figure 2 represents the choices available

to the perfumer shrinking as the severity of the operational media increases; i.e., the density of the "odour spectrum" diminishes.

At the extremes a perfumer can use virtually any chemical in a room freshener blend of the wick evaporation type. But in sodium hypochlorite solution the pH increases with the age of the solution: the available chlorine and oxidizing environment destroys a large number of chemicals leaving the perfumer a very restricted palette with which to work. Thus there are few citrus and floral notes among the commonly known fragrance chemicals that are stable to hypochlorite bleach. The chemist is stimulated to develop chemically inert molecules for this medium. Note that such activity nowadays has to be balanced against the need for molecules to be biodegradable. A conflict!

Experimentation and Evaluation

Once a concept is accepted as suitable for the R&D program the development process begins. The literature will have been reviewed to verify

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originality of concept and to locate previous relevant work. Initial experiments are carried out and the approximate production cost calculated (at this stage really only an order of magnitude). The product obtained is analyzed and gas liquid chromatographic traps of the major components are prepared to allow all structures present to be defined and to permit review by other disciplines—particularly by the perfumers and marketing people. The stability of the chemical is only postulated at this time.

If the chemical is considered to be of interest, a series of events can be initiated. Perfumers will be given experimental quantities of the product in order for them to make trial formulations which will help establish the worth of the new chemical compared to existing products. Patent possibilities are considered by the legal department; the corporate safety assurance personnel subject the material to preliminary screening and will initiate testing if no obvious negatives arise. The chemical stability of the product will be tested in all major media.

When the foregoing work has been completed, and if all factors seem encouraging, the project will be given "active" status and be made several times by one or more syntheses in order to select the best route. Also the reproducibility of odour and chemical composition will be established. Based on various inputs an assessment will be made of the possible annual volumes likely to result after five and ten years. Here I should stress that one does *not* need input from those possessed of the Will Rogers type philosophy; i.e., "I never smelt a chemical I couldn't use." Such people are excessively optimistic and have been responsible for the subsequent plant introduction of products that never achieve acceptable volumes. A "hard" realistic judgment is essential.

Further assessments will include the cost of further development and plant introduction, the cost of manufacturing the product, and the cost of testing to meet all safety and regulatory requirements on a *worldwide* basis. The market place today is truly international with the result that a successful fragrance in one country is quickly spread to others. Try telling your customer that it is not possible to also launch his product in Country X because a key fragrance ingredient is forbidden there!

Critical Screens

It should be stressed that the foregoing activities may not all be carried out if certain *critical factors* arise:

1. Management requirements and priorities change; e.g., other chemicals in the programme

are considered to be more worthwhile and take priority.

2. Manufacturing or other hazards occur or are strongly suspected possibilities.

3. Perfumer/marketing opinion. The odour-cost-performance combination is unsatisfactory; e.g., the chemical is worth \$5 but costs \$10 to make.

4. Potential volume usage may be too small to justify cost of process development and/or specialized equipment required and/or all safety, regulatory testing necessary.

Any one of the above combination of events may result in the project being discontinued.

Of particular concern, as it is likely to be a major reason for discontinuing, is the cost of safety testing. All around the world various countries have differing regulations. However, if we consider the comprehensive requirements of the OECD which apply to all new chemicals not listed in their inventory prior to September 1981, we can appreciate the costs involved.

OECD Requirements—This is only a sampling. For details, see the official "OECD Guidelines for Testing of Chemicals."

1. Name and empirical and structural formula
2. Composition of substance including stabilizers, inhibitors
3. Methods of detection and determination
4. Types of use and application
5. Estimated production quantities—1, 10, 50, 100, 500, 1,000, 5,000 ton net
6. Methods and precautions in handling, storage and transportation
7. Likely hazards and emergency measures
8. Physical chemical properties (s.g., m.pt., b.pt., surface tension, etc.)
9. Solubility in water, solvents
10. Partition coefficient (n-octanol/water)
11. Flammability—oxidizing properties
12. Toxicological studies—oral, inhalation, percutaneous, skin irritation, eye, subacute toxicity, mutagenicity, carcinogenicity, teratology, fertility
13. Ecotoxicological—effects on fish, daphne, earthworm
14. Possibilities for rendering substance harmless—recovery, neutralization, destruction
15. Labeling—packaging

A one ton per year product will have to sustain a high selling price indeed to justify the cost of testing alone. During the last five years IFF R&D has synthesized and/or reviewed approximately 2,500 "new" chemicals. Due to the critical factor considerations, less than 5% survived.

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Status "GO" (Develop and Produce)

Assuming the interest is sustained and the product survives all the pitfalls outlined, a senior fragrance management committee comprised of production, R&D, perfumery, and sales personnel will make the decision to commercialize the product. Thus the next step is to develop the process for regular manufacture whether it be for large or small scale. The development engineers will be fully briefed by the chemists involved and commence the task of increasing batch size in the pilot plant equipment. Here they will "learn" the characteristics of the process; i.e., heat transfer requirements, stirring dynamics, etc.

During this phase marketing tries to zero in on the economics involved. This is difficult to achieve and to plagiarize President Harry S. Truman, one wishes for a "one armed" development engineer who, when questioned what the cost to produce will be, does not reply "on the one hand . . ." When the engineers are satisfied they have a developed process they will liaise with the manufacturing plant technicians to transfer and practice the procedure in the large scale equipment. After the successful plant introduction and establishment of quality and manufacturing cost, the final specifications are set and safety sheets and promotional literature developed.

The product is known only to IFF's perfumers at this stage and some time may lapse before it is introduced to perfumers outside of the company. The name selected for a new chemical is very important to its future. If a strict chemical nomenclature is not going to be used the "fantasy" trivial name should be carefully chosen. It should be pronounceable by the various nationalities and not have an "unfortunate" sound or meaning in one language or another.

The Introduction

The approach to the fragrance industry perfumers warrants very careful consideration. Symposia such as this one organized by the British Society of Perfumers seem to be a way of "pulling" new products out of companies that might otherwise have taken longer to show. Sending samples by mail with accompanying literature is probably the quickest way to blanket the industry. Be warned that many perfumers are somewhat resistant to this method and the sample may find its way to the waste bin, unopened.

Articles by third parties in trade magazines can be helpful and from time to time one receives requests for products that the perfumer

has read about. Advertising a product can be selectively done to achieve maximum benefit. Another route for introduction occurs when one's competitors find your new product in a recently introduced fragrance won by your company. Possibly the most effective route would be demonstration to perfumers on a one-to-one basis. This is an extremely time consuming process on a worldwide basis.

The most common approach is to show the new product to perfumers collectively by company. This has its pluses as well as its minuses; experience dictates that one will do well to consider the idiosyncratic factors pertaining to individual companies and their perfumers.

The format of the presentation is, of course, very much an individual matter. Typically the presenter will have with him the following: the concentrated oil and dilutions of it as appropriate, demonstration fragrance formulae using the product to advantage, finished product samples; i.e., soap, detergent and shampoo incorporating the chemical, and stability data and generalized use suggestions.

Successful—Yes or No?

The new chemical has been "introduced" but the key question is, with what success? There are, of course, indications at the presentation itself; e.g., expressions of like, dislike or promises to test. Such observations are unreliable as the perfumer has yet to work with the product. Subsequent requests for samples over and above those left at the presentation do constitute a tangible expression of interest. Small trial orders are even more meaningful. Of course it is important to realize that winning a new fragrance is a highly competitive matter these days so that even if every perfumer in the target company loves your new chemical and works with it, the odds are against their fragrance winning any new product brief.

The "success" so far, although encouraging to the sales force, offers little consolation to the management of a company and minimal contribution to profit. Of course, in the long term the only thing that counts is volume orders for the product, preferably from a wide range of customers. If this results there is still something to bear in mind.

In any one company use of your new product by *only one* perfumer can result in substantial business. Great! But you may have missed the target with the other perfumers. So at judicious intervals follow-up and repromotion is quite in order, especially if new ideas have subsequently developed for the use of the chemical in fragrance creations.