Perfume Raw Material Safety—The Role of IFRA

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The International Fragrance Association (IFRA) was formed in 1973. It is an international organization with scientific aims concerned with all aspects of safety evaluation and regulation of the fragrance industry. The headquarters of IFRA are in Geneva, Switzerland. The members of IFRA are the national associations of fragrance manufacturers from, at present, thirteen countries: Australia, Belgium, Brazil, France, Germany, Italy, Japan, Mexico, the Netherlands, Spain, Switzerland, The United Kingdom and the USA. Each ordinary member country has a voice in the General Assembly and a representative on the Board of Directors. Individual companies are members of the national associations in these countries; therefore, IFRA represents the entire fragrance industry of the member countries.

By a unanimous decision of its members, IFRA established a self-regulatory discipline within the fragrance industry. In October 1975, IFRA issued a "Code of Practice for the Fragrance Industry" to which all members adhere. This code regulates the control which the fragrance industry itself exercises over its activities in all domains not covered by national or international regulations. It contains basic standards of good manfuacturing practice dealing with personnel, hygienic requirements in the manufacturing areas, storage, manufacturing operations, labeling and packaging, as well as quality control.

A major part of the Code concerns the use of fragrance ingredients. They must only be used under conditions where they present no risk to health. Fragrance materials can be divided into two groups: those for which no adequate in-use experience is available and those which have been in use over a long period of time.

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Fragrance ingredients for which no adequate in-use experience exists should be used only after satisfactory evaluation according to the test requirements in Annex I of the IFRA Code of Practice. The test procedures should be in accordance with the following minimum standards: tests for acute oral toxicity and acute percutaneous toxicity if oral $LD_{50} \leqq 500$ mg/kg, tests for skin and eye irritation potential, test for skin contact sensitization potential and test for phototoxicity and skin photosensitization potential. Fragrance ingredients which do not meet recognized analytical specifications, or which deviate from specifications of products of good commercial quality, and which have not been in use over a long period of time should be used only after satisfactory evaluation according to the above test requirements. It is the responsibility of the manufacturer of a new ingredient to ensure that the testing is done and that the safety of his product is properly evaluated.

The safety of fragrance ingredients which have been in common use over a long period of time may be assessed by the absence of reports of adverse reactions. These fragrance ingredients are also included in the continuing safety evaluation programme of Research Institute of Fragrance Materials (RIFM). More and more fragrance ingredients will be tested, but it is unlikely that all substances in use will be tested in the near future.

RIFM does not issue guidance on safe use or safe use levels; it confines itself to the compilation and careful evaluation of data and test results by experts and ends with publications of its findings. These publications summarize the studies done through RIFM and those published in the scientific literature; however, they do not include practical recommendations which can be used by perfumers.

Each company has to decide in its own responsibility how to use fragrance ingredients. If the conclusions on the use of certain ingredients are made individually by each company, considerable differences in the interpretation will occur. It is highly unsatisfactory if fragrance companies or their clients reach different conclusions on the safety of the same fragrance ingredient. That certain substances can only be used for some clients and not for others is already an inconvenience for the inventories and compounding operations of fragrance manufacturers.

An even more serious problem is that the credibility of the whole industry is suffering; it is indeed difficult to explain why one ingredient is safe for one company and unsafe for another company. It is therefore necessary to present these scientific results in the form of practical recommendations concerning the use of fragrance materials.

In the absence of specific regulations for fragrances, IFRA is issuing guidelines to fragrance manufacturers on the safe usage of perfume ingredients with particular relevance to certain materials considered to have a potential for undesirable effects.

The IFRA Guidelines are elaborated by the Technical Advisory Committee (TAC) and have to be endorsed by the Board or the General Assembly of IFRA. In the IFRA Technical Advisory Committee each member country is represented by one delegate and one or two alternates. The industry experts are perfumers and product safety managers of fragrance companies. They are especially qualified in the fields of organic chemistry, fragrance creation, fragrance manufacturing, safety assessment and regulation. This Committee represents the technical and scientific experience of the fragrance industry. Therefore, the conclusions adopted by the whole Committee carry more weight than those which individual experts could have reached alone.

The TAC makes recommendations on the use of ingredients after having considered all available data including that of RIFM and other published and unpublished data such as testing results made available by the sponsors of these tests, and reports of adverse reactions due to fragrance materials placed at the disposal of IFRA by fragrance material manufacturers.

IFRA cooperates with RIFM; mutual exchange of information enables the RIFM Expert Panel to study data collected by IFRA, and the results of the RIFM testing programme are made available to IFRA. Effective collaboration between RIFM and IFRA is assured by the Joint Advisory Committee (JAC). It consists of the President of RIFM, the Secretary General of IFRA and four industry experts from each organization. The JAC submits its conclusions and advice to those bodies of IFRA and RIFM which, according to their statutes, have the responsibility for making decisions. This close relationship assures essential agreement between the two organizations on the guidelines established.

The IFRA Guidelines deal exclusively with the use of substances and materials as fragrance ingredients. The Guidelines advise against the use of fragrance materials under conditions that might provoke irritation and sensitization reactions or phototoxic effects. The recommendations of the Technical Advisory Committee of IFRA are based on data available at present. These recommendations will continually be updated as

necessary when further data become available.

At present, recommendations for sixty-six fragrance ingredients have been issued in the Guidelines. IFRA recommends that twenty-nine fragrance ingredients should not be used at all while certain restrictions of use are recommended for other ingredients. Certain purity criteria are required for four ingredients and special manufacturing procedures for five others. It is recommended to use five fragrance ingredients only in conjunction with other substances. The presence of four ingredients in other raw materials is limited.

Quantitative restrictions are recommended for nineteen fragrance ingredients. These restrictions are expressed in percentage of the fragrance compound. All ingredient restrictions are based on a use level of the fragrance compound of 20% in a consumer product. A fragrance compound formulated in this way is in accordance with the IFRA Guidelines; if a fragrance compound is to be used at more than 20% in a consumer product, the maximum limits of any restricted ingredient it contains must be lowered proportionately. The reference level of 20% was chosen since a use level of 20% or less covers most of the applications in perfumes, cosmetics and toiletry products.

Unless otherwise stated in the ingredient recommendations, a fragrance compound which will be used at less than 20% in a consumer product may contain proportionately higher levels of restricted ingredients. In this case, fragrance suppliers should inform users that because of the presence of materials restricted by IFRA, this compound should be only used in appropriate concentration for well-defined applications. Such uses can then be considered to be in compliance with the IFRA Code of Practice. It is understood that the necessary information to be given to fragrance users does not include disclosure of fragrance formulas.

Among the fragrance ingredients with quantitative restrictions, there are nine materials which have been found to be phototoxic. If combinations of phototoxic fragrance ingredients are used, the use levels have to be reduced accordingly. The sum of the concentrations of all phototoxic fragrance ingredients, expressed in percent of their recommended maximum level, shall not exceed 100.

The fact that the Committee recommends not using a certain material as a fragrance ingredient does not exclude its use due to its natural presence in a natural fragrance material, provided that such a material has been proven harmless in a relevant test programme.

By recommending not to use a certain fragrance ingredient, IFRA has also to consider the difficult problem of the possible replacement of this ingredient. A fragrance ingredient with a certain sensitizing potential used in small amounts can relatively easily be replaced by another ingredient with a lower sensitizing potential, as determined in predictive tests. But the situation is different if a large volume ingredient can no longer be used. This means that large amounts of a relatively well-known substance may be replaced suddenly by equally large amounts of a substance with a limited use experience and with no reported clinical incidence due to the hitherto low usage and significant lack of interest in testing. Particular care has to be given not to replace a material with a low risk of rare reported reaction by an alternative material which has not been investigated so thoroughly and on which adverse data may not be available.

Another problem is the difference between the results of predictive and diagnostic testing. A considerable number of substances which have been found safe in predictive testing have been identified as sensitizers in some isolated case reports. Adverse reactions, especially positive clinical skin patch tests, should be assessed in conjunction with data on volume used, concentration and mode of use and size and type of population at risk. If the reported adverse reactions are set in relation to the total exposure, they may become relatively acceptable.

These considerations applied to the available data have been used to reach conclusions for certain materials for which quantitative restrictions are recommended.

Like all scientific opinions the recommendations of IFRA are open to revision in the light of new evidence. Amendments of the guidelines are distributed regularly to fragrance manufacturers, government authorities, interested scientists and cosmetic manufacturers. The amendments are also published in this journal, *Perfumer & Flavorist* (Allured Publishing).

The recommendations of IFRA are a description of good manufacturing practices of the fragrance industry. Since the recommendations have been published, they are open to scientific criticism. The fact that they remain unchallenged gives additional weight to their status as a generally accepted expert opinion.

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