



Research Institute for Fragrance Materials, Inc.
www.rifm.org
For more information email: rifm@rifm.org



Regulatory notes

Roles in the Safe Use of Fragrance Materials^a

RIFM and IFRA's process and guidelines for fragrance Standards

Ladd Smith, Research Institute for Fragrance Materials Inc.; John Middleton, Quest Fragrances International; David Bickers, Columbia University; and Matthias Vey, International Fragrance Association

The fragrance industry has maintained a strict system of safety assurance for more than 30 years. Originally designed to be self-regulatory, it is based primarily on a scientific assessment of potential hazards and exposure to fragrance materials by the scientific staff of the Research Institute for Fragrance Materials Inc. (RIFM) and subsequent evaluation by the RIFM Expert Panel, whose role has recently been strengthened. The International Fragrance Association uses conclusions from the process to issue a Standard, when needed, which can restrict or ban the use of an individual ingredient. The International Fragrance Association (IFRA) then disseminates the information worldwide to its national and regional associations, for subsequent distribution to member companies.

The Foundation: RIFM

RIFM, the independent scientific organization, evaluates the safety of fragrance ingredients. On the basis of the safety evaluations of over 1,000 materials by the body, IFRA has banned or restricted the use of nearly 100 substances. The IFRA rulings, originally called guidelines, and recently renamed "Standards," are binding for its members. These determinations reflect the industry's stewardship and are interpreted to have the same legal value as other sources of law, such as legislation. The process is transparent in that RIFM publishes in open scientific literature, its group summaries and individual fragrance material reviews (formerly called ingredient monographs). In addition, IFRA distributes its Standards within its membership, among major customer associations in the United States, Europe and Asia, and other stakeholders, while also publishing them on the organization's public web site.

RIFM was formally chartered as a non-profit, international organization on April 12, 1966, and is based in New Jersey. RIFM is administered by a board of directors, which meets four times a year and is elected by the general membership during its annual meeting. Membership categories include "active," for those companies primarily engaged in the manufacture and/or sale or distribution of fra-

grance materials at other than the retail level; "supporting," for those companies at the retail level of consumer products using or consisting of fragrance or fragrance ingredients; and "associate," for those companies engaged as brokers or dealers in the fragrance industry.

RIFM's stated vision is: "To be the international scientific authority for the safe use of fragrance materials." Its stated mission is: "Engage in research and evaluation of fragrance materials through an independent Expert Panel; determine safety in use; gather, analyze and publish scientific information; distribute scientific data and safety assessment judgments to RIFM members, industry associations and other interested parties; maintain an active dialogue with official international agencies."

The primary objectives of RIFM are: "Gather and analyze scientific data from the industry and the open literature; engage in the evaluation and testing of fragrance ingredients; review and evaluate the standards and methods employed by the industry for testing on a continuous basis." RIFM has a comprehensive research and testing program in the areas of fragrance allergy, respiratory safety, human health and environmental methodology, group safety evaluations, and use level support. Results of RIFM-sponsored studies are published in open, peer-reviewed scientific literature. In addition to sharing data with official international agencies, RIFM actively works with international industry associations. RIFM also maintains, for its members, the most extensive technical database of human health effects, environmental fate and product regulations on flavor and fragrance ingredients. All scientific efforts are reviewed by an independent Expert Panel (REXPAN) of academic dermatologists, toxicologists and environmental

^a Further specifics are available in the References section.

scientists. Conclusions of REXPAN on safe use, drawn from critical evaluation of all available hazard data and exposure information provided by industry, form the basis for Standards issued by IFRA.

The Next Step: IFRA

IFRA was founded in Geneva in 1973 to represent the collective interests of the fragrance industry worldwide with the predominant aim of ensuring the safe use of fragrance materials for the consumer and the environment. The organization has offices in Brussels and Geneva, and is administered by a board of directors on which all ordinary member associations are represented. The general assembly is the governing body of IFRA. Each national delegation/ordinary member has one vote. The general assembly meets at least once a year. IFRA membership is open to all countries or regions and currently comprises the national/regional associations of fragrance manufacturers from Australia/New Zealand, Europe, the Far East, and North and Latin America. Since there is no company membership in IFRA, individual fragrance companies belong to IFRA through its member associations.

Activities: The main thrust of IFRA's activities consists of developing, communicating and implementing a Code of Practice for the international fragrance industry. The Code of Practice provides Standards of good operating practice and product safety. Amendments and updates are issued on a regular basis. Specifically, actions occur through:

- development and implementation of a Code of Practice and Standards for the good manufacture and safe use of fragrances, based on broadly recognized scientific principles and utilized worldwide with the final objective to protect the consumer and the environment
- promotion of the self-regulatory practices of the industry, in keeping with the idea that the adaptation of worldwide industry rules to new scientific findings can occur more quickly through self-regulation, as opposed to a change of legislation in different countries on different continents
- analysis and review of pending regulation applicable to fragrances, as well as legislative trends in related areas such as cosmetics, intellectual property, chemicals, and occupational health and safety
- development and maintenance of open communication and cooperation with national and international government bodies, concerned members of the medical and scientific community, the customer industry (e.g. cosmetics or household products and detergents), and other stakeholders
- dissemination of timely and comprehensive information to membership on matters of relevance to the industry
- promotion of the merits of fragrances and the role they play in enhancing the quality of life

Evaluation Process

The primary goal of safety evaluation and management is to ensure the safe use of fragrance materials. Objectives are to strengthen the scientific opinion provided by REXPAN and to further improve the global recognition of IFRA Standards, in particular with scientific advisors to regulators and interested parties. The process gains transparency through publication of the REXPAN conclusions and of the underlying science in peer-reviewed literature. Steps in the process include the following:

1. A new or revised Standard may be prompted by RIFM, REXPAN, IFRA, official agencies or other stakeholders. IFRA requests will identify the specific material(s) and question(s) to be addressed, which ultimately will result in the rationale for selection of critical effect and acceptable level of exposure to be used in the Standard.
2. RIFM is responsible for setting priorities, and consults with IFRA and interested parties during the process.
3. RIFM compiles the necessary information primarily through a current search of its flavor and fragrance database and open literature. Identified data gaps become part of RIFM's research and testing program. The IFRA scientific committee (SC) supplies exposure information, which includes production volume, application and use data.
4. A draft "fragrance material dossier" is prepared by RIFM for REXPAN review of hazard and exposure. Any further information is requested by REXPAN and RIFM may consult with the IFRA SC.
5. As REXPAN evaluates the draft dossier, additional expertise may be used through outside "adjuncts," such as in the area of genetic toxicology, inhalation science, environmental fate, dermatology, reproductive toxicology and chemistry. (F-1 describes the sequence of events, from request to adoption.)
6. REXPAN's conclusion includes definition of the critical effect and a safety evaluation based on reported use. Current conclusion statements include one or more of the following (which may be amended in the future due to ongoing quantitative considerations):
 - recommended no action or Standard
 - recommended no change to the Standard (there is a general five-year review of all Standards)
 - determined "effect" to be the critical effect,

such as “sensitization,” which is detected through an induction (primary prevention) assay

- decision was based on an effect level of, or a no-effect level of “x”
- using an uncertainty factor of “y”
- while no changes are recommended, suggests shortened review cycle
- based on the fact that “effect” (such as irritation) is easily detected and is considered to be self-limiting
- date

7. RIFM communicates the dossier, along with REXPAN’s conclusion, to the IFRA secretariat.

An IFRA Standard is drafted that is consulted through the IFRA SC, IFRA member associations and the client industry regarding implementation.

8. If being of relevance and able to alter the earlier REXPAN conclusion, results of the consultation phase are included in a proposed final wording of the Standard that is then communicated to RIFM for REXPAN approval.

9. REXPAN adopts the final wording of the Standard, which is communicated via RIFM to the IFRA SC. (The main elements of the process are described in F-2.)

10. IFRA is responsible for the publication and enforcement of the Standard, following the procedure listed below. (T-1 is a sample IFRA Standard format, showing synonyms, history, limits in finished product, contributions from other sources, critical effect, REXPAN conclusion and references.) While in the past all Standards were published and distributed in written form within the membership and interested parties, they are now disseminated in electronic form and are also available on the IFRA Web site (www.ifraorg.org).

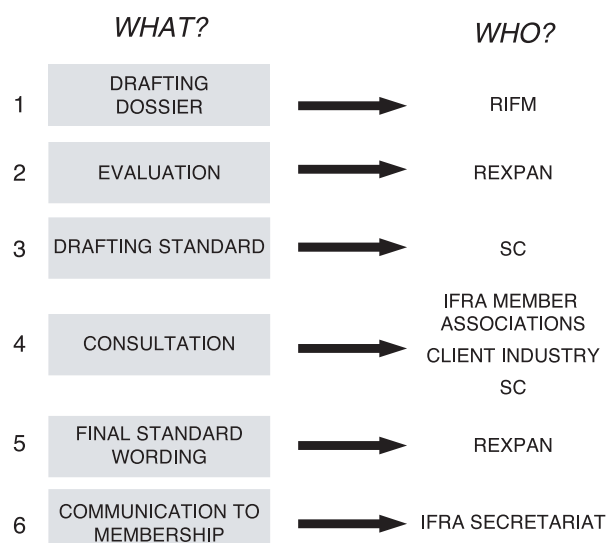
IFRA Standard process

F-1

- Three Scientific Committee meetings/year
- Request to RIFM for safety evaluation
 - Current use conditions
 - Usually skin sensitization
- REXPAN review
- Human Repeated Insult Patch Test
 - Phased approach to panelist exposure
 - No-effect level
- REXPAN conclusion
- Draft IFRA Standard
- Consultation phase
- Final Standard language and rationale
- Adoption/communication_{F3}

Elaboration of a Standard

F-2



Compliance Considerations

All major international fragrance manufacturers belong to IFRA and obey the IFRA Standards, even though they are not formal pieces of legislation. Although a voluntary approach for the non-IFRA members, these Standards are binding for all members of the association, all of whom understand that compliance with the Code of Practice and Standards is conditional for membership.

The cosmetic industry, which the fragrance industry supplies with materials, does not belong to IFRA. In Europe, however, certificates of conformity to be established by cosmetics companies in accordance with the agreement between the European Cosmetics Industry Association (COLIPA), the European Detergent and Cleaning Products Association (AISE), and the European Fragrance and Flavor Association (EFFA, which is a member association of IFRA) require that consumer products comply with the Cosmetics Directive and the IFRA Code of Practice, thus encouraging cosmetics companies to follow the IFRA standards. Client companies expect that their fragrances comply with IFRA Standards; therefore, they may be considered to materially assume the role of an external auditor.

This is a collective effort to properly manage fragrance ingredients and to support their safe use. A more canonized interpretation might hold that the sources of law are fourfold and comprise doctrine, legislation, case-law and sectoral practices. IFRA Standards can be considered to belong to the latter source, and, by declaring that sectoral practices have the same legal value as any of the other sources of law and therefore do not require legislation, the voluntary compliance approach is further strengthened.

The IFRA Code of Practice is comprehensive and applies to the manufacture and handling of all fragrance materials for all types of applications. The Code formulates the basic principles, which should be standards of good operating practice by the fragrance industry. Future

Basic Info

CAS#: 4360-47-8; 1885-38-7

Empirical formula: C₉H₇N

Synonyms: cinnamionitrile (mixed isomers); cinnamic nitrile; cinnamionitrile (E); trans- α -phenylacrylonitrile; 2-propenenitrile, 3-phenyl-, (E)-

History

Initial reviews: Not applicable, new standard

Current revision date: Not applicable

Implementation date: July 3, 2002 for new submissions;* July 3, 2003 for existing fragrance compounds*

Next review date: July 2007

Standard: Restricted

Limits in the Finished Product

Skin contact products (leave-on): 0.125 percent

Skin contact products (rinse-off): 0.125 percent**

Non-skin contact products: 1.25 percent

Purity: Not applicable

Others: Not applicable

Contribution from other sources: None known

Critical effect: Human skin sensitization

RIFM Summaries

There are two human repeated insult patch tests with a 2.5 percent solution of cinnamyl nitrile in specially denatured alcohol (SDA) 39C that show that the material is a sensitizer (RIFM, 1965; 1980). In two different groups of subjects tested with a solution of 1.25 percent cinnamyl nitrile in SDA 39C, no sensitization reactions were induced (RIFM, 1966; 1977). Based on the results of these studies, the no observed effect level (NOEL) was determined to be 1.25 percent. Using the 10-fold uncertainty factor, the maximum skin level concentration calculates to be 0.125 percent. For non-skin contact products, the concentration should not exceed 1.25 percent.

REXPAN Rationale/Conclusion

The sensitization data for cinnamyl nitrile were reviewed by the RIFM Expert Panel, which concluded that the NOEL for sensitization was 1.25 percent. These data support a maximum dermal skin level of 0.125 percent.

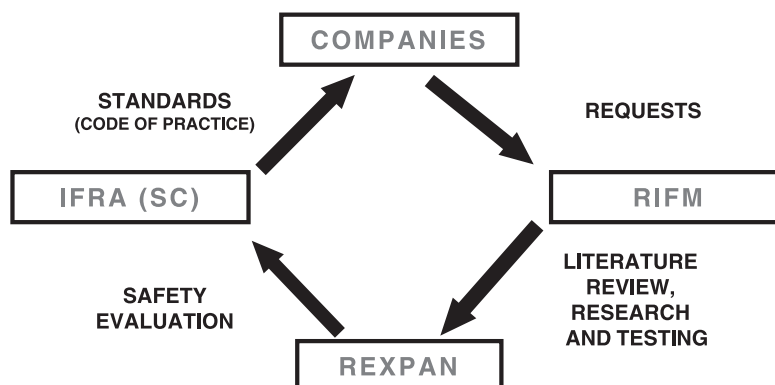
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^bFurther information available via Reference section.

^{*}This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

^{**}Including household cleaning products.



developments in the industry may require supplementation, revision or adaptation from time to time. The application of this Code of Practice does not dispense individual manufacturers from the obligation to comply with all national or international regulations, which are relevant to their operations.

The IFRA Code of Practice contains a self-policing chapter. In practice, if and when IFRA is informed about a suspected infringement to the code, the staff investigates the facts and contacts the parties in question, as required. In the few cases that have arisen in the past, a satisfactory resolution has been achieved. However, the IFRA board maintains the ultimate sanction of expulsion.

Communication

Recently, the IFRA board adopted an updated communication process, consistent with the roles of all parties involved in development, evaluation and distribution of IFRA Standards.

- After the Standard's wording has become final, the IFRA secretariat communicates the notification of the new or revised Standard to the membership of IFRA (national and regional associations), with a copy to RIFM.
- The communication indicates the date of entry into force (effective date of the notification), which is four weeks after the date of the dissemination of the Standard by IFRA for new submissions, and one year later (unless otherwise provided) for existing fragrance compounds (end of the transition period). The notification itself is regarded as an amendment to the IFRA Code of Practice and carries the appropriate amendment number. The communication mentions

that the Standard will appear on the IFRA Web site six months after the notification date, and that compliance with the Standard is mandatory. It requests that the member associations immediately inform their members.

- Two weeks after the communication to the IFRA membership, the IFRA secretariat informs major client trade associations. The information contains the date of entry into force for new submissions (notification date), and the date by which existing fragrance compounds must be modified.
- Once the work required to comply with the new Standard is well under way, the amendment is published on the Web site, normally six months after the date of the notification to the IFRA membership (unless otherwise provided). The Web site shows dates of entry into force and placement on the Web site. It further indicates whether the Standard is new or amended, and with which amendment of the IFRA Code of Practice the Standard has been introduced.
- Interested regulatory bodies are informed of all changes to the Standards.

In the course of this process, fragrance producers are reminded of the importance of communication with their customers, to ensure that customers are aware of the consequences of a change to the IFRA Standards and to provide them modifications for continued compliance. Wording of such communication is encouraged to include:

- Date of issue and amendment number of the new Standard(s)
- Date of appearance on the Web site (six months later)
- Date for compliance of existing fragrances (12 months after notification)
- List of fragrances affected and program of notification
- Request for product type and concentration, if unknown, for compliance verification

Summary

Available data forms the substance for beginning the safety evaluation process. Published and sponsored studies are summarized by RIFM for critical evaluation by its Expert Panel. Exposure information provided by the industry, through IFRA, is used to reach a conclusion of appropriate use levels, and whether or not a new or revised IFRA Standard is required. A consultative step ensures review by technical experts, the client industry and interested parties. Once a final conclusion is reached, and/or an IFRA Standard, IFRA communicates with national and regional associations worldwide for implementation of safe use practices. Compliance is encouraged throughout the supply chain by a system of notifications and potential enforcement action.

The safety evaluation approach applied to IFRA Standards can be characterized as: interactive, such that any scientist in the process who wishes to contribute has an opportunity to do so; transparent, as all the conclusions of RIFM and IFRA are publicly available; working, since the past has demonstrated the initiative to restrict and ban ingredients; and efficient, striving to prevent problems linked to the transposition of conflicting directives into national legislation, as Standards are simultaneously and internationally applied. F-3 models the process after the National Academy of Sciences' description of hazard identification, exposure assessment and risk characterization. In this way, technical information sponsored by companies throughout the chain of commerce is critically evaluated through an independent function, such that safety conclusions are delivered to all interested parties for product management.

Readers are referred to the supplied references for more technical descriptions of discrete elements of the process. More specifically described are the research prioritization process for human health and environmental effects, the characterization of exposure, decision trees and criteria for safety evaluation, and the publication of summaries and individual dossiers for chemically related groups of fragrance materials. The importance of exaggerated human exposure

considerations should be noted, where total volume of use and "top 10," or 97.5th percentile, use exposures are used as predictors. The effort culminates in peer-reviewed publications, which openly document the evaluations.

Address correspondence to Ladd Smith, Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ 07677.

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