



# SAFETY EVALUATIONS IN THE FRAGRANCE INDUSTRY

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## Abstract

The Research Institute for Fragrance Materials (RIFM) was formed in 1966 to analyze, evaluate and distribute scientific data, cooperate with official agencies and encourage safety standards for the use of fragrance ingredients. All scientific findings are evaluated by RIFM's independent, international Expert Panel (REXPAN). REXPAN's evaluations are used by the International Fragrance Association (IFRA) to develop standards on fragrance material usage. RIFM maintains the largest database available on fragrance materials, classifying more than 2600 materials. RIFM's safety evaluation process is modeled after the National Academy of Sciences' Elements of Risk Assessment and Risk Management (NRC, 1994). Criteria for development of a database for safety evaluation of fragrance materials (Ford, et al., 2000) provides a method to establish a database based on chemical structure, quantity of use and consumer exposure. A Framework for prioritizing fragrance materials for aquatic risk assessment (Salvito et al., 2002) supplements human health criteria with physicochemical properties and annual volume of use to predict environmental concentrations. Consumer exposure to fragrance ingredients: providing estimates for safety evaluation (Cadby et al., 2002) explains how to estimate a maximum level in products through patterns of use and fragrance material concentrations. The Safety assessment of fragrance materials (Bickers et al., 2003a) presents chemical groupings and decision trees for dermatological, systemic and environmental endpoints, to conclude safety under reported conditions of use. The risk management paradigm is completed when REXPAN publishes a Group Summary on structurally representative material, and Fragrance Material Reviews (FMRs) on individuals within the group (RIFM Toxicologic and Dermatologic Assessments of Linalool and Related Esters When Used as Fragrance Ingredients. (Bickers et al., 2003b).

## RIFM VISION STATEMENT

TO BE THE INTERNATIONAL SCIENTIFIC AUTHORITY FOR THE SAFE USE OF FRAGRANCE MATERIALS

## RIFM MISSION STATEMENT

ENGAGE IN RESEARCH AND EVALUATION OF FRAGRANCE MATERIALS THROUGH AN INDEPENDENT EXPERT PANEL

DETERMINE SAFETY IN USE

GATHER, ANALYZE AND PUBLISH SCIENTIFIC INFORMATION

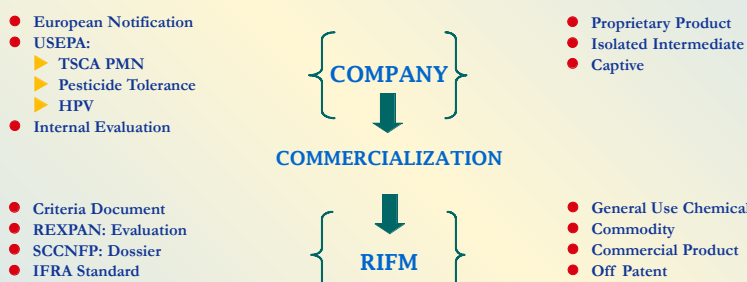
DISTRIBUTE SCIENTIFIC DATA AND SAFETY ASSESSMENT JUDGMENTS TO RIFM MEMBERS, INDUSTRY ASSOCIATIONS AND OTHER INTERESTED PARTIES

MAINTAIN AN ACTIVE DIALOGUE WITH OFFICIAL INTERNATIONAL AGENCIES

## IMPORTANT PUBLICATIONS

- Two criteria documents establish the basis of RIFM's priorities for research and testing fragrance ingredients (and group summaries).
- In addition, these documents establish the basis for RIFM's Proactive Program.
  - Criteria for development of a database for safety evaluation of fragrance ingredients—Ford *et al.*, Regulatory Toxicology & Pharmacology, 31, 166-181, 2000
  - A Framework for prioritizing fragrance materials for aquatic risk assessment—Salvito *et al.*, Environmental Toxicology & Chemistry, 21, 1301-1308, 2002
  - Consumer exposure to fragrance ingredients: providing estimates for safety evaluation—Cadby *et al.*, Regulatory Toxicology & Pharmacology, 36, 246-252, 2002
  - The Safety assessment of fragrance materials—Bickers *et al.*, Regulatory Toxicology & Pharmacology, 37, 218-273, 2003
  - RIFM toxicologic and dermatologic assessments of linalool and related esters when used as fragrance ingredients—Food and Chemical Toxicology 41, 917-1027, 2003

## MATERIAL SAFETY: RESPONSIBILITY

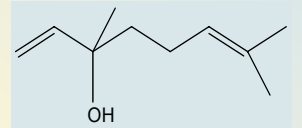


## RIFM TESTING PROGRAM—CHEMICAL GROUPINGS

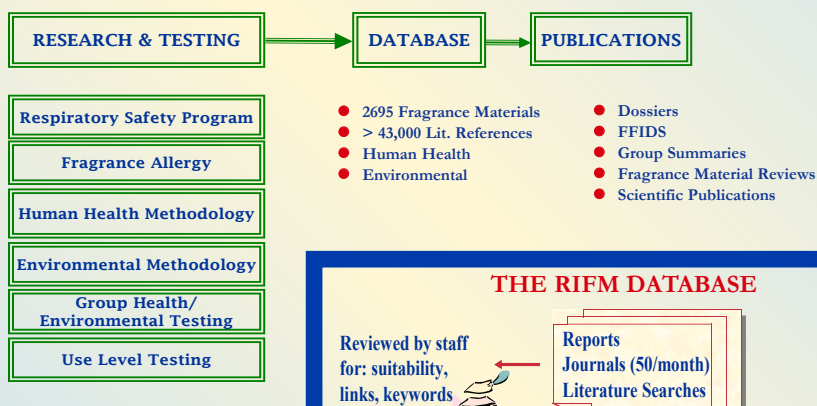
- A means to defend structurally related materials, without having to test every material in the group.
  - ~ 2,000 chemically defined fragrance ingredients
  - 22 Groups (e.g. Acids, Acetals, Alcohols)
  - > 150 Subgroups (e.g. Straight chain saturated, straight chain unsaturated etc.)

## A HIGH PRIORITY MATERIAL

- Linalool
- Structural Alerts
  - H2C=CCOH (topical, acute/systemic and carcinogenicity/mutagenicity effects)
  - Tertiary alcohols and their esters (acute/systemic effects)
  - Structural Alert Combined Score 2, 2, 6
- Volume of use >1000 metric tons (Score 16)
- Maximum Dermal use level 4.3% (fine fragrances) (Score 8)
- Total Score 34



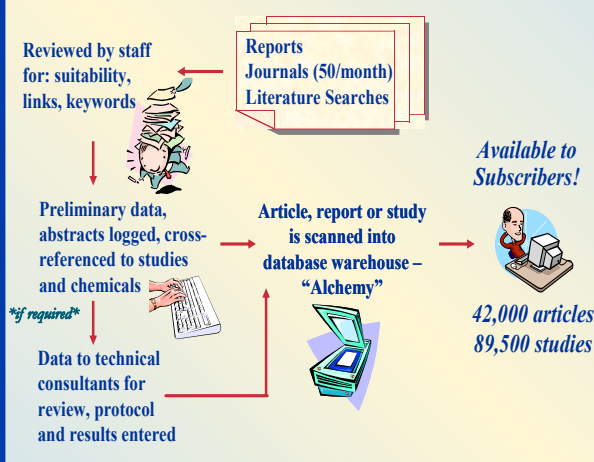
## RIFM SCIENTIFIC PROGRAM



## LINALOOL & RELATED ESTERS

- Low order of acute toxicity
- No significant toxicity in subchronic tests
- Negative in short-term mutagenicity tests
- Metabolic fate is either known or is assumed from analogies with structurally related substances that indicate no production of toxic or persistent metabolites and
- Structural analogies indicate no concerns
- In human dermatological studies: non-irritating, non-phototoxic, non-sensitizing
- Low levels of exposure relative to doses that elicit adverse effects. Safety factor is 167 times the maximum daily exposure for linalool and 500 times the maximum daily exposure for the linalyl esters even with the conservative assumption of 100% absorption.

## THE RIFM DATABASE



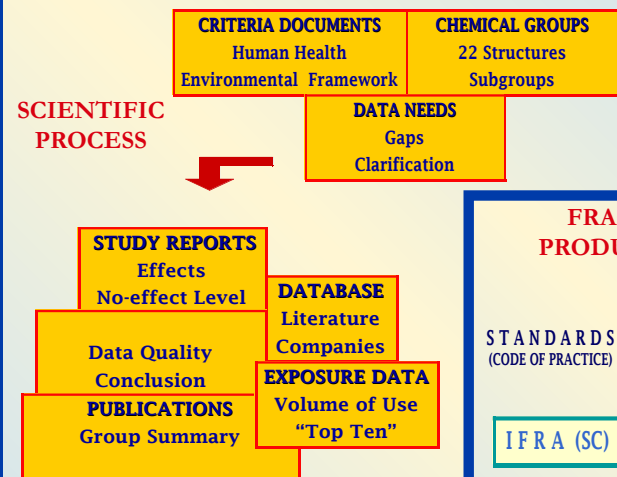
## RIFM PANEL OF EXPERTS

David R. Bickers, MD (Chair)  
Columbia University

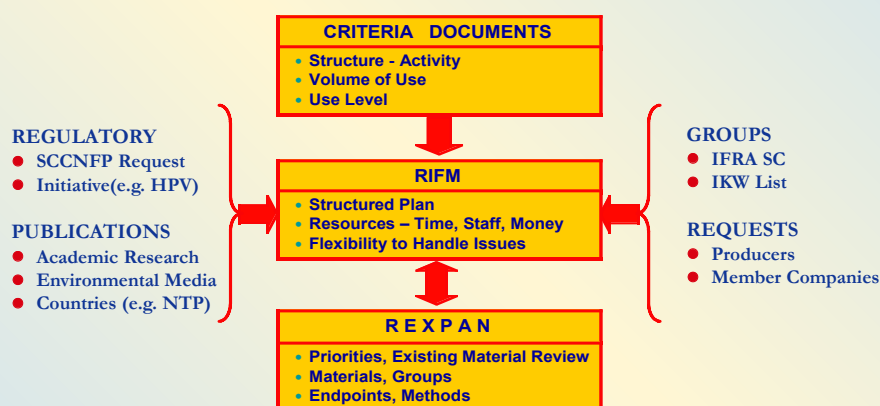
Donald V. Belsito, M.D.  
University of Kansas Medical Center  
Professor Magnus Bruze  
Malmo University Hospital  
Jon M. Hanifin, MD  
Oregon Health Sciences University  
Prof. Dr. Med. Helmut A. Greim  
Technical University of Munich  
Adrienne E. Rogers, MD  
Boston University School of Medicine

Prof. Robert L. Smith  
Imperial College School of Medicine  
Prof. Jean-Hilaire Saurat  
Universitaire de Genève  
Prof. Hachiro Tagami  
Tohoku University School of Medicine  
I. Glenn Sipes, PhD  
University of Arizona  
Prof. Peter Calow  
University of Sheffield

## SCIENTIFIC PROCESS



## RESEARCH PRIORITIES



## FRAGRANCE INDUSTRY PRODUCT RISK MANAGEMENT

