



RIFM: SAFETY ASSESSMENTS OF FRAGRANCE INGREDIENTS

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Journée Arômes & Parfums

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THE “NEW” IFRA

**Joint Executive Committee
Director General**





RIFM: VISION

April 2002

**To be the International Scientific
Authority for the Safe Use of
Fragrance Materials**



RIFM: MISSION

September 2002

- 1. Engage in research and evaluation of fragrance materials through an independent Expert Panel**
- 2. Determine safety in use**
- 3. Gather, analyze and publish scientific information**
- 4. Distribute scientific data and safety assessment judgments to RIFM members, industry associations and other interested parties**
- 5. Maintain an active dialogue with official international agencies**



RIFM INTERNATIONAL MEMBER CATEGORIES

ACTIVE (57)

Manufacture and/or sale or distribution at other than the retail level

SUPPORTING (16)

Manufacture for sale or distribution at the retail level of consumer products

ASSOCIATE (2)

Brokers or dealers engaged in a business related to the fragrance industry

- Conveys research theme
- Secure database access
- Growing awareness or presence. Members and non-members are submitting their questions through the web site.
- “White papers” section started
- More comprehensive site in test stage



The International Scientific Authority for the Safe Use of Fragrance

The Research Institute for Fragrance Materials (RIFM) evaluates and distributes scientific data on the safety assessment of fragrance raw materials found in perfumes, cosmetics, shampoos, creams, detergents, air fresheners, candles and other personal and household products. RIFM's safety evaluation process is modeled after the National Academy of Sciences Elements of Risk Assessment and Risk Management and all of RIFM's scientific findings are evaluated by an independent, scientific Expert Panel (REXPAN)—an international group of dermatologists, pathologists, toxicologists and environmental scientists.



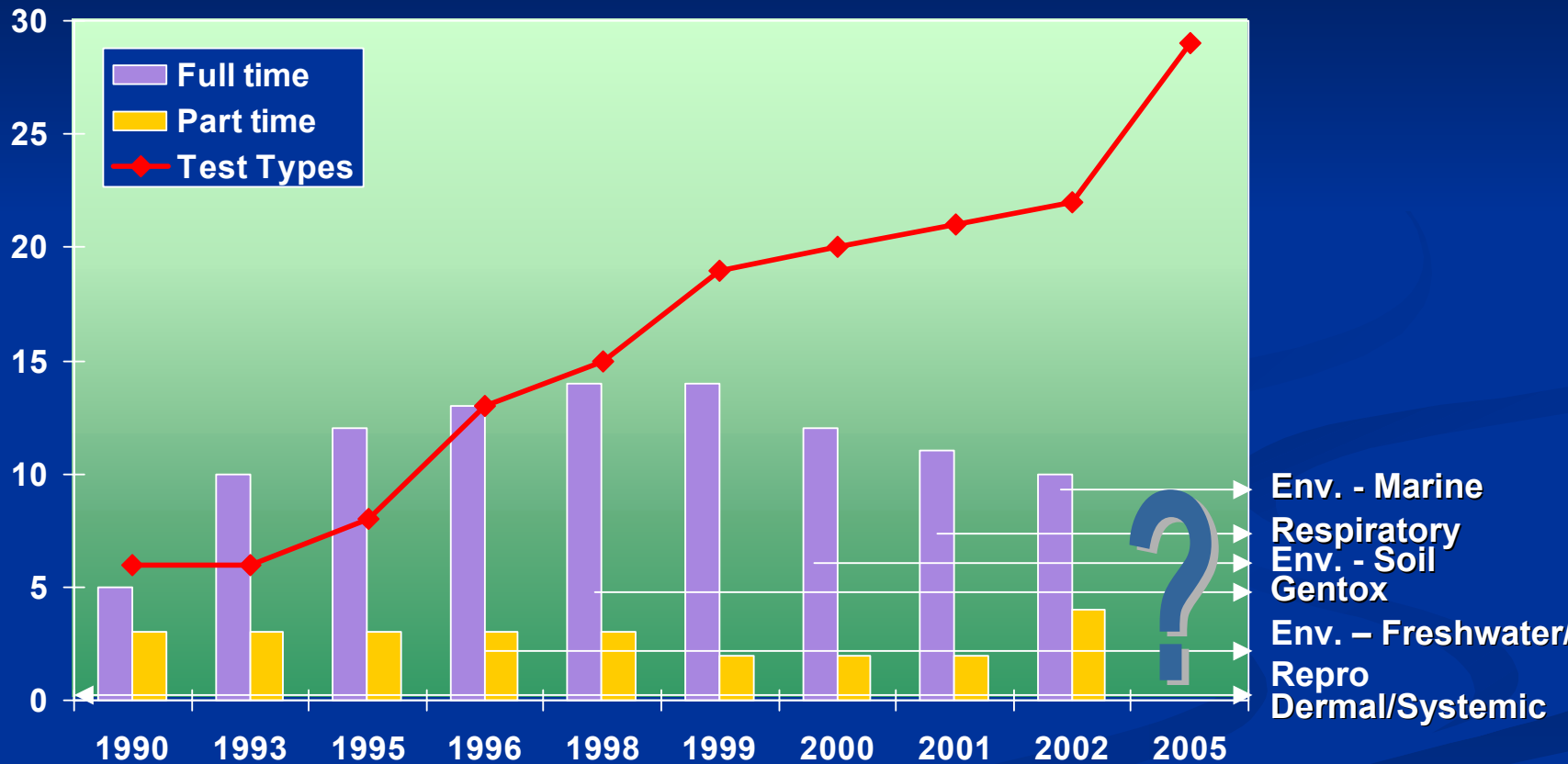


R I F M

The organization that tested for
“sensitization.”

We’re not just *“sensitization”*
anymore!

GROWTH OF STAFF & STUDIES





RIFM SCIENTIFIC PROGRAM

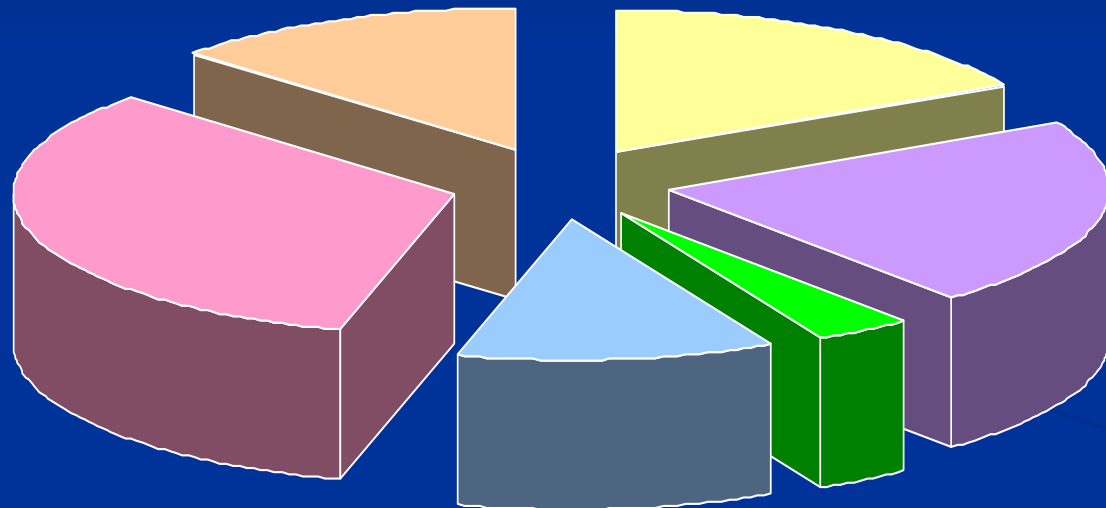
6 MAJOR FUNCTIONS

- **Research & Testing**
- **FFIDS**
- **Safety Assessments**
- **Database**
- **Publications**
- **Communication**

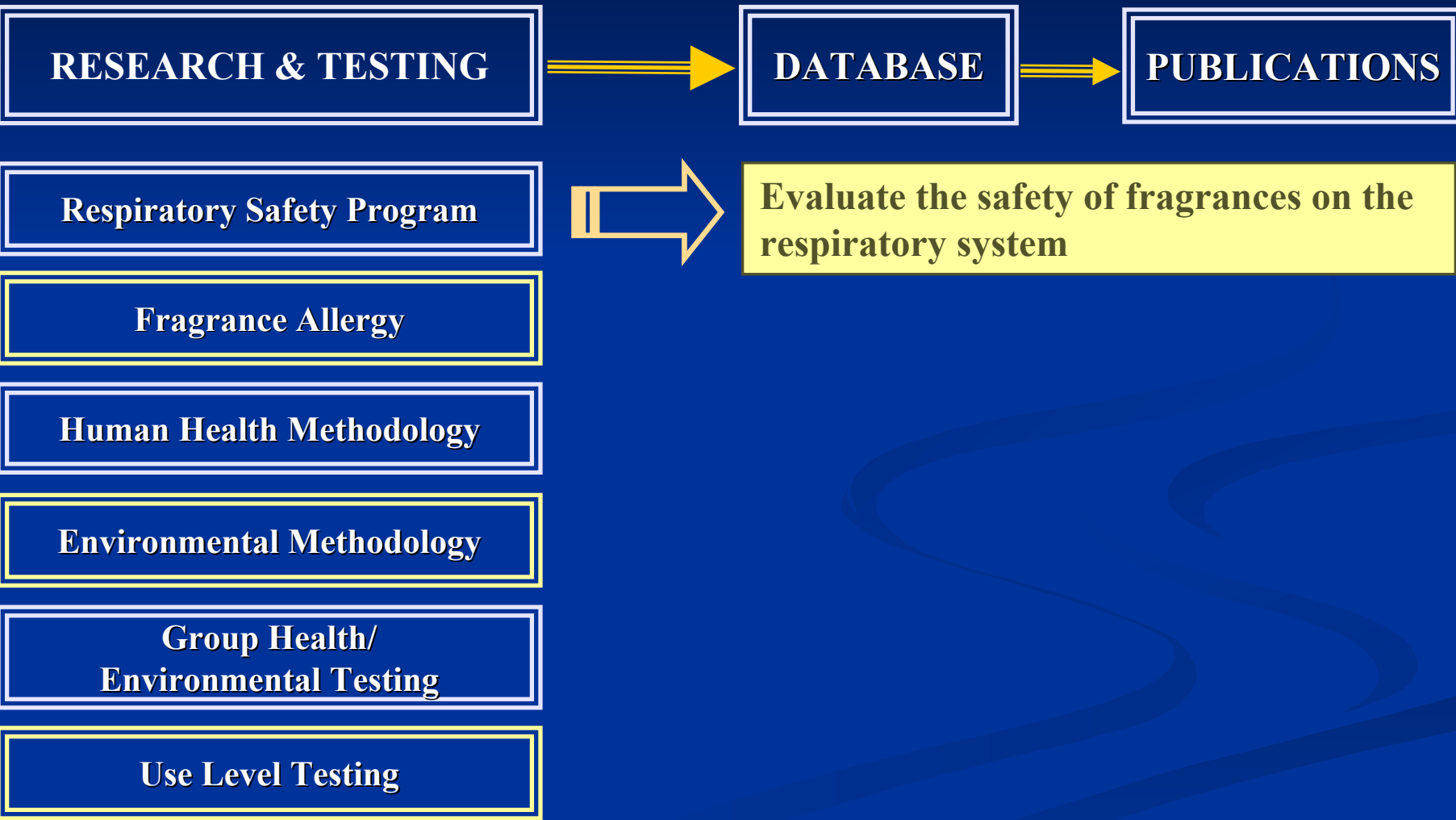


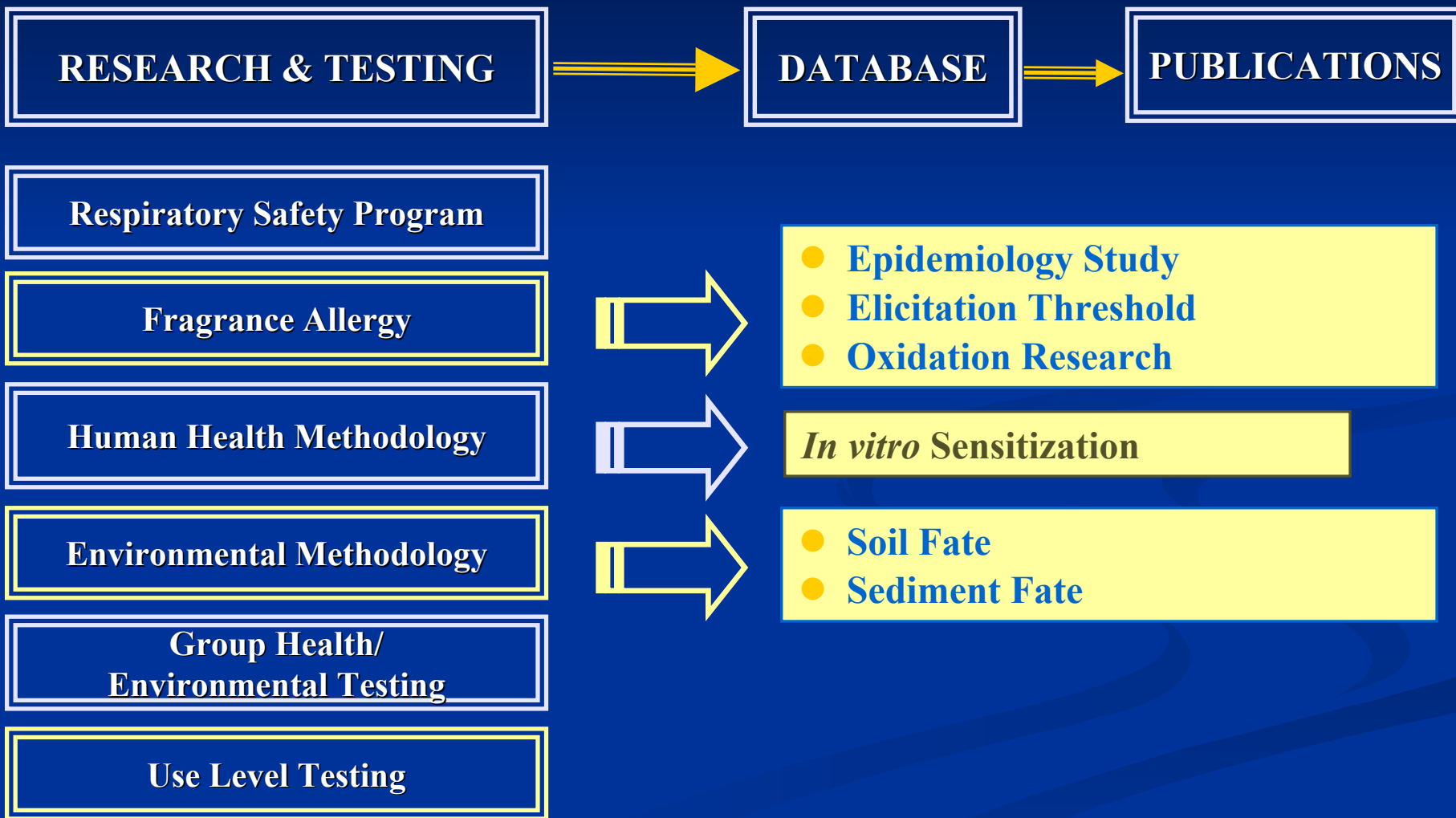
**Science
Support**

2004 RESEARCH & TESTING



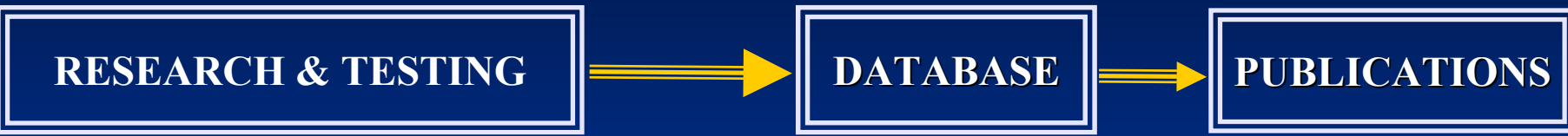
- Respiratory
- Fragrance Allergy
- Human Methods
- Environ. Methods
- Group Testing
- Use Levels







RIFM SCIENTIFIC PROGRAM



Respiratory Safety Program

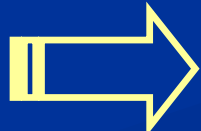
Fragrance Allergy

Human Health Methodology

Environmental Methodology

Group Health/
Environmental Testing

Use Level Testing

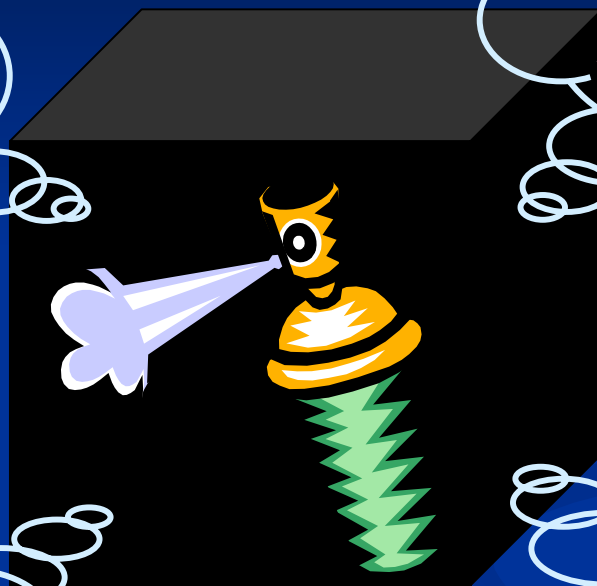


High priority materials (proactive program) – fill data gaps for multiple endpoints to allow completion of group summaries

Support of IFRA Standards

*HOW DOES RIFM
CONDUCT
SAFETY
EVALUATIONS?*

*HOW DOES RIFM
SELECT ITS
PRIORITIES FOR
RESEARCH AND
TESTING PROJECTS?*



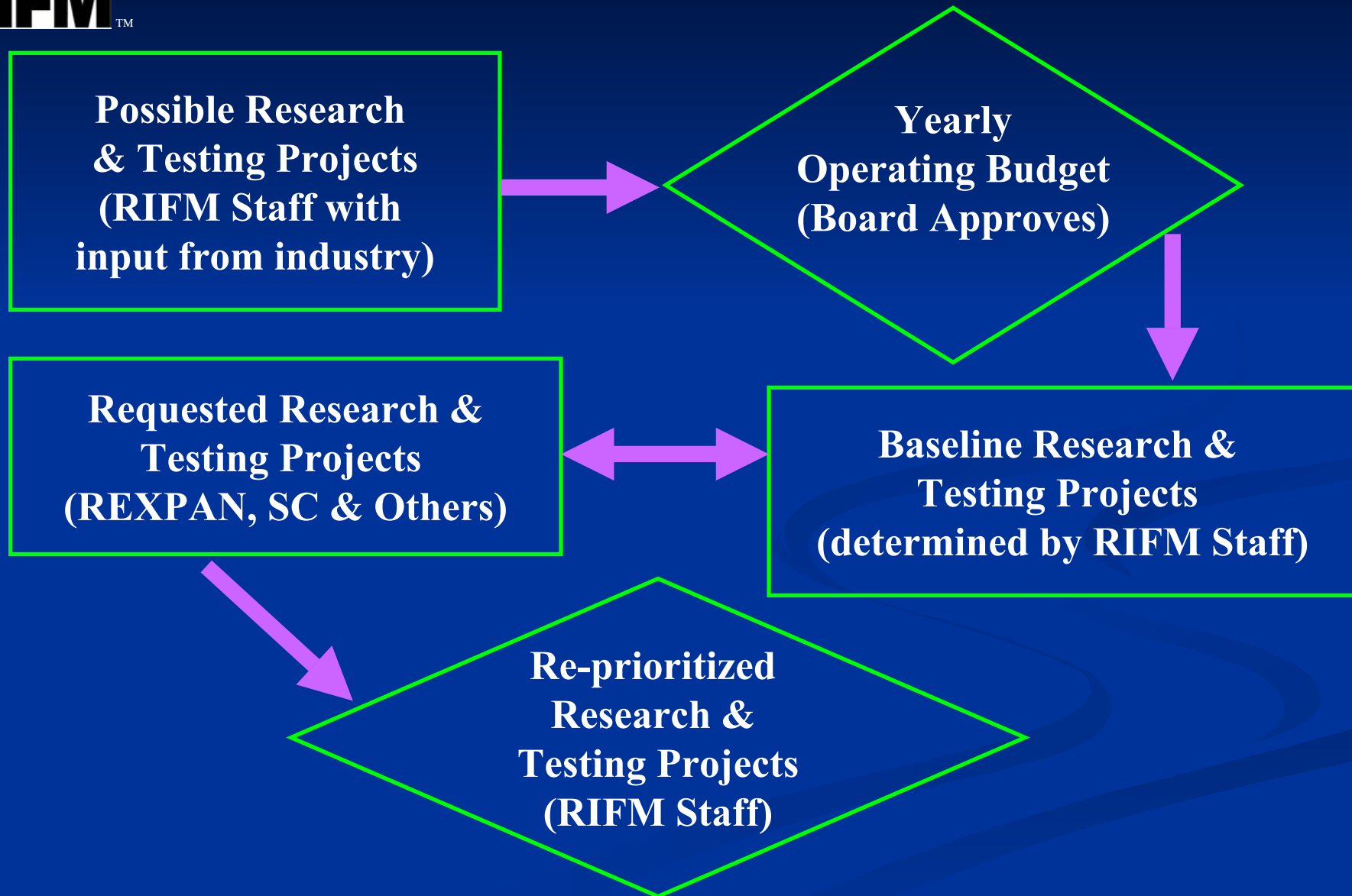
*HOW MANY
FRAGRANCE
MATERIALS DOES
RIFM EVALUATE?*

*WHAT IS THE EXPOSURE
TO FRAGRANCES?
HOW IS IT DETERMINED?*

FOUR IMPORTANT PUBLICATIONS

- *Human Health Criteria Document*
Reg. Tox. & Pharm., 31, 166-181, 2000
- *Environmental Framework Document* Env. Tox. & Chemistry, 21, 1301-1308, 2002
- *RIFM Expert Panel Safety Evaluation Process –*
Reg. Tox. & Pharm., 37 (2), 218-273, 2003
- *Industry Exposure Consideration Practices -* Reg. Tox. & Pharm., 36, 246-252, 2002

PRIORITY DECISION TREE





RIFM PRIORITIES

RIFM Proactive Program

- 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



RIFM TESTING PROGRAM

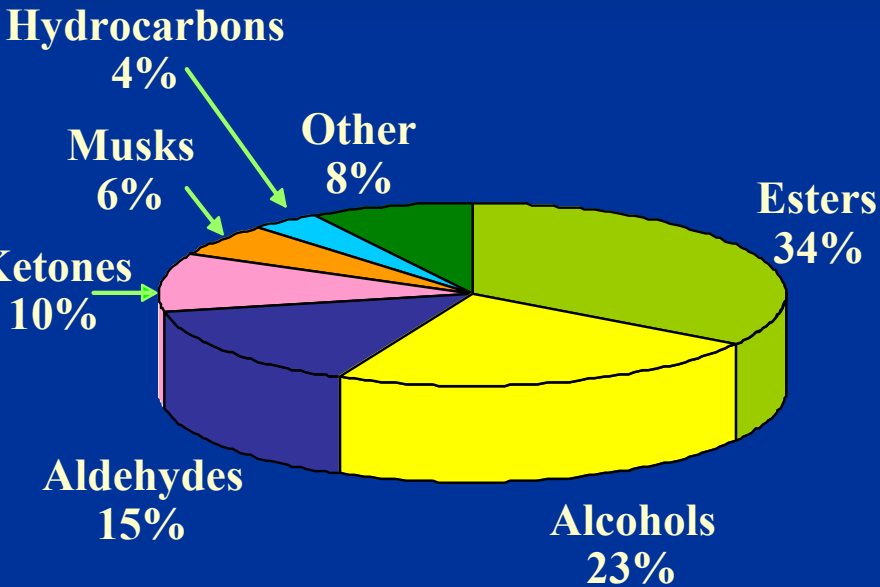
CHEMICAL GROUPINGS

- **A means to defend structurally related materials, without having to test every material in the group**
 - ▶ **~ 2,100 chemically defined fragrance ingredients**
 - ▶ **22 Groups (e.g. Acids, Acetals, Alcohols)**
 - ▶ **> 150 Subgroups (e.g. Straight chain saturated, straight chain unsaturated etc.)**

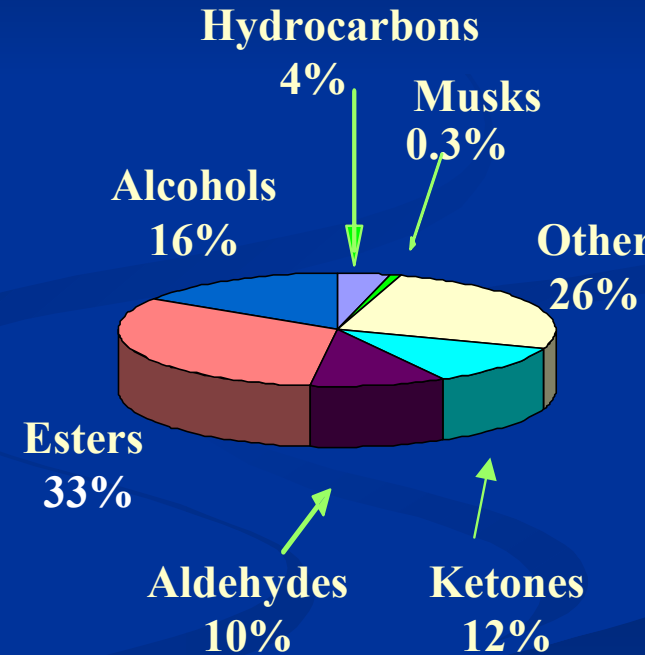


CHEMICAL CLASSES FOR FRAGRANCE MATERIALS

Volume of Use



Number of Materials

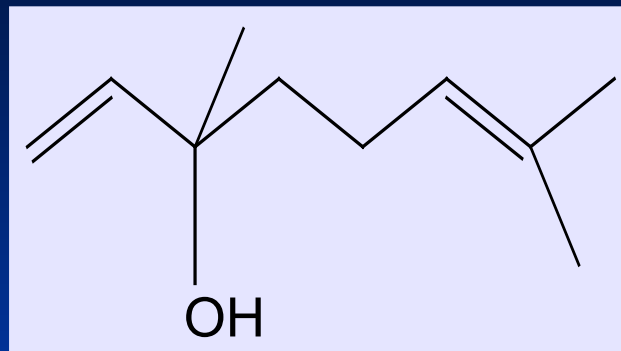


AMERICAN HEALTH CRITERIA DOCUMENT— *HOW DOES IT WORK?*

- **Considers dermal route as most relevant for fragrance ingredients**
- **Chemical structure reviewed for structural alerts**
- **Exposure**
 - ▶ **Volume of use**
 - ▶ **Dermal use**
 - ▶ **Consumer systemic exposure**

Linalool

Structural Alerts



- ▶ $\text{H}_2\text{C}=\text{CCOH}$ (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



CRITERIA DOCUMENT DIRECTS TEST PROGRAM & GROUP SELECTION

- High priority - linalool and linalyl acetate
- Linalool & Related Ester Group

Linalool

Linalyl acetate

Linalyl benzoate

Linalyl butyrate

Linalyl cinnamate

Linalyl formate

Linalyl hexanoate

Linalyl isobutyrate

Linalyl isovalerate

Linalyl phenylacetate

Linalyl propionate

- Evaluation of linalool will support linalyl ester group (11) AND terpene alcohol group (34)



LINALOOL & RELATED ESTERS

The Panel concluded “*there are **no safety concerns** regarding the materials in this group **under the present declared levels of use and exposure...***”



RIFM PANEL OF EXPERTS

- **David R. Bickers, MD (Chairman)**
Columbia University
- **Magnus Bruze, MD**
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. Peter Calow**
University of Sheffield, Dept. of Animal &
Plant Sciences
- **Jean-Hilaire Saurat, MD**
Universitaire de Genève
- **Donald Belsito, MD**
University of Kansas Medical
Center
- **Hachiro Tagami, MD**
Tohoku University
School of Medicine
- **I. Glenn Sipes, PhD**
University of Arizona
- **Prof. Robert L. Smith** Imperial
College School of Medicine
University of London



GROUP SUMMARY IMPACT

- For the first time, REXPAN makes a conclusion in a peer-reviewed, scientific publication (*Food & Chemical Toxicology*, 41 (7), 917-1028, 2003).
- Exposure data (from IFRA) is included.
 - ▶ Use Levels (dermal & systemic)
 - ▶ Worldwide Volume of Use (in ranges)
- Can the materials be used at higher levels? Yes, but the data needs to be reviewed again.
- Low volume materials will NOT need the same amount of test data.



CINNAMIC ALCOHOL, ACID & ALDEHYDE

Manuscripts were recently published in Food and Chemical Toxicology, Volume 43 (6) 2005.

The Panel concluded, “*there are **no safety concerns** regarding the materials in this group under the present declared levels of use and exposure for the following reasons:*”



CINNAMIC ALCOHOL, ACID & ALDEHYDE

- Low order of acute toxicity by the oral and dermal route of exposure
- Chronic tests reveal a NOEL of 200 mg/kg/day in rats and 550 mg/kg/day in mice after 2 years of dietary administered *trans*-cinnamaldehyde
- No significant potential to produce genotoxic effects
- The metabolic fate of cinnamyl alcohol, cinnamaldehyde and cinnamic acid is well known in that the alcohol is transferred to the aldehyde which is further metabolized to the acid. Toxic or persistent metabolites are not formed



CINNAMIC ALCOHOL, ACID & ALDEHYDE

Low levels of exposure relative to doses that elicit adverse effects. **Safety factors > 5000** times the maximum daily exposure for all three materials even with the **conservative assumption of *in vitro* human percutaneous absorption data** (highest percent absorbed under occluded conditions).



CINNAMIC ALCOHOL, ACID & ALDEHYDE

In Human Dermatological Studies:

- **No irritation was observed with cinnamyl alcohol or cinnamic acid and the NOEL for irritation caused by cinnamaldehyde is 1.25%.**
- **Phototoxic and photoallergic effects have not been evaluated in humans, but concentrations as high as 1% cinnamaldehyde and 20% cinnamic acid did not produce skin changes indicative of phototoxicity or photoallergy in guinea pigs.**
- **The NOEL for sensitization caused by cinnamyl alcohol has been determined to be in the region of 4%; quenching was not verified for cinnamaldehyde - the NOEL for sensitization caused by cinnamaldehyde has been established at 0.5%; cinnamic acid is non-sensitizing.**



CINNAMIC ALCOHOL, ACID & ALDEHYDE

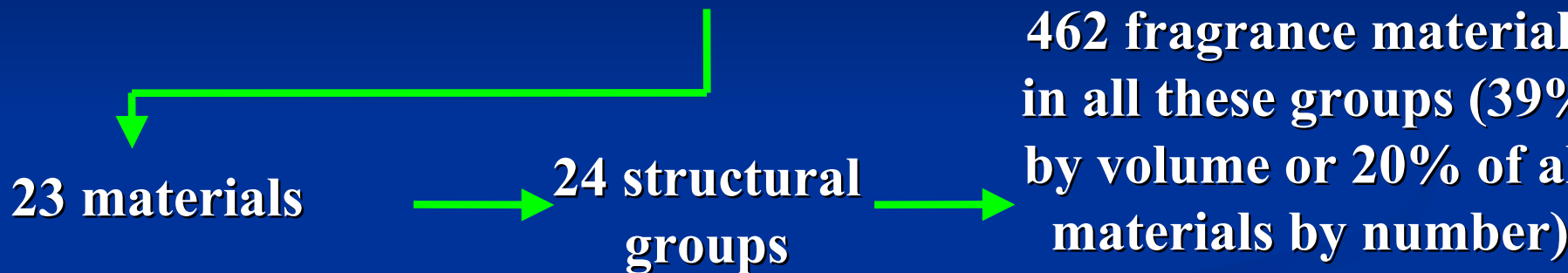
As a result of the sensitization findings:

- The IFRA Standard restricting the use of **cinnamyl alcohol** (based on its sensitization potential) has been lowered to **0.4% (leave-on and rinse-off products); 4% for non-skin contact products.**
- The IFRA Standard on **cinnamaldehyde** is completely different. Quenching was removed and the use of cinnamaldehyde is limited to **0.05% (leave-on and rinse-off products).**



IMPACT OF RIFM TESTING: 2002/3

\$880,988 for studies of discrete materials



- **Support IFRA Standards**
- **Building the database by filling data gaps**
- **Contributions to Group Summaries and FMRs**

SAFETY EVALUATION PUBLICATIONS

GROUP SUMMARY
Author: REXPAN

Safety
Evaluation

~~Monographs~~

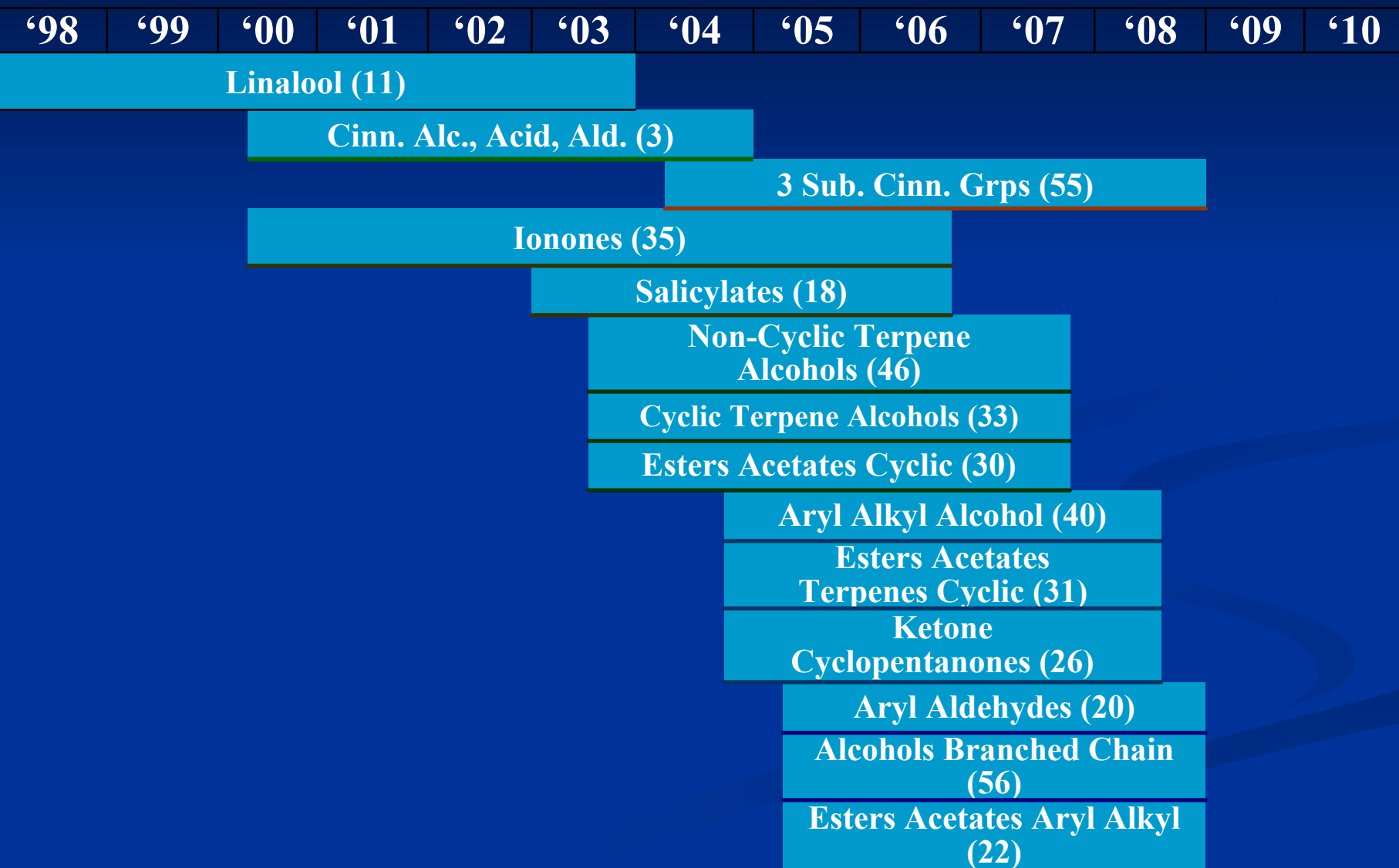
FMR
Author:
RIFM
STAFF

FMR
Author:
RIFM
STAFF

FMR
Author:
RIFM
STAFF

Material
Details

GROUP SUMMARIES (FMRs)



Understanding fragrance allergy using an exposure-based risk assessment approach

Understanding fragrance allergy using an exposure-based risk assessment approach

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¹The Procter & Gamble Co., Miami Valley Laboratories, Cincinnati, OH, USA

²St. John's Institute of Dermatology, St. Thomas' Hospital, London SE1 7EH, UK

³SEAC Toxicology Unit, Unilever, Colworth House, Sharnbrook, UK

G. FRANK GERBERICK,
MICHAEL K. ROBINSON,
SUSAN P. FELTER, IAN R. WHITE
AND DAVID A. BASKETTER

Conducting a sound skin sensitization risk assessment prior to the introduction of new ingredients and products into the market place is essential. The process by which low-molecular-weight chemicals induce and elicit skin sensitization is dependent on many factors, including the ability of the chemical to penetrate the skin, react with protein, and trigger a cell-mediated immune response. Based on our chemical, cellular and molecular understanding of allergic contact dermatitis, it is possible to carry out a quantitative risk assessment. Specifically, by estimating the exposure to the allergen and its allergenic potency, it is feasible to assess quantitatively the sensitization risk of an ingredient in a particular product type. This paper focuses on applying exposure-based risk assessment tools to understanding fragrance allergy for 2 hypothetical products containing the fragrance allergen cinnamic aldehyde. The risk assessment process predicts that an eau de toilette leave-on product containing 1000 ppm or more cinnamic aldehyde would pose an unacceptable risk of induction of skin sensitization, while a shampoo, containing the same level of cinnamic aldehyde, would pose an acceptable risk of induction of skin sensitization, based on limited exposure to the ingredient from a rinse-off product application.

Keywords: skin; allergic contact sensitization; fragrances; exposure; potency; risk assessment; margin of safety. © Munksgaard, 2001.

Accepted for publication 1 August 2001

For new products or product ingredients that contact the skin, it is necessary, prior to their introduction to the market, to conduct a thorough skin sensitization risk assessment to assure that the product will be well tolerated. The skin sensitization testing and risk assessment process for new ingredients and products generally follows a stepwise approach that may involve analytical assessments, preclinical skin sensitization testing, clinical testing, and benchmarking of resulting data against similar ingredients and product types. The details of these various elements and the overall process have been reviewed previously (1-5).

Critical to conducting a sound skin sensitization risk assessment is having a thorough understanding of ingredient exposure, as well as allergenic potency and dose response. Clearly, the potential for an ingredient to cause a skin sensitization response is dependent on a variety of other factors including, for example, the application vehicle system (6, 7), the number (8) and duration (9) of exposures, underlying skin irritation (10, 11) and the use of

occlusion (12). The importance of exposure and potency estimation in assessment of skin sensitization risk has recently been reviewed in a paper highlighting an exposure-based risk assessment process using methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) as a case study (5). The paper shows how one can judge the sensitization risk for different products containing MCI/MI using an exposure-based risk assessment approach.

This paper focuses on applying exposure-based skin sensitization tools to understanding the fragrance allergy potential for 2 distinct product types. Fragrance allergy is reported to be on the rise (13-16) and has received much attention recently regarding the skin sensitization risk of a number of specific perfume raw materials found in perfumes that are used in a variety of products. The goal of this paper is to illustrate how one can quantitatively evaluate the skin sensitization risk of a specific fragrance allergen by estimating the exposure and potency of the allergen under evaluation. It is important to note, however, that the

Based on induction of sensitization



QRA FOR DERMAL SENSITIZATION

Application to **induction** of skin sensitization - also a threshold phenomenon

- **Determine potential (hazard) to induce sensitization**
 - Pre-clinical studies e.g. Guinea-Pig Test, Local Lymph Node Assay (LLNA)
 - Human data (historical)
 - Structure based predictive approach
- **Dose Response**
 - Determine the No-Expected-Sensitization Induction-Level (NESIL) based on the Weight of Evidence (WoE)
 - Dose metrics: expressed in Dose/Area
 - Calculate Sensitization Assessment Factor (SAF)
- **Exposure**
 - Understand consumer exposure in different product categories
 - How consumer are exposed to a material in terms of amount, duration and frequency
- **Risk assessment conclusions**



DERMAL SENSITIZATION OF FMs

Current Practice

Based on qualitative scientific principles

TWO Product Categories

- Skin Contact = NOEL/10
- Non-Skin Contact = NOEL

QRA Approach

Based on general (quantitative exposure- based RA

Weight of Evidence approach to NOEL setting

Limits for different product categories

- Some more restrictive than before
- Some less restrictive than before



RIFM SCIENTIFIC PROGRAM

RESEARCH & TESTING

Respiratory Safety Program

Fragrance Allergy

Human Health Methodology

Environmental Methodology

Group Health/
Environmental Testing

Use Level Testing

DATABASE

- 4,557 Materials
- 2,600 Fragrance Materials
- > 48,000 Lit. References
- > 95,00 Studies
- Human Health
- Environmental

PUBLICATIONS

- Dossiers
- FFIDS
- Group Summaries
- Fragrance Material Reviews
- Scientific Publications

RESEARCH & TESTING

- Forefront of research
- Method development & Evaluation
- Safety Evaluation
- Support IFRA Standards

DATABASE

- Best centralized international collection
- Reduce testing & use of animals
- Member assistance

PUBLICATIONS

- Recognition by scientific & regulatory communities

CREDIBILITY



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graph TD; RT[RESEARCH & TESTING] --> C[CREDIBILITY]; DB[DATABASE] --> C; PUB[PUBLICATIONS] --> C;
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