INTERNATIONAL DIALOGUE FOR THE EVALUATION OF ALLERGENS

ANNUAL REVIEW: PROGRESS MONITORING

December 17th, 2014

IDEA
International Dialogue for the Evaluation of Allergens

Content

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

www.ideaproject.info

IDEA
International Dialogue for the Evaluation of Allergens

Introduction

The primary aim of the IDEA project can be summarised as 'to establish and adopt a transparent and robust risk assessment framework, based on the best available science, for the identification of use conditions of individual and mixtures of fragrances (alone and in different formulations) that will, when properly utilised, prevent induction and consequently skin sensitisation of all consumers and others who may be exposed'. This is a very challenging task and will inevitably take some considerable time to achieve. The starting point for this work was the RIFM QRA model published in 2007 and already in common use. The first target for IDEA has been to produce a revised interim version of this QRA (QRA 2) for review by DG SANCO within the first eighteen months.

The aims of IDEA will only be achieved through the development of effective collaboration and the continuing commitment by all stakeholders i.e. industrial scientists, dermatologists, academic scientists, regulators and consumer representatives. The focus of the first year of IDEA was to build this collaboration, to characterise the scope of the task, to identify priorities for action and by whom and how the actions should be taken forward. The main activity of the second year has been to develop QRA 2 and ensure that it was completed and submitted by the deadline of July 2014.

The **Supervisory Group (SG)**, which I have the privilege to chair, is an independent group of very experienced scientists whose role is to oversee and scrutinise the IDEA process to ensure that:

- The project remains founded on high quality, up to date science.
- There is active involvement of key experts in the field from different disciplines, organisations and countries.
- Through the workshops priorities are identified and actions taken to fulfil them.

In a project of this nature misunderstandings can arise from time to time and therefore transparency and a prompt response by the SG to concerns is crucial. To try to ensure complete transparency:

- The workshop participants and presenters are drawn from many disciplines and organisations and the discussions are open.
- The workshop report is produced by a member of the Supervisory Group and is circulated to all participants for their comments prior to it being made accessible to all stakeholders via the website without delay.
- Actions taken and progress towards completing them are published on the website.
- There is an annual meeting where stakeholder views are followed up with the active involvement of the Supervisory Group. This meeting provides a crucial opportunity to chart the best way forward.

Prof Jim Bridges
Chairman of the IDEA Supervisory Group

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IDEA ANNUAL REVIEW 2014

Progress monitoring

December 17th, 2014

1. Draft agenda
2. Attendance list
3. Presentation: The IDEA Project After Two Years (Prof. Jim Bridges)
4. Presentation: Refinement and Validation of the Dermal Sensitization QRA (Prof. Jim Birdges)
5. Presentation: Risk Assessment of Pre- and Pro-Haptens (Dr. Matthias Vey)
6. Presentation: Characterization of Fragrance Allergens – September 23-25th, 2014 (Dr. Ian R. White)
7. Key conclusions for the Annual Review (Prof. Jim Bridges)
8. IDEA Annual review 2014: key discussion points
9. Key conclusions from the Annual Review 2014 (agreed by the participants)

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Scientific work plan on allergens (project IDEA[1])
Annual Review: progress monitoring

Venue

Ground floor meeting room of the
EUROFORUM building (EUFO)
10 rue Robert Stumper, L-2557 **Luxembourg** (close to HTC building – cloche d'OR).

Meeting date: Wednesday 17 December 2014, starting at 10.00 AM

Draft Agenda

10.00-10.15 WELCOME AND OPENING BY THE COMMISSION (JOHN F. RYAN – DIRECTOR DG SANCO)

The IDEA project, initiated by industry, managed by an independent Supervisory Group, is politically supported by the Commission through an annual review. The project's objective, to develop high quality safety assessment in the area of fragrance allergens, is of key concern for the Commission.

10.15 – 10.30 THE IDEA PROJECT AFTER TWO YEARS (PROF. JIM BRIDGES – CHAIR OF IDEA SUPERVISORY GROUP)

The IDEA project is designed to provide a broadly agreed and transparent framework for assessing fragrance sensitizers globally via the development of strong partnerships between the international fragrance industry and its stakeholders. Two years after its official kick-off, this Annual Review should allow to monitor the progress made and identify the key priorities to be addressed.

10.30 – 11.15 REFINEMENT AND VALIDATION OF THE DERMAL SENSITIZATION QRA (PROF. JIM BRIDGES)

One of the four important tasks to be tackled by the IDEA project was the development of a systematic and scientifically-robust methodology to prevent consumers from getting sensitized to allergens. In that end, significant time and efforts have been dedicated to the revision of the Dermal Sensitization QRA. An interim report has been submitted to the EU Commission (DG Sanco – B2).

11.15 – 12.00 RISK ASSESSMENT OF PRE- & PRO-HAPTENS (DR. MATTHIAS VEY)

Based on the recommendations produced at the 2013 pre- & pro-hapten workshop, the IDEA Hydroperoxydes TF has been formed and convened for the first time on March 24th, 2014. A progress report on the discussions and main recommendations made by the experts represented in this task force will be presented along with a report of the actions taken so far.

[1] IDEA: International Dialogue for the Evaluation of Allergens

12.00 – 13.00 LUNCH

13.00 – 14.00 CHARACTERIZATION OF FRAGRANCE ALLERGENS – SEPTEMBER 23-25TH, 2014 (DR IAN WHITE)

A progress report on the discussions and main recommendations made by the experts who attended the workshop will be presented along with a report of the initiatives and actions taken so far.

14.00 – 14.20 THE COMMISSION'S EVALUATION OF THE IDEA PROJECT (IZABELA TABORSKA – DG GROWTH F3)

14.20 – 14.45 KEY CONCLUSIONS OF THE IDEA ANNUAL REVIEW 2014 (PROF. J. BRIDGES AND DR H BENDER)

14.45 – 15.00 INDUSTRY'S COMMITMENT TO CONTINUOUS DELIVERIES (MICHEL BONGI – CHAIRMAN IFRA)

15.00 – 15.15 CLOSING BY THE COMMISSION (STEFAN SCHRECK – HEAD OF UNIT DG SANCO)

MEETING: **SCIENTIFIC WORK PLAN ON ALLERGENS (PROJECT IDEA) – ANNUAL REVIEW : PROGRESS MONITORING**

MEETING DATE: **17 DECEMBER 2014 AT EUFO BUILDING (GROUNDFLOOR)**

NAME	Attendance	Signature
SCCS + external experts		
1. Dr. Ulrike BERNAUER	**confirmed**	
2. Prof. Pieter-Jan COENRAADS	**confirmed**	
3. Prof. Dr. Gisela DEGEN	**confirmed**	
4. Dr. Werner LILIENBLUM	**confirmed**	
5. Dr. Elsa NIELSEN	**confirmed**	
6. Prof. Thomas PLATZEK	**confirmed**	
7. Dr. Suresh Chandra RASTOGI	**confirmed**	
8. Dr. Jan van BENTHEM	**confirmed**	
9. Dr. Alfred Bernard	**confirmed**	

IFRA	Attendance	Signature
10. Mr Michel Bongi (chairman of IFRA Board)	**confirmed**	
11. Mr Rob Edelman (Chairman of IFRA EU executive committee)	**confirmed**	
12. Pierre Sivac, President International Fragrance Association (IFRA)	**confirmed**	

13. Dr. Matthias Vey Scientific Director (IFRA)	**confirmed**	
14. Charles Laroche, Senior Advisor Public Affairs (IFRA)	**confirmed**	
15. Cécile Gonzalez (IFRA)	**confirmed**	
16. Stephen Weller, Communication Director (IFRA)	**confirmed**	
17. Shawn Blythe (IFF),	**confirmed**	
18. Graham Ellis (Givaudan),	**confirmed**	
19. Boris Müller (Symrise),	**confirmed**	
20. Cristina Arregui (IFRA)	**confirmed**	

IDEA Governance (6)	**Attendance**	**Signature**
21. Prof. Jim Bridges (IDEA Supervisory Group, Rapporteur workshops 1 and 2)	**confirmed**	
22. Prof. Helmut Greim (IDEA Supervisory Group)	**confirmed**	
23. Dr. Alain Khaiat (IDEA Supervisory Group)	**confirmed**	

24. Dr. Ian White (IDEA Supervisory Group, Rapporteur workshop 3)	**confirmed**	
25. Mr Hans Bender (Moderator IDEA Workshops),	**confirmed**	
Academics and experts	**Attendance**	**Signature**
26. Dr. David Basketter (Consultant in toxicology)	**confirmed**	
27. Dr Alain Chaintreau (Firmenich)	**confirmed**	
28. Dr. Nicola Gilmour (Unilever),	**confirmed**	
29. Dr Christeine Lally (Procter&Gamble)	**Confirmed (replacing 53.PK)**	
30. Dr Maja Krasteva (L'Oreal)	**confirmed**	
31. Dr. David Lovell (University of Surrey)	**confirmed**	
32. Prof. Hans Merk (Universitätsklinikum Aachen, Germany)	confirmed	
33. Prof. David Roberts (Liverpool John Moores University and Member of the ex-SCCS WG on Fragrance Allergens participating in 1st workshop)	**confirmed**	
34. Dr. Bob Safford (Consultant)	**confirmed**	
35. Prof Axel Schnuch (IVDK/ University of Göttingen)	**confirmed**	

36. Benjamin Smith (Firmenich)	**confirmed**	
37. Prof. Wolfgang Uter, (University Erlangen)	**confirmed**	
38. Marc Vocanson (INSERM)	**confirmed**	
39. Prof Ann-Therese Karlberg (University of Gothenburg)	**confirmed**	
Key Downstream trade associations and NGO	**Attendance**	**Signature**
40. Gerald Renner (Cosmetics Europe)	excused - Replaced by 71. FS	
41. Florian Schellauf (Cosmetics Europe)	**Confirmed (replacing 72.GR and 71. PA)**	
42. Sylvie Lemoine (A.I.S.E.)	**confirmed**	

Representatives from Commission	**Attendance**	**Signature**
43. Mr John F. RYAN (SANCO C)	confirmed	
44. + 2 scientific officers (JRC), e.g. 45. Mrs Raffaella CORVI - JRC – ISPRA and Ms Valérie ZUANG - EURL ECVAM	Andrew Worth **confirmed**	
47. Mr Stefan Schreck (SANCO C2)	confirmed	
48. Ms Meroni Donata (SANCO C2)	confirmed	
49. Ms Natacha Grenier (SANCO C2)	confirmed	

50. Mrs Diana Herold (SANCO C2)	confirmed	
51. Mrs Izabela Taborska (SANCO B2)	confirmed	
52. Mr Gaetano Castaldo (SANCO B2)	confirmed	
53. Mrs Federica de Gaetano (SANCO B2)	confirmed	
54. Ms Petronille Bogaert (SANCO C2)	confirmed	
55. Mrs Martine Wampach(Lux)	confirmed	

IDEA Annual Review

The IDEA Project after two years

December 17th, 2014

Prof. Jim Bridges

Emeritus Professor of Toxicology and Environmental Health and Chair of the IDEA Supervisory Group

The aim of the IDEA Project

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To establish and adopt a transparent and robust risk assessment framework, based on the best available science, for the identification of use conditions of individual and mixtures of fragrances (alone and in different formulations) that will, when properly utilised, prevent induction and consequently skin sensitisation of all consumers and others who may be exposed.

Principal roles of the Supervisory Group (SG)

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To ensure that:

- The project remains founded on high quality, up to date science.
- There is active involvement of key experts in the field from different disciplines, organisations and countries.
- Priorities are identified through the workshops and task forces and actions taken to fulfil them.
- All relevant activities are transparent.

IDEA: Mode of operation

- Workshops with participants from many disciplines and organisations in which discussions are open. SG Reports are circulated to all participants for their comments and then put on the website.

- Actions taken as a result of each workshop and their progress are displayed on the website.

- The Annual Meeting enables the views of other stakeholder to be heard and addressed. It also provides a crucial opportunity to chart the best way forward.

IDEA - The first year

The focus of the first year of IDEA was to build an effective collaboration between stakeholders i.e. industrial scientists, dermatologists, academic scientists and regulators and to draw on this expertise to:

* characterise the scope of the task,
- identify the actions to be taken forward
- ensure that the agreed actions are implemented

IDEA – The second year

The priorities have been:

- To further improve effective collaboration between stakeholders
- To develop QRA 2 as an interim tool for the protection of consumers from skin sensitisation from fragrance ingredients and ensure that this was submitted by the deadline of July 2014 to DG SANCO.
- To identify key issues that meet the aims of IDEA

Conclusions on progress of IDEA in the first two years

- QRA 2 constitutes a significant improvement on the original QRA. It has benefitted enormously from the input of many academic and industrial scientists and clinicians who were involved in the original QRA.
- QRA 2 is an important interim step towards achieving the IDEA aim. There is much still to be done and a continuing input from all the stakeholders is crucial to achieving this.

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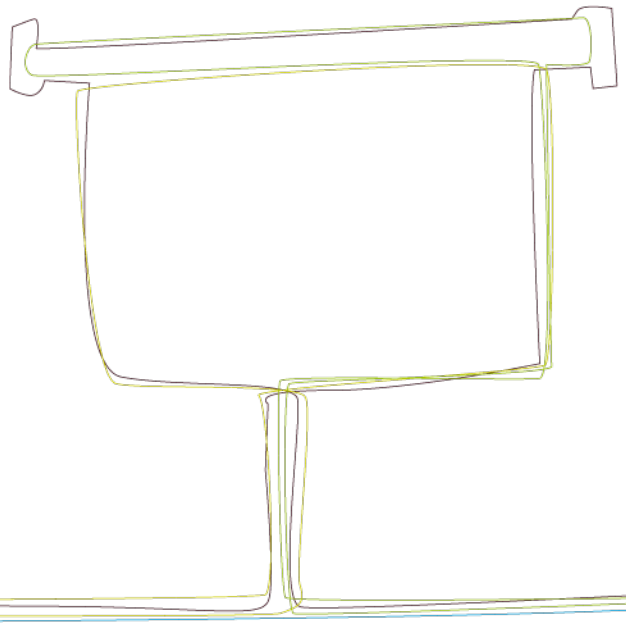
Thank you very much for your attention



IDEA Annual Review

Development of the dermal sensitisation QRA (QRA 2)

December 17th, 2014

Prof. Jim Bridges

Emeritus Professor of Toxicology and Environmental Health and Chair of the IDEA Supervisory Group

Background to the QRA

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In 2008, the fragrance industry published a detailed, exposure-based approach which was termed the Quantitative Risk Assessment (QRA) methodology (Api *et al*., 2008). This methodology has since been used to set worldwide limits (IFRA Standards) for fragrance ingredients which are potentially capable of sensitization. For all fragrance materials assessed for sensitization using the QRA methodology, more than 100 have been assigned such standards by IFRA.

Theoretical basis for QRA

Two stages in the development of skin sensitization:

a) *induction* during which contact allergy to the substance develops

b) *elicitation* leading to allergic contact dermatitis, following subsequent exposure to the substance in sensitized individuals.

Premise : Both stages have a threshold assigned. By prevention of induction, elicitation can be avoided (primary prevention).
The QRA aims at preventing the induction step to happen

QRA 1.

External exposure

(single product only)

↓

↓

SAF's

Hazard assessment

(LLNA)

(checked using HRIPT)

↓

NESIL

→ **CEL** → ↓ **AEL** ← ← ←

↓

SAF's

Risk assessment

Priorities for development of QRA 2

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- To consider the general appropriateness of the methodology;
- To carry out specific reviews of two important areas where completion within the initial two year time frame was considered achievable:

a) Review of each of the uncertainty factors (SAFs) ;

b) Introduce dermal aggregate exposure to replace the original individual product exposure assessment.

Aim for July 2014 (QRA 2)

External exposure

(aggregate for an ingredient)

↓

Revised **SAF's**

Hazard assessment

(LLNA)

(checked using HRIPT)

↓

NESIL

→ **CEL** → ↓ ← **AEL** ←

↓ Revised **SAF's**

Risk assessment

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Review of
SAFETY ASSESSMENT FACTORS (SAF)

SAF- **Inter-individual variability**

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* **General**: The Human Repeated Insult Patch Test (HRIPT) uses 100 or more healthy subjects of both sexes and a wide age range It is uncertain whether this is sufficient to allow for possible variations in consumer sensitivity.

* **Skin condition:** is more significant than age, sex and ethnicity. Subjects with diseased skin not necessarily more prone to the induction of skin sensitization. However, the generation of inflammation in skin, (particularly from contact with irritant substances) may increase sensitivity to skin sensitisers.

SAF's - Product effects

- **Vehicle / matrix**- The most common solvents used in the HRIPTs are diethyl phthalate/ethanol or petrolatum as they are considered to be optimal for the induction of sensitisation. Unclear whether enhancement of penetration promotes the induction of skin sensitisation.

- **Irritation by product**- Irritation caused by the product itself, during or following use, may increase susceptibility to the induction of skin sensitisation.

SAFs -Application conditions

- **Occlusion-** May result in multiple effects, including increases in the hydration of the stratum corneum, skin temperature, microbial count, pH, and dermal irritation. The HRIPT employs full occlusion.
- **Frequency/Duration-** Products may be used daily over periods of months or years). Unclear if sensitisation can be significantly increased if product use continues over longer periods.

Conclusion in QRA 2 on the SAFs

- **Interim status**. The SAF values still require additional examination and evaluation. The SAFs on frequency/duration and site inflammation versus product inflammation need to be further reviewed.
- **Application**. The product SAFs are calculated by multiplying the inter-individual variability, product effects, frequency and skin considerations/site SAFs.

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THE RIFM/Crème Model

AGGREGATE EXPOSURE TO INDIVIDUAL FRAGRANCE INGREDIENTS

Data needed to assess dermal aggregate exposure for consumers

- Frequency of product use (consumer habits)
- Skin sites of application of the products
- Amount per use of each product
- Chemical concentration of fragrance ingredient in the product
- Retention factor
- Subject bodyweight and height
- Surface area of product application body sites

Exposure assessment

- The measurement of exposure ('dose metric') is dose/area (µg/cm^2).
- Applied dose and delivered dose can differ due to losses from evaporation, binding/ sequestration in the skin (particularly in the stratum corneum with subsequent loss through exfoliation) and metabolism (inactivation and activation).

NB The applied dose is used as a conservative estimate of actual consumer exposure.

The Dermal Aggregate Exposure Model

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- Based on real habits and practices from 36,446 panelists across Europe and the USA. Each panelist supplied diary data on which products they used during the day for seven consecutive days, as well as the application sites of most products.
- This data has been used to create a statistical representation of the population whose product usage habits are as close as possible to the real population

Conservative aspects of the model

- Uses the worst day of exposure (e.g. the day with the highest use) for each panelist in the database.
- Aggregate exposure for each body part is calculated by summing all exposures to each individual body part over a 24 hour period (even though washing or other factors may remove some earlier product).
- Selection of 95th percentile for each body part as the value to be used.

.

The aggregate exposure model

Uses custom built software system to enable probabilistic exposure calculations.

* It determines exposure per unit area of skin for a defined body site to a particular fragrance.

- It estimates the exposure from each fragrance in a variety of products and aggregating these across all body sites.

NB In order to consider dermal aggregate exposure in the QRA, the body site SAFs need to be aligned with the list of application sites from survey data.

Current status of QRA 2

- Report sent to DG-SANCO/JRC in July 2014. It comprise 120 pages, 21 tables and 13 figures.
- In addition to setting out the methodology and using worked examples of its application, it also proposes next steps in optimising risk assessment.
- Work to ensure scientifically justified SAF are available by May 2015 is taking place.

Current status of QRA 2

If we want things to stay as they are, things will have to change

Di Lampedusa in The Leopard 1957

IMPROVEMENTS NEEDED IN QRA 2

- Other sources of exposure should be considered for a number of fragrance ingredients
- Evidence of the effectiveness of the QRA 2 in preventing sensitisation among consumers is needed
- Suitable replacement(s) for the LLNA test are urgently required

Conclusions on QRA 2

- Good progress has been made in developing the methodology due to excellent collaboration.
- The methodology for the QRA 2 is now comparable with those used for the risk assessment of other effects of human exposure to chemicals.
- Areas for further work have been identified.
- Relevant data to check on the impact of the QRA on the prevention of adverse effects in consumers in the real world is needed

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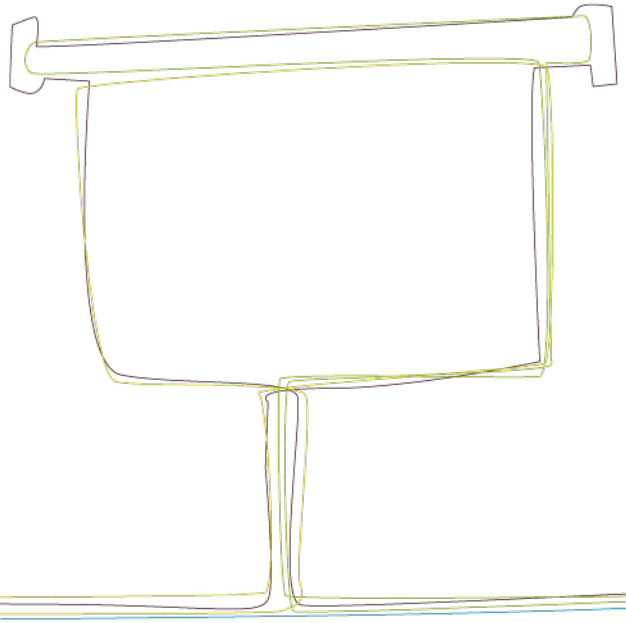

IDEA Annual Review

Risk Assessment of Pre- & Pro-Haptens

2014 Update

Matthias Vey – IDEA Management Team

Alain Chaintreau
Chair of the IDEA Hydroperoxide TF

Definitions of Pre- & Pro-haptens

- A **hapten** is a small low molecular weight molecule that can induce and elicit an immune response.

- **To be effective, a hapten needs to:**
  a. Gain access in sufficiently high concentrations to the target protein(s) responsible for triggering the induction of skin sensitization.
  b. React with these target protein(s) without also causing marked cellular damage.

The difference between pre- & pro-haptens

- **Pre- & pro- haptens** are hapten precursors and are often non-sensitizing themselves.

- A pre-hapten is a substance that needs to be chemically (**abiotically**) activated.

- A pro-hapten is a substrate for biotic activation (often involving the so-called drug-metabolising enzymes).

Key conclusions of 2013 WS

- There is clear qualitative indication that sensitizers can be formed in some formulations under realistic conditions as a result of abiotic hydrolysis of fragrance ingredients. The importance of biotic hydrolysis in the epidermis will require further investigation.

- Contact allergy (positive patch-tests) to oxidation products of some fragrance ingredients (like Linalool or Limonene) is common. There is presently insufficient data on exposure to these oxidation products to make a correlation to disease (allergic contact dermatitis).

Key conclusions of 2013 WS

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- On biotic and abiotic oxidation, the data available show the complexity with great challenges for predictability and analytical testing.

- The models do not sufficiently reflect exposure conditions or co-factors that interfere with sensitization.

- The development of new analytical methodologies such as HR MAS-NMR is a key requirement to clarify in situ phenomena.

Priorities identified during 2013 WS

- Identify and characterize the actual consumer exposure from all sources to fragrances and closely related structures.
- Select and ensure the general availability of a suitable range of pure reference fragrance ingredients.
- Develop new analytical techniques for the detection and quantification of haptens derived from pre/pro-haptens (e.g. hydroperoxides) in fragranced consumer products and biological media (e.g. skin).
- From a clinical perspective, focus on pre- and pro-haptens that have been well characterized in laboratory studies.

High Resolution-Magic Angle Spinning Nuclear Magnetic Resonance

HR-MAS NMR

HR-MAS NMR Project

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Research project with University of Strasbourg (J-P Lepoittevin)

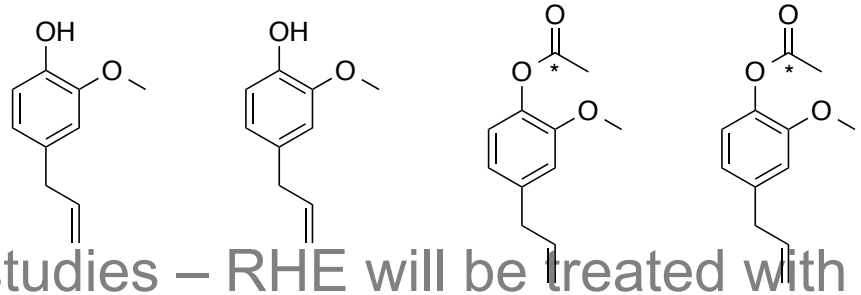
Pilot study to investigate if HR-MAS NMR (High Resolution-Magic Angle Spinning Nuclear Magnetic Resonance) spectroscopy in association with Reconstructed Human Epidermis (RHE) could be used to follow and characterize the metabolic transformation / activation of pro-haptens and their subsequent interactions with epidermal proteins (nucleophilic residues on amino-acid side chains)

HR-MAS NMR Project

- **Study materials**: Eugenyl acetate, Isoeugenyl acetate
- **Rationale**: Eugenol and Isoeugenol are used as pure materials but also in form of esters such as acetates. Clinical studies have shown that individuals sensitized to the parent material also reacted when patch tested with the ester – mechanism underlying this observation is still not clear, even so there is the hypothesis that the esters are hydrolized either enzymatically (epidermal esterases) or chemically (hydrolysis).
- **Aim**: initial phase to assess the potential of the HR-MAS NMR / RHE model to investigate and characterize the behavior of the study materials in a living tissue.

HR-MAS NMR Project

- Synthesis of 13C substituted eugenyl- and isoeugenyl acetates



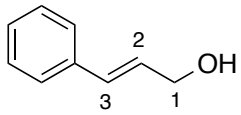
- Qualitative studies – RHE will be treated with the above mentioned materials and samples analyzed at 24h by HR-MAS NMR spectroscopy for identification of hydrolysis products. Experimental options for quantification of released acetate will be investigated
- Time/response and dose response of the 13C samples on RHE will be investigated to characterize the enzymatic / hydrolysis reaction

HR-MAS NMR Project

- **Study material**: Cinnamyl alcohol
- **Rationale**: Cinnamyl alcohol is considered as the model of pro-hapten being activated by alcohol dehydrogenase to form cinnamaldehyde – however, about half of the patients sensitized to cinnamyl alcohol do not react when patch-tested with cinnamaldehyde – strongly suggesting that at least one alternative metabolic pathway is taking place in human epidermis activating cinnamyl alcohol into an unknown reactive hapten
- **Aim**: initial phase to assess the potential of the HR-MAS NMR / RHE model to investigate the metabolism of cinnamyl alcohol in living tissue

HR-MAS NMR Project

- Synthesis of carbon-13 substituted cinnamyl alcohol



1-(^{13}C)
2-(^{13}C)
3-(^{13}C)

- Initial metabolic studies
  RHE will be treated with with the carbon-13 substituted material and samples analysed at 24h by HR-MAS NMR to characterize the formation of cinnamic aldehyde in RHE and check if other metabolites are formed.

HR-MAS NMR Project

- Project started in July 2014 and mid term will be reached in December 2014.

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Develop suitable SAR tool(s) to identify likely pre- and pro-haptens

Develop suitable SAR tool(s) to identify likely pre- and pro-haptens

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- RIFM collaborates with Prof. Ovanes Mekenyan, Department of Physical Chemistry, Laboratory of Mathematical Chem., University of Bourgas, Bulgaria
- A SAR for pre- and pro-haptens is part of a model called the TIMES SS (Tissue Metabolism Simulator Skin Sensitization), parts of which are incorporated in the OECD Toolbox.
- RIFM has a license for the TIMES SS model and agreed with Prof. Mekenyan to identify specific refinements to the SAR rules. It is not envisioned that a new tool needs to be added, but rather a review and potential refinement of the SARs that already exist in the model.
- Plan to be completed by the end of 2015.

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Scheduled: Study to better understand Pro-hapten Metabolism

Pro-hapten metabolism study

- Research Project with the Leibnitz Institute for Environmental-Medical Research, Düsseldorf, Germany
- Most of the mechanisms proposed for the activation of pro-haptens in the skin are based on theoretical knowledge and have not been experimentally demonstrated
- The fact that a chemical is a good substrate for a defined enzymatic system and is forming reactive intermediate(s) able to react with nucleophilic residues is not a demonstration that the same pathway is taking place in the skin

Pro-hapten metabolism study

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- The study shall demonstrate a possible approach to assess the role of pro-hapten metabolism in the formation of a hapten in allergic reactions to small molecular weight compounds
- A protocol has been provided beginning of December and is undergoing review.
- The project, which could become a model for studying further compounds, is planned to start in 2015

Synthesis and quantification of hydroperoxides

IDEA Hydroperoxides TF

- First meeting March 24, 2014
- Team from the Academia and the Industry
  - Jean-Marie Aubry — University of Lille
  - Anna Börje — University of Gothenburg
  - Hugues Brevard — Robertet
  - Michael Calandra — Firmenich
  - Alain Chaintreau — Firmenich; chair (also of IFRA-AWG)
  - Elena Gimenez — University of Strasbourg
  - Ann-Therese Karlberg — University of Gothenburg
  - Clémentine Marteau — IFF
  - Andreas Natsch — Givaudan
  - Ulrika Nilsson — University of Stockholm
  - Neil Owen — Givaudan
  - Veronique Rataj — University of Lille
  - David W. Roberts — University of Liverpool
  - Matthias Vey — IDEA Management Team

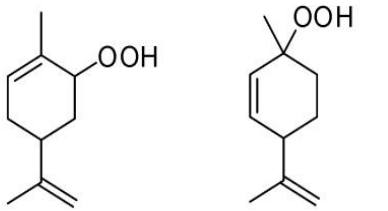
Objectives

- Ensure the general availability of a range of pure reference materials resulting from abiotic transformation
- Because some products may be unstable, investigate for the half life as well as any other parameters related to their conservation
- Use the reference materials to develop an analytical method for the reliable detection and quantification of chemically defined haptens resulting from abiotic transformation
- Methods should be sensitive, specific, with target limits of quantification below the estimated induction levels and limits of detection below the estimated elicitation levels
- This analytical method is critical for the subsequent execution of *in vitro* / biological assays and clinical investigations

Targeted analytes

- Oxidation products from
  - Limonene, Linalool, Linalyl acetate and Citronellol
- Selection based on
  - Consumer exposure, oxidation potential
  - Existing knowledge and great difference of skin sensitization potency between parent compound and hapten
- Priority (strong skin sensitization potency)

  Linalool and Limonene hydroperoxides



***cis/trans*-Limonene-2-OOH EC3 = 0.83%** | *cis/trans*-Limonene-1-OOH EC3 = 0.33%

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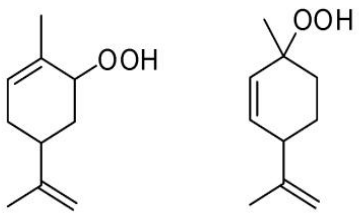

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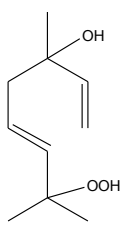
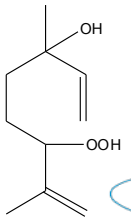


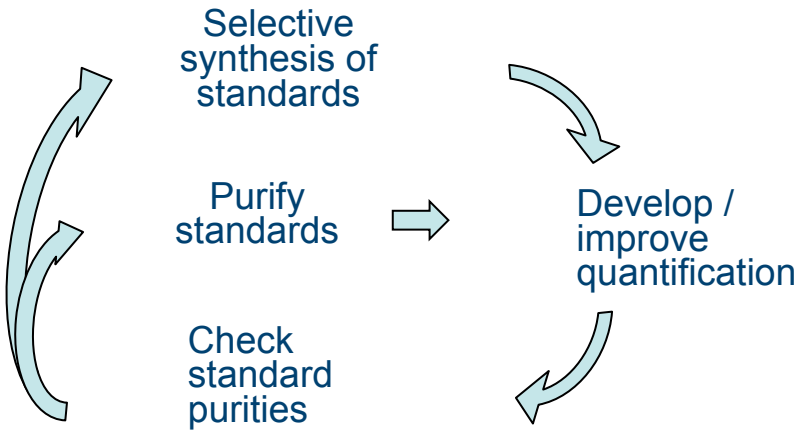
Linalool-7-OOH
EC3 of 5:3 mixture = 1.6%



Linalool-6-OOH

Synthesis

- Two potential manufacturers
  - Contract signed with Greenpharma S.A.S., Orléans (F)
- Preparing pure standards → an iterative process



- Feasibility study in progress
  - 4 isomers to be prepared separately
    - Limonene-1- and -2-OOH, and linalool-6- and -7-OOH
    - Expected purity: > 95%

Expected method performances

- Selectivity towards the hydroperoxides, or convenient means to locate hydroperoxides in a chromatogram
- (Once the calibration of hydroperoxides has been achieved) use of recorded (relative) responses to avoid the further use of standards
- Alternatively, if these two criteria cannot be met by a single method, several methods would be developed if each of them meets one of these criteria
- Methods based on a spectrometric detection should comply with the state-of-the-art practices. Notably, the identity of quantified peaks should be checked to avoid analyte confusion and detect coelutions

Level of detection needed

- *Target set: "Methods should be sensitive, specific, with target limits of quantification (LOQ) below the estimated induction levels and limits of detection (LOD) below the estimated elicitation levels"*

- Estimated induction levels:
  - Linalool-OOH 16'000 ppm in LLNA [1]
  - Limonene-2-OOH 8300 ppm in LLNA / 15'000 ppm in guinea pigs [2,3]
  - 5000 ppm maybe taken as a default induction level

- Estimated elicitation level:
  - Linalool: Lowest elicitation level in humans = 560 ppm * [4]
  - No data on limonene in humans, Lowest elicitation level in guinea pigs = 3000 – 10'000 ppm [3]

  * Patients in elicitation study were exposed simultaneously over three weeks twice daily to a 5640 ppm dose on same arm, LOEL for elicitation may thus be clearly higher under realistic application of single low dose.

- Note: Above levels are final levels in a preparation. If a fragrance oil or raw material is considered, dilution factor in product must be taken into account

[1] M. Sköld, A. Börje, E. Harambasic, A. T. Karlberg, *Chemical Research in Toxicology* **2004,** *17*, 1697-1705.
[2] S. Johansson, E. Gimenez-Arnau, M. Grotli, A. T. Karlberg, A. Borje, *Chem Res Toxicol* **2008,** *21*, 1536-47.
[3] A. T. Karlberg, L. P. Shao, U. Nilsson, E. Gafvert, J. L. Nilsson, *Arch Dermatol Res* **1994,** *286*, 97-103.
[4] Y. Andersch Bjorkman, L. Hagvall, C. Siwmark, B. Niklasson, A.T. Karlberg, J. Brared Christensson, *Contact Dermatitis* **2014,** *70*, 129-38.

Quantification method comparison

- Objective: testing the performances of published and unpublished methods
- Five participants = five different methods
  - LC-TOFMS using a calibration curve
  - LC-MSMS using a standard addition
  - LC-Chemiluminescence
  - GC-MS (after reduction in the case of limonene-OOH)
  - GC-derivatization
- Identical samples were sent to all participants
  - Orange oil: 1 blank + 2 samples spiked limonene-OOH
  - Lavender oil: 1 blank + 2 samples spiked linalool-OOH
  - Coded samples (blind test)
- Results shared with the hydroperoxide-TF but not yet discussed
  - Next meeting: end of January 2015

Preliminary learnings

- A combination of methods could be required to quantify:
  - At all concentrations (induction and NOEL levels)
  - Different hydroperoxides
- Methods not yet satisfactory but one step has been achieved
  - Quantification feasible at known induction levels
  - With some methods also at lowest observed elicitation level
  - Determination of standard purity
  - Pure standards required to refine the methods at low levels

→ More work is required ←

Future steps

- Once fully developed, the quantification methods of pre- & pro-haptens will be used to monitor the market:
  - First to gather useful information on actual consumer exposure
  - Then to ensure the level of haptens (e.g. hydroperoxides) in marketed products is acceptable.
- Further raise awareness of good operating practices known to reduce the level of haptens in consumer products amongst all stakeholders along the supply chain.

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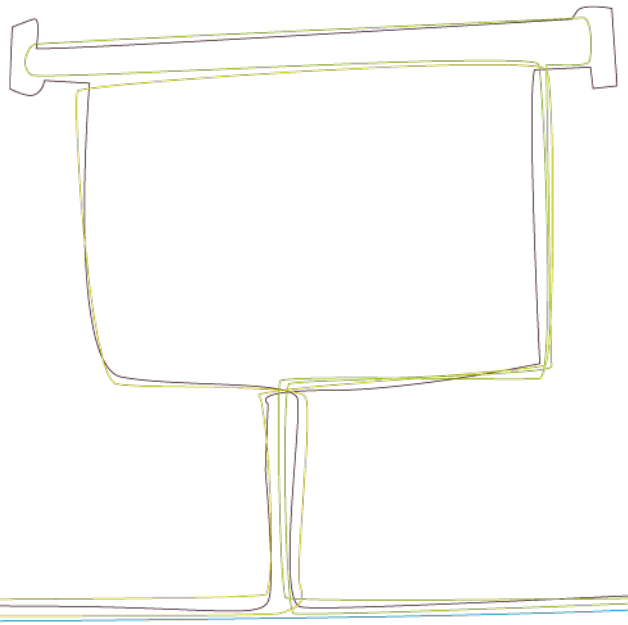
Thank you for your attention



IDEA Annual Review

Characterisation and Categorisation of Allergens

September 23-25, 2014

Ian R. White

Objectives

- To lay the foundation for an allergen characterisation and categorisation procedure which feeds risk management steps towards reduction of allergic contact dermatitis and which can be subject to continuous review, correlation and improvement.

Definition of a Contact Allergen for the purposes of IDEA
(Workshop August 27-29, 2013)

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- A contact allergen is a substance that is capable of inducing delayed type sensitisation in humans, which may manifest as allergic contact dermatitis.

- The elicitation of allergic contact dermatitis requires sufficient exposure and is subject to significant inter-individual variability.

Relationship between Contact Allergy and Allergic Contact Dermatitis

- Contact allergy may be induced by skin contact with low molecular weight haptens and may evolve into allergic contact dermatitis if the exposure exceeds the individual threshold in sensitized individuals.

- Contact allergy is demonstrated by a positive patch test and identifies the population at risk of developing allergic contact dermatitis.

Clinical relevance of a contact allergy in relation to dermatitis

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- Current
  - Exposure to the allergen is causing the dermatitis
- Old (past)
  - Exposure to the allergen caused a past dermatitis
- Unknown
  - No obvious history of exposure or related dermatitis but there must have been exposure to have induced allergy

Knowledge about allergic contact dermatitis

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- Clinical case reports
- Clinical studies of patient groups
- Statistical compilation of patch test reports
- Studies of small outbreaks of dermatitis

Dose-response thresholds

- Important to consider both for induction and elicitation
- In general, more individuals will become sensitised with higher doses or repeated lower doses (exposure)
- Similarly for elicitation reactions (allergic contact dermatitis)

Diagnostic patch testing

- Standardised; ‘gold standard’ to determine presence of contact allergy
- ESCD drafting new guidelines
- Patch test concentrations should cause minimum of irritant/ doubtful reactions (few false positives) and a maximum of allergic reactions (few false negatives)
- For fragrance substances, evidence that Finn Chamber technique is better than TRUE Test

Baseline indicators for fragrance allergy

- Fragrance mix I (*Evernia prunastri*, isoeugenol, cinnamal, cinnamyl alcohol, eugenol, hydroxycitronellal, geraniol, amyl cinnamal)
- Fragrance mix II (HICC, citral, farnesol, citronellol, hexyl cinnamal, coumarin)
- *Myroxylon pereirae* (Balsam of Peru)

How many patients have contact allergy to the baseline indicators?

- Denmark (Gentofte):
  - Fragrance mix I: 8%
  - Fragrance mix II: 5%
  - *Myroxylon pereirae*: 4%
  - HICC: 2%

- Germany (IVDK); Fragrance mix I, standardised for age, sex
  - 2005-2008: 6.58%
  - 2010: 7.4%
  - 2011: 8.1%
  - 2012: 9.1%
  - 2013: 8.8%

Perfumes are mixtures

- Such mixtures of allergens reflect normal consumer exposure
  - May contain up to 12 labelled fragrance allergens
  - Deodorants, scented lotions, fine fragrances, aftershaves….
- In animal experiments it has been shown that mixtures may enhance induction and elicitation

Exposure

- Dose required for induction of contact allergy is (usually) higher than required for elicitation of allergic reaction (dermatitis);
- Consumer exposure should be such as to prevent induction of contact allergy (**primary prevention**);
- **Secondary prevention** is protecting sensitized group from developing elicitation reactions (dermatitis);

- To date, only available method to achieve above has been restrictions based on elicitation data;
- In future, scientifically valid and applied QRA may be used

Agreed Conclusions (1)

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- Properly conducted patch tests are the ‘gold standard’ for the clinical detection of contact allergy;
- Positive patch tests are the indication that exposure to a substance is causing contact allergy with a risk of allergic contact dermatitis and should trigger a re-evaluation of the risk;
- Epidemiological evaluation of patch test results allow a compilation of the relative importance of contact allergens in terms of frequency of reaction and indicate contact allergy trends over time;
- Positive patch test data represent the relevant endpoint in humans and are core data which assist in making decisions for preventive strategies in public health.

Proposal for additional conclusion (1a)

- Exposure information is crucial for diagnosing contact allergy and allergic contact dermatitis, for advising patients and for prevention. The most important source of exposure information concerning cosmetic products is ingredient labelling.

Methods to determine sensitisation potential

- Previously:
  - Local lymph node assay (LLNA)
  - Guinea pig maximisation test (GPMT)

- Now:
  - *in silico*
  - *in vitro / in chemico* methods
  - OECD Integrated Approach to Testing and Assessment
  - Hazard identification but not potency assessment

Agreed Conclusion (2)

- Non-clinical methods including non-animal approaches (e.g. those with OECD guidelines) have the potential to allow for the identification of a contact allergens. However non-animal test systems require further refinement for characterisation and categorisation.

Characterisation and categorisation

- For allergic hazard potential, ‘sensitivity’ is:
  - Clinical diagnostic capability > limit of predictive toxicology > regulatory limits

- Regulatory classification:
  - Sensitiser/not classified
  - Extreme/strong/moderate/weak/very weak/non-sensitiser
  - CLP, ECHA, SCCS, GHS

Genetic factors

- Normal (Gaussian) distribution of reactivity in humans;
- Polysensitisation can be regarded as a clinical sign of increased susceptibility;
- (increasing age may be a risk factor for polysensitisation);

- **Whatever the influence of genetic susceptibility on sensitization, the relative influence is considerably lower than exposure (dose) and sensitizing potency of an allergen**

Agreed Conclusion (3)

- The role of genetic factors in susceptibility to contact allergy is yet to be defined

Improving dialogue between industry and dermatological community

- Industry → Dermatologists: provide reference materials to help diagnosis of contact dermatitis
- Dermatologists → Industry: provide results of clinical testing as feedback into risk assessment/management process

- Full ingredient labelling seen as essential by dermatological community…
- In absence, requirement to develop strategy to inform consumer of presence of non-labelled fragrance substances to which they have contact allergy

Agreed Conclusion (4)

- Readily accessible product ingredient information including labelling is critical for evaluating exposure, reliable diagnosis and prevention.

Break out reports (1)

- Studies
  - Retrospective studies problematic;
  - Need for accurate baseline data for prevalence to assess effectiveness of QRA and develop procedure for clinical alerts;
  - Common protocol;
    - Fragrance mixes I & II, 14 individual ingredients, *Evernia furfuracea*, oxidised linalool and oxidised limonene
    - Other substances, routine testing of 'blocks'
  - Detailed information on exposures etc
  - Primary readout is prevalence of contact allergy (endpoint of concern)
  - Secondary readout is prevalence of allergic contact dermatitis

Break out reports (2)

- Suggested criteria for ranking relative concern of fragrance allergens:
  - **Major**: many reported cases (100), or few reported cases (10) where low exposure, or some severe cases;
  - **Potentially major**: cases but no existing epidemiological survey; non-clinical data indicates a risk;
  - **Moderate**: more than minor but does not fit criteria for major;
  - **Minor**: isolated sporadic cases where there is large/frequent exposure and epidemiological data demonstrates rarity;
  - No current concern.

Break out reports (3)

- Communication
  - Ingredient labelling is central to providing consumer (patient) a means to avoid future exposures that may elicit dermatitis;
  - Ingredient information must be available at time of assessment; ‘apps’ and similar digital resources are considered important supportive systems.
  - Key to monitoring safety is good feedback from clinician/patient and industry

Overall discussion (1)

- Risks to human health presented by contact allergens must be rigorously assessed and properly managed;
- Patch testing is sensitive and specific as a diagnostic tool;
- Relevance is a matter for the clinician investigating the patient;
- A positive patch tests is first indication that exposure to a substance is causing allergy in population;
- Data from individual clinics is a means to compare relative importance of contact allergens;
- Exposure information is crucial for diagnosing contact allergy and allergic contact dermatitis

Overall discussion (2)

- QRA must be evaluated by its impact in minimising frequency of contact allergy;
- Classification and potency sub-categorisation is useful for prioritizing work but does not substitute for primary and secondary prevention strategies;
- Studies are now required to examine effectiveness of QRA;
- Monitoring and evaluation should be independent.

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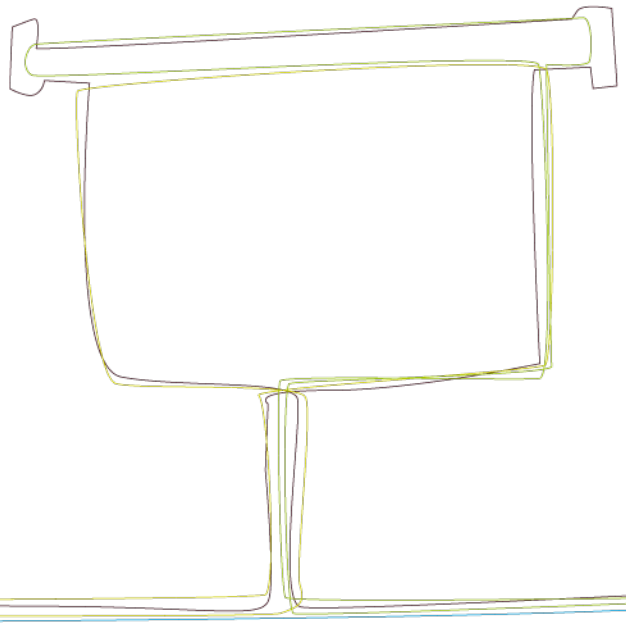

IDEA Annual Review

Key conclusions of the IDEA Annual Review

December 17th, 2014

Prof. Jim Bridges

Emeritus Professor of Toxicology and Environmental Health and Chair of the IDEA Supervisory Group

QRA 2 (July 2014)

External exposure

(aggregate for an ingredient)

↓

Revised **SAF's**

Hazard assessment

(LLNA)

(checked using HRIPT)

↓

NESIL

→ **CEL** → ↓ ← **AEL** ←

↓ Revised **SAF's**

Risk assessment

IDEA-Next steps

- Improved collaboration with the clinics eg to address the effectiveness of the QRA.
- Assessment of the importance of other sources of exposure to fragrance materials
- A fundamental review of the methodology for hazard identification and characterisation

Feedback from the clinics on the effectiveness of QRA 2

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A high quality, coordinated prospective study involving leading clinics which requires:

-harmonisation of both patch testing technique and test materials,

-collection of relevant exposure information eg occupation, consumer habits, past and present topical drugs used, product type, body site of initial and present dermatitis, etc.

QRA developments: hazard assessment

- **Predictions using structural considerations**

Identification and characterisation of haptens and pre- and pro-haptens. Identification of a TTC like system to identify priorities for in depth consideration.

- **Replacement of the LLNA test by non-animal alternatives**

Utilising understanding of toxicokinetics, modes of action and causes of human variability.

QRA development: Exposure assessment

- **Other sources of exposure to a specific fragrance ingredient.**
  - Professional use
  - Household and aromatherapy products
- **Exposure to combinations of fragrance ingredients** (Cummulative exposure).
  - Requires MoA /SAR data.
- **Estimate of internal dose**
- Hapten formation (pre-and pro-haptens).

QRA 3 (201?)

Internal exposure
(total aggregate and cummulative plus toxicokinetics)

↓

New **SAF's**

Hazard assessment
Non animal evaluation (SAR/ MoA based)

↓

↓

NESIL

→ **CEL** → ↓ **AEL** ← ←

↓

New **SAF's**

Risk assessment

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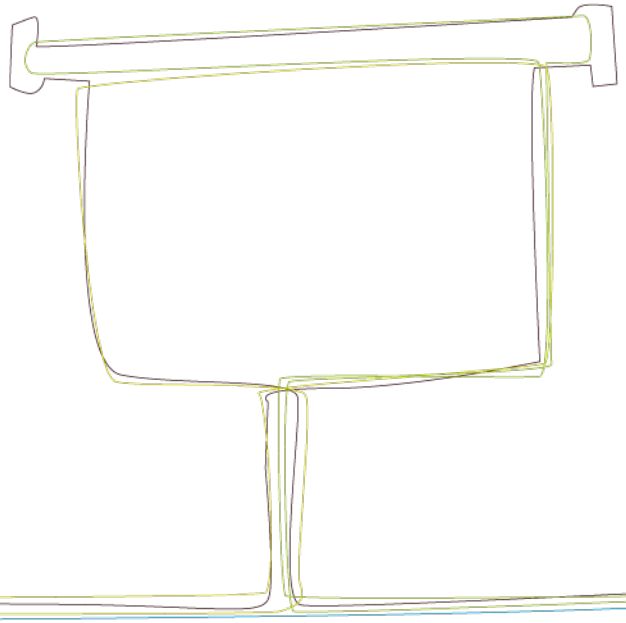

IDEA Annual Review 2014

EUROFORUM building (EUFO)
10, rue Robert Stumper
L-2557 Luxembourg

December 17th, 2014

During the Annual Review, following the presentations made, several issues were highlighted or statements were made by the attendees such as:

General Remarks

- The IDEA project developed into a very useful tool in enabling a solution oriented, forward looking dialogue of the various stakeholders engaged in the topic of (fragrance) allergy. In this context it is very important to respect the different roles of all stakeholders.
- A lot of the learnings and outcome of IDEA could be valuable beyond the fragrance industry and be meaningful for the whole range of allergens and thereby become useful for other areas.
- Understanding exposure (volume, use levels, product types in which typically used) is a critical element in understanding clinical observations and deserves a separate activity.
- Product ingredient labelling is still an important tool for the clinician.

QRA Refinement

- It was clarified that the HRIPT is not used as a predictive tool by the industry but only as a confirmative tool. This should address ethical concerns.
- Concern was expressed regarding the future use of the HRIPT and the opportunity was raised to move away from the confirmatory HRIPT once integrating new methodologies (alternatives to animal testing) for hazard assessment.
- The aggregate exposure model, which is valued very much, should be presented in more detail and it should be aimed to make it more user friendly in its application for those not too familiar with it. It was stated that the model is based on the Monte Carlo principles and that two publications are under way to describe the model in more detail. Once available they will be shared with the IDEA WS participants.
- The degree of uncertainty around the EC3 value was raised and discussed. It was mentioned that there is publications out there linking the EC3 value with human data. The mouse being a good, but not

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

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perfect predictor for human effects is a reason why the fragrance industry does run the HRIPT as a confirmatory test.

- The potential impact of vehicles as potential skin penetration enhancers and the potential resulting effect on the outcome of the LLNA was raised and it was stated that there is a reasonable amount of published data demonstrating that most vehicles have a moderate impact on the observed sensitization compared to effects from biological variation or the chemical properties.
- With regard to 'validation', the best would be to work with a new ingredient (not necessarily a fragrance ingredient) as for existing materials usage trends can have a big impact on the clinical observations.
- 'QRA2' has to be understood as a snapshot in time and QRA be looked at as an evolving tool.

Pre- and pro-haptens

- When investigating into the oxidation issue, give sufficient consideration to changes potentially resulting during shelf- life by including experiments that would mimic the shelf- life.
- When investigating pro-haptens potentially go beyond fragrance ingredients and look into the area of carcinogens, where the metabolic pathways are often better characterized. In this context it was stated that while this is true, there is the issue of metabolites sometimes being very cytotoxic and therefore not suitable to be investigated in in-vitro systems.
- Regarding hydroperoxides the bigger issue seems to be with the abiotic formation but when it comes to secondary oxidation products, those might also be formed biotically.
- When investigating for biotic oxidation pathways ensure that the testing material well characterized and not already transformed to a certain extent.
- When investigating for effect levels of hydroperoxides, consider clinical studies (patch test and ROAT) with product under suspicion (based on analytical results) involving sensitized patients for which relevance has been demonstrated.
- Investigate for the hydroperoxide levels in patch tests to confirm standardization.

Characterization and Categorization of Allergens

- A confirmed positive patch test is a reconfirmation that an ingredient is an allergen.
- Regarding genetic factors, when doing clinical studies, more focus on sensitive subpopulations could be considered.
- Do not focus too much on classification of allergens based on hazard as the categories can become somewhat artificial – the most potent allergen can be safely used if the exposure is adequately managed (and vice versa) – it is important to look into the whole picture (potency and exposure).
- Identifying the cause for the induction of contact allergy is tricky, especially for reactions on body seats where a multitude of exposures (workplace and consumer product related) can happen (e.g. axilla versus hands).
- Consider the presence of potential impurities when investigating an issue with a material and assessing exposure.

IDEA Annual Review

Summary 2014

December 17th, 2014

IDEA Annual Review 2014
Key conclusions

- Two years into IDEA, we are seeing tangible progress in the quality of the multi-stakeholder dialogue and in the application of the appropriate science towards minimizing fragrance induced allergy:
  - There is a leading role of a Supervisory Group in setting the agenda, in accompanying the dialogue, in shepherding the projects and in reporting results.
  - The submission of the interim QRA dossier, which importantly includes an aggregate exposure model, to the JRC marked one milestone in the level of cooperation of the group.
  - The pre- and pro-hapten issue, while scientifically challenging, is being tackled in a multi-disciplinary fashion with major initial focus on analytical understanding, structure activity (SAR) modeling and work on understanding metabolic pathways.

IDEA Annual Review 2014
Key conclusions

- Looking ahead to 2015, progress is expected in:
  - Refinement and validation of QRA including JRC input.
  - Clinical work to monitor contact allergy trends, also in the context of QRA validation.
  - Better understanding of exposure to allergens
  - Better understanding the pre- and pro-hapten issue.

- The IDEA annual review proved again useful and should be repeated in 2015.

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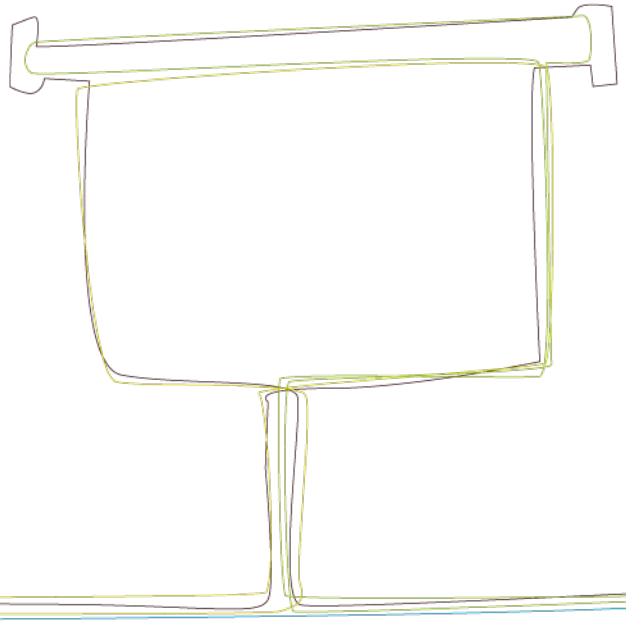

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IDEA WORKSHOP

Validity of the QRA Methodology & Possibilities of Further Refinement

March 11-13th, 2014

1. Program
2. Report on the IDEA Workshop
3. Key conclusions of the IDEA Workshop

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Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

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IDEA
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IDEA Workshop

Validity of the QRA Methodology & Possibilities of Further Refinement

March 11-13th, 2014

Dolce La Hulpe Brussels
Chaussée de Bruxelles, 135
B-1310 La Hulpe, Belgium
Tel: +32 (0)2 290 98 00, Fax: +32 (0)2 290 99 00

Program

Tuesday, March 11th – Workshop opening
All plenary lectures and discussions of this workshop will take place in the meeting room 'Teck'.

3:00 - 6:30 pm	Welcome and registration
5:00 - 5:15	Workshop opening – *Hans Bender and Matthias Vey*
5:15 - 6:15	Summary presentation of the Dermal Sensitization QRA and outcome of the first QRA workshop (March 19-20th, 2013) *Speaker: Anne Marie Api*
6:30 - 9:30	Standing buffet (Oak bar, Dolce La Hulpe)

Wednesday, March 12th (9:00 am to 6:00 pm) – Day 1 (Presentations and plenary discussion)

First session – Refinement of the QRA SAF (Sensitization Assessment Factors)

9:00 - 9:30 am	(Re-)consideration of the underlying science *Speaker: David Basketter*
9:30 - 10:00	Practical considerations in defining the SAFs *Speaker: Bob Safford*

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10:00 - 11:00 Questions and discussion

11:00 - 11:15 Coffee break

Second session – Refinement of the exposure assessment

11:15 - 11:35 Re-introduction of the RIFM/Creme exposure model
Speaker: Cronan Mc Namara (and introduction by Anne Marie Api)

11:35 - 12:05 Incorporating aggregate exposure in the QRA
Speaker: Bob Safford (and follow-up on exposure by Anne Marie Api)

12:05 – 1:00 pm Questions and discussion

1:00 – 1:45 Lunch

Third session – Measure of the QRA effectiveness

1:45 – 2:10 Prospective and retrospective studies
Speaker: Anne Marie Api

2:10 – 2:40 Questions and discussion

Fourth session – Communication

2:40 – 2:50 Impact of the first IDEA workshop on the IFRA Standards development process
Speaker: Matthias Vey

2:50 – 3:00 Towards a revamped IFRA compliance program
Speaker: Matthias Vey / Fred Lebreux

3:00 – 3:10 The scope of the QRA as applied by IFRA. Informing Regulators and unregulated sectors about the risks of contact allergy to fragrance allergens
Speaker: Matthias Vey / Fred Lebreux

3:10 – 3:30 Questions and discussion

3:30 – 4:00 Coffee break

Fifth session – Plenary discussion

4:00 – 4:20 Preliminary progress report
Speaker: Rapporteur of the workshop

4:20 – 5:30	Evaluation of what was presented on Day 1
5:30 – 6:00	End of Day 1
6:30 – 9:30	Reception followed by a dinner (Brasserie 135, Dolce La Hulpe)

Thursday, March 13th (9:00 am to 4:30 pm) – Day 2 (Open discussion)

9:00 – 9:30 am	Adoption of the agenda and wrap-up of Day 1
9:30 – 12:30	The participants will be subdivided into three working groups:
Meeting Room	*Theme*
Teck (1st floor)	Working group 1 – Theme and participants to be agreed at the end of Day 1 *Working group Rapporteur: to be determined*
Ebene (ground floor)	Working group 2 – Theme and participants to be agreed at the end of Day 1 *Working group Rapporteur: to be determined*
Delfino (ground floor)	Working group 3 – Theme and participants to be agreed at the end of Day 1 *Working group Rapporteur: to be determined*
12:30 – 1:15	Lunch
1:15 – 3:00 pm	Presentation of the conclusions / recommendations of the three working groups and establishment of priorities.
3:00 – 3:15	Coffee break
3:15 – 4:30	Conclusions of the workshop and next steps
4:30 pm	End of Day 2 and workshop closing

List of participants (37):

Dr.	Jay	Ansell	PCPC *(Observer)*, USA
Dr.	Eric	Antignac	L'Oréal, France
Dr.	Anne Marie	Api	RIFM, USA
Dr.	David	Basketter	RIFM Consultant, UK
Prof.	Donald	Belsito	Columbia University Medical Center and REXPAN Member, USA
Dr.	Hans-J.	Bender	Consultant *(Moderator)*, Germany
Prof.	James	Bridges	Chairman of the IDEA Supervisory Group *(Rapporteur)*, UK
Prof.	Magnus	Bruze	Lunds Universiteit and REXPAN Member, Sweden
Dr.	Dagmar	Bury	L'Oréal
Dr.	Peter	Cadby	Chanel, France
Dr.	Gaetano	Castaldo	EU Commission – DG Sanco – Risk Management Unit, Belgium
Dr.	Federica	de Gaetano	EU Commission – DG Sanco – Risk Management Unit, Belgium
Prof.	Thomas	Diepgen	Ruprecht-Karls University, Germany
Dr.	Janine	Ezendam	RIVM, The Netherlands
Dr.	Peter	Friedmann	University of Southampton, UK
Prof.	David	Gawkrodger	Royal Hallamshire Hospital and Vice-chairman of the SCCS, UK
Dr.	Nicola	Gilmour	Unilever, UK
Dr.	Peter	Griem	Symrise, Germany
Dr.	Etje	Hulzebos	I.F.F., The Netherlands
Dr.	Petra	Kern	Procter & Gamble, China
Dr.	Christine	Lafforgue	Université Paris sud 11, France
Dr.	Christeine	Lally	P&G, Belgium
Dr.	Fred	Lebreux	IFRA *(IDEA Management Team)*, Belgium
Dr.	Sylvie	Lemoine	A.I.S.E., Belgium
Dr.	Cronan	McNamara	Crème Global, Ireland
Dr.	Andreas	Natsch	Givaudan, Switzerland
Prof.	David	Roberts	Liverpool John Moores University, UK
Prof.	Vera	Rogiers	Vrije Universiteit Brussel, Belgium
Dr.	Bob	Safford	RIFM Consultant, UK
Dr.	Joanne	Salverda	RIVM, The Netherlands
Dr.	Florian	Schellauf	Cosmetics Europe *(Observer)*, Belgium
Dr.	Scott	Schneider	Firmenich, USA
Prof.	Axel	Schnuch	IVDK / University of Göttingen, Germany
Mr.	Pierre	Sivac	IFRA (Observer), Belgium
Ms.	Izabela	Taborska	EU Commission – DG Sanco – Risk Management Unit, Belgium
Dr.	Matthias	Vey	IFRA *(IDEA Management Team)*, Belgium
Dr.	Ian	White	Guy's & St Thomas' NHS Hospitals, UK

IDEA
International Dialogue for the Evaluation of Allergens

Report on the IDEA Workshop on

Validity of the QRA Methodology & Possibilities of Further Refinement

March 11-13, 2014

Dolce La Hulpe Brussels
Chaussée de Bruxelles, 135
B-1310 La Hulpe, Belgium

1. Background information regarding the International Dialogue for the Evaluation of Allergens (IDEA):

Fragrance Allergy is a topic of high interest for the fragrance industry, its customers and the Authorities as expressed through the 2012 SCCS Opinion on Fragrance Allergens. The fragrance industry is determined to address this issue and provide solutions supported by a broad, multi-stakeholder approach.

To fulfil this objective, a work plan (att.01) was developed in the course of 2012 and submitted to DG Sanco Risk Assessment Unit for scrutiny. All comments and suggestions were taken into consideration and the final document, having received the Commission's support, is a clear roadmap intended to deliver positive outcomes for the consumers, the Authorities and the industry. This work plan has now moved into its execution phase and the International Dialogue for the Evaluation of Allergens (IDEA) represents its transposition into concrete actions and investments. Through the organization of experts' workshops and the planning of scientific studies, IDEA aims at providing an agreed and transparent framework for assessing fragrance sensitizers in a prospective way and, ultimately, to find optimal solutions to the issue of fragrance induced skin allergies.

The objective of this workshop was to improve the current Dermal Sensitization Quantitative Risk Assessment methodology ('QRA) and to understand how far it can already be commonly agreed for application to fragrance allergens as a risk management tool. To reach this objective, the participants of this workshop were mandated to review the methodology as used today by the fragrance industry in view to identify the areas of further refinements. This event will be the opportunity to review and discuss the status of action items recommended by experts who participated in the first workshop on QRA, held on March 19-20, 2013.

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

www.ideaproject.info

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2. Summary agreed at the workshop:

The workshop participants identified a set of elements that should be taken into consideration for the development of a QRA 2.0.

The starting point of the QRA is the NESIL which is defined as the threshold known not to induce skin sensitization, considering all available hazard data in a weight of evidence approach, under the specific exposure conditions of a standard protocol HRIPT.

- Considerations related to Humans:
  - The variation in individual human susceptibility to skin sensitization is substantial. The biological basis of this variability is largely unknown, with ethnicity, gender, age (including infants), genetics each making only a minor contribution.
  - Regarding skin diseases / conditions:
    - Atopic dermatitis, psoriasis and dry skin have probably no impact on skin sensitization.
    - Irritant dermatitis is known to promote skin sensitization.
  - The inter-individual variability not accommodated in the NESIL is reflected by a SAF of 10.

- Considerations related to Products:
  - The impact of product use factors such as degree of occlusion, frequency / duration of product use and the product matrix itself are reflected in SAFs that range between 0.3 and 3.
  - The role of skin condition / site is determined by a stepwise consideration of pre-existing inflammation, irritation by product, and penetration / permeation of product and is reflected in SAFs each between 1 and 3.

In conclusion, the assumptions for the SAFs underpinning QRA 1.0 have been reviewed: QRA 2.0 represents a more detailed and transparent assessment with regard to aggregate exposure, skin condition, product type and site of application.

Factor	Consideration	Influence	New proposed SAF values
Occlusion	Some areas of skin are semi-occluded by clothing, or product with moisturising agents may lead to semi-occlusion.	Semi-occluded = Non-occluded ↓	1 0.5
Product matrix	Role of vehicle	Delivery	0.3 or 1 or 3
Frequency / duration of product use	Products may be used over extended periods of time resulting in bio-accumulation	↑	1 or 2
Skin condition / site	Pre-existing inflammation Irritation by product Penetration / permeation of product	Increase of induction susceptibility	1 or 3 1 or 3 1 or 3

IDEA
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3. Report of the Rapporteur :

A. The primary purposes of the workshop

The primary purposes of this workshop were to:

- Provide an update on progress in the development of the RIFM Quantitative Risk Assessment methodology for the identification and characterisation of allergenic fragrances since the previous workshop held in March 2013 and consider those aspects of the QRA that were not addressed previously.
- Identify how these developments can be incorporated in a revised methodology (QRA II) which is required to be submitted to the Commission Services (JRC) at the end of June 2014.
- Discuss ways in which QRA II might be advanced further in the future.

In the light of the above, aspects of the QRA that were given particular attention at the workshop were:

i) factors responsible for human variability,
ii) exposure assessment,
iii) the scientific basis for the use of sensitization assessment factors or SAFs, which are safety/default/uncertainty factors
iv) the content, validation and application of QRA II.

NB. The replacement of laboratory animal studies to identify thresholds for induction by *in vitro* and *in silico* studies was regarded as a priority for further work. However, in view of the short time scale for the submission of QRA II it was agreed that this topic should be left to a future workshop(s)

B. Quantitative Risk Assessment (QRA)

B.1. The purpose of the QRA

QRA should provide a reliable, easy to use, consistent to apply and transparent methodology, based on current scientific understanding, that will identify a safe level of exposure to each fragrance material assessed. A safe use level is defined in this context as one that will not induce skin sensitisation in consumers.

The most relevant expression of exposure is a critical consideration for risk assessment purposes. It is not certain whether it is the currently used metric, the total dose applied to the body (mg applied per cm^2 skin), or the dose applied to a particular area that drains to a particular lymph node(s) that is the more critical factor in initiating induction. Based on current understanding of modes of action it might be expected to be the latter. However, for QRA II, the current metric needs to be retained. There is also uncertainty as to whether exposure per day is the best matric in all cases.

B.1.a. *Relationship between induction and elicitation of sensitisation*

The underlying premise of the QRA is that if induction can be prevented subsequent allergic elicitation reactions will not occur. The QRA relies primarily on animals tests, in particular the local lymph node assay and/or guinea pig maximisation test, to estimate the induction threshold. Safety assessment factors (SAF's) are then used to allow for differences between animals and humans in responsiveness, for possible differences in responsiveness between humans (human variability or inter-individual differences) and for potential differences between experimental and real-life conditions (matrix effects / use considerations).

Human data on fragrance allergy relates primarily to sensitisation. Clinical examination of patients by experienced dermatologists, using diagnostic patch testing, is the gold standard to determine the prevalence of skin sensitisation to allergens in the general population). The relationship between induction of contact allergy and the development of an allergic elicitation reaction is complex. The threshold level for induction is considered to be higher than the threshold for allergic elicitation reactions. However this has only been evaluated for moderate to strong sensitisers. Whether this relationship is the same for weak and extremely weak sensitizers remains uncertain. There is considerable uncertainty too on whether the biological variables that have been identified in humans for elicitation reactions are identical, and of comparable magnitude, for the induction of contact allergy in humans.

B.2. Short summary of QRA 1

Details of RIFM QRA I were published in a series of articles in 2008 (See reference section below). The aim of QRA I is to identify a safe (acceptable) dose for each fragrance application (product type) and compare this with the current/potential exposure of consumers to it. The safe /acceptable level (AEL) is derived from the equation:

AEL = NESIL / SAF's

Where NESIL is the no expected sensitisation induction level and SAF's are default/safety/uncertainty assessment factors used to extrapolate from the experimental (defined and controlled exposure conditions) to real life consumer exposure (variable exposure controlled by the consumer).
If the calculated consumer exposure level (CEL) is below the safe dose then contact allergy is very unlikely to arise in the vast majority of consumers. In other words:

AEL/CEL >= 1 is deemed a safe value.

QRA I is based on the same principles that are generally used in the risk assessment of chemicals for many other spheres of use. Namely identify an acceptable exposure level based primarily on animal testing, and estimate consumer exposure based on use and other relevant considerations.

- *Hazard identification and characterisation*. In principle this is more straightforward than in other areas of toxicology in that the endpoint of interest is pre-defined. Nonetheless the identification of a soundly based threshold (NESIL) is crucial. The NESIL should be based on a weight of evidence approach in which all sensitisation data are considered (animal and human). The primary methods for identifying the NESIL are currently animal based; the guinea pig tests and the local lymph node assay. Characterisation of the dose response relationship may also draw on human data (on sensitisation) and/or structure based predictions The NESIL derived from the above may be supported by HRIPT data.
- *Exposure assessment.* Professional exposure groups who may receive considerably higher levels and durations of exposure to some fragranced products and the ingredients they contain) are not considered in QRA I for exposure assessment purposes. For consumer exposure a deterministic approach is used. Currently QRA I is applied to the assessment of the risk from the application of one fragrance ingredient at a time in one product only. Use patterns, areas of skin exposed etc. are based on 11 product categories. Frequency of use for a particular product is based on the estimate of the upper (97.5^{th})percentile of use by consumers for

that type of product. The assessment also includes consideration of dermal retention based on the nature of the product.

- *Use of SAF's.* Uncertainties that are intended to be taken into account through the application of SAF's are: human inter-individual variability (SAF = 10), product matrix effects (SAF = 1, 3 or 10) and use patterns (SAF = 1, 3 or 10). Selection of the most appropriate SAF is a matter of judgement, and, may result in a total SAF in the range 10-1000.

B.3. Description of QRA II

QRA II should be based on experience in the use of QRA I and advances in scientific understanding since 2007/8. Experience can be drawn on from three main sources:

- Experience of company scientists and others using or reviewing the outputs from the QRA of a particular fragrance;
- Feedback from clinicians in the dermatological community of their findings in patients with established contact allergy to fragrance substances that had been through the QRA and ' safe use levels applied (IFRA Standards)
- Information on exposure to fragrance chemicals

There is considerable information on frequencies of contact allergy to those fragrance substances that are required to be identified on cosmetic ingredient labels, but not to other fragrance substances.
Proposed improvements to QRA should be justified and be compatible with accepted regulatory frameworks for the risk assessment of cosmetic ingredients as set out in the SCCS's guidelines (SCCP 19th December 2008, Notes of Guidance for the Testing of Cosmetics Ingredients and their Safety Evaluation).

C. Human variability in response

C.1. Issues that need to be taken into account

Langerhans cells are fairly evenly distributed between areas of skin. It was argued that this implies that the responsiveness of different areas of skin to a directly acting allergen is likely to be comparable.
It has been shown that following sufficient exposure to allergenic substances, T lymphocytes may become activated but that the expression of sensitisation is suppressed in many people (tolerance). Atopic individuals may be more difficult to sensitise through the skin (delayed hypersensitivity) although the mechanism behind this is different.

In our present state of knowledge is not possible to pick out an at risk group of the population (save for anatomical sites of application). There may be an inverse relationship between the potency of a sensitiser (ie the threshold for sensitisation) and the range of consumer responsiveness. Thus, for a strong allergen, there may be far less variability in human response than is the case for a much weaker sensitiser. If this hypothesis is accepted then it is reasonable to argue that to understand the extent and causes of human variability in sensitisation the focus should be on weak sensitisers rather than on strong ones.

In regard to the threshold for induction of sensitisation in the human population, it is much less clear, than for elicitation of contact allergy, what the range and causes of variability are or whether weak sensitisers should be focussed on in order to understand human variability in the induction of contact allergy. Key factors contributing to variations in induction thresholds between individuals are considered to be:

- Dermal penetration and dermal bioavailability,
- Chemical and/or biological (metabolism) and clearance processes and,
- Interaction of the fragrance chemical (or pre-hapten, pro-hapten products) with Langerhans cells and subsequent steps in the induction process.

C.2. Estimate of the magnitude of variability

An important question is the extent to which variability in the threshold for induction in animals and variability in human sensitization can provide valuable information on the principal causes of variations in induction initiation in humans.

D. Exposure assessment

D.1. Context

There is some ambiguity in risk assessment methodology in general as to which topics should be included as components of exposure assessment. Some regard exposure assessment as being restricted to the level/concentration of a chemical and/or its contaminants/breakdown products at the external surfaces of the body (skin, gut, lungs), others include absorption. Distribution, metabolism and excretion (toxicokinetics) are also sometimes included as additional elements of exposure assessment. This ambiguity was also apparent at the workshop and was not resolved.

The most widely used metric for assessing exposure *via* the dermal route is currently mg per cm^2 skin per day. However exposure per day is unlikely in every case to be the most appropriate metric. For instance the question was raised as to whether 0.1 mg applied 10 times during 24 hours would have potentially similar consequences to 1mg applied as a single dose.

D.2. Topics discussed

Relevant topics discussed at the workshop were:

- Variables affecting bioavailability;
- Comparison of exposure conditions for human repeat insult patch test (HRIPT) with those of typical consumer exposure;
- Aggregate exposure, including frequency and nature of use and other sources of exposure to the same fragrance.

D.2.a. Factors affecting bioavailability

Important considerations are fragrance chemical stability and nature and levels of pre- and pro hapten products and the level and duration of external exposure to a fragrance and related chemicals.

Other important variables to consider are:

- Influence of occlusion,
- Skin permeability (including variations due to damaged or inflamed skin),
- Site(s) of exposure,
- Matrix effects due to other components in a formulation,
- Potential for the build-up of a fragrance substance within the skin and,

- Extent to which QRAI / QRAII covers not only haptens but also pre- and pro-haptens. This issue was not considered further in any detail although in the guinea pig test and to a rather lesser extent in the LLNA assay the metabolic capacity to form haptens from pro-haptens was assumed to be largely present.

D.2.b. Comparison of exposure conditions for HRIPT and typical human exposure

The fragrance industry uses HRIPT data f on human sensitisation to fragrance materials (before consumer exposure) to assess effects of exposure and thresholds. It relies on a standard protocol to maximise the potential for reproducibility of results, which includes a standard population sample of +100 volunteers (excluding those with skin disease), application (usually to the arm or back) of the fragrance material in a simple solvent under full occlusion for 24 hours, three times a week for three weeks. It would be helpful to characterise the extent of human variability represented by such population samples.

Of necessity the HRIPT exposure scenario differs from that expected from the consumer population as a whole, where factors such as matrix effects exposure of other sites, different frequencies and duration of use, lack of occlusion and use by individuals with a variety of skin conditions may apply. This needs to be considered in the estimates of the consumer population exposure and in the appropriate selection of SAF values.

D.2.c. Aggregate exposure

One of the main advances, since the original QRA I methodology was published, is the development of a model for estimating aggregate exposure by Creme supported by RIFM. Compared to the simple way to derive the consumer exposure level (CEL) in QRA I, the aggregate exposure model is a substantial advance in many respects including the following:

- It is probabilistic not deterministic,
- It draws on a very large number of consumer diaries and therefore a much wider range of the population,
- It is based on actual consumer use habits and actual areas of application to the skin rather than the use of standard assumptions,
- It covers access to both acute and chronic exposure estimates,
- It takes into account multiple product use throughout the day,
- The dermal retention factor derived from both frequency and amount of use.

As a consequence of the above the RIFM / Creme aggregate exposure method is very likely to give a much more reliable measure of the total exposure to a fragrance in a day. As it is allows to some extent for accumulation it will in many cases result in higher estimates of consumer exposure (CEL) to individual fragrances than is the case using the current QRA I methodology.

Not surprisingly there are a number of challenges in the application of the RIFM / Creme model to specific products that will need to be addressed including:

- Individual products containing the same fragrance material may be applied over multiple sites. This needs to be considered in the context that the critical concentration to initiate induction is the concentration reaching a particular lymph node;
- Different products containing the same fragrance material may be applied to the same site(s). This may entail that a site has a number of matrices applied concurrently to the same site which may compromise bioavailability.

As a result it is challenging to use, in the most appropriate manner, the aggregate exposure for each application site/ product use and to define the most suitable SAF values in a simple QRA II.
The risk of induction and elicitation of sensitisation from a particular use of a fragrance is also increased if there is exposure to other chemicals with the same mode of induction and elicitation of sensitisation (cumulative exposure) however there is insufficient data yet to introduce a suitable cumulative exposure model.

E. Selection of suitable SAF's

E.1. Context

It was noted that safety /default/uncertainty factors are widely used for regulatory risk assessment purposes in the EU. They are intended to cover:

- Intrinsic variability in data
- Variability due to the methodology used
- Uncertainties due to either deficiencies in the quality, relevance and/or comprehensiveness of the data available.

Applications of safety factors include the risk assessment of food additives and contaminants (EFSA) and industrial chemicals (ECHA). It is important in selecting a SAF to ensure that some balance is achieved between ensuring protection of the exposed population and the unnecessary curtailment of the use of valuable products. A particular issue in this regard is the avoidance of double accounting through overlapping default factors.
The workshop provided an interesting debate on two contrasting approaches to setting SAF's:

i) Select a larger SAF, and for companies that wish to reduce this value, putting the onus on them to generate extra data and to use weight of evidence to reduce the SAF for their product.

ii) Set a lower generic set of SAF which Companies would use, unless there were greater data gaps or uncertainties to require higher SAF's.

The industry-associated participants opted for option ii).

In general toxicology, most commonly in the extrapolation of NO(A)EL (no observable effect adverse effect levels in laboratory animals) to a safe level for chronic exposure of consumers, a factor of 10 is used for extrapolation to man and a further factor of 10 is applied to allow for variations in inter-individual human responses. These factors may be varied for particular chemical according to the quality and comprehensiveness of the database available. The extent to which this approach may be relied upon for allergic sensitisation is unknown.

E.2. Considerations in selection of numerical SAF values

In the selection of appropriate SAF values the following overlapping issues are important:

- The variables that need to be considered and how many separate SAF's are therefore required. This aspect was discussed in some detail at the workshop.
- The percentage of consumers that the SAF's are designed to protect against fragrance chemical contact allergy. Should only consumers be considered or should professional exposures also be considered? Is the aim to protect 100% of consumers, or, as in other areas of risk assessment should it be accepted that it is impossible to guarantee the protection of every member of the population however sensitive they may be?

It is noted that in terms of exposure in the RIFM / Creme model the 97.5th percentile exposure for consumer use was used.

- Other factors that affect the size of SAF's such as the degree of confidence needed in the achievement of this protection.

The main variables discussed considered were:

E.2.a. Exposure factors

In particular the following need to be considered:

- Influence of occlusion. It was queried whether a separate SAF was needed. -
- Site(s) of exposure. Some areas of skin are more permeable than others and appear to be more likely to develop an allergic reaction but this cannot necessarily be taken to imply that exposure at these sites is more likely to be the cause of induction. As Langerhans cells are fairly evenly distributed between areas of skin responsiveness of different areas of skin to a directly acting allergen might be assumed to be comparable. It was queried whether a SAF was needed.
- Matrix effects due to other components in a formulation. Solvent and other matrix effects were considered to be in general relatively small (1 or 3).
- Duration of exposure and potential for the build-up of a fragrance within the skin/ lymphocytes. As noted above it was questioned whether per day exposure was always the most appropriate metric however discussion of alternative approaches was rather limited.

It was not generally agreed whether these factors should be represented by one or more SAF values. Some factors for specific fragrances may justify a SAF of less than one.

Further discussion at the next workshop is necessary on both the number of SAFs and their magnitude.

E.2.b. Human variability in response

This arises from a combination of genetic and environmental contributors including:

- Skin permeability/bioavailability (including variations due to damaged or inflamed Skin). It was felt that variation was likely to be greatest for damaged/inflamed skin. The question was raised as to whether a factor of 10 was enough for severely inflamed skin.
- Metabolism, distribution and clearance. Variations in these parameters were not considered specifically at the workshop.
- Langerhans cell interaction(s) and subsequent interactions and responses. Variations in these parameters were not considered specifically at the workshop.

Older studies by Kligman et al, Maibach et Al, and others had identified that the scale of variability can be several orders of magnitude for specific fragrance chemicals.

How to use these data to identify a SAF for protection against induction in consumers' needs further discussion at the next QRA workshop.

F. Application of QRA II and related issues

QRA II methodology and the guidelines for its use need to obtain the formal approval from the Commission (through the JRC) and are likely to require approval as appropriate for risk assessment purposes by the SCCS.

Application of the findings from the use of QRA II needs to actively involve other stakeholders. In particular a meaningful dialogue is needed with the community of clinical dermatologists on the output of QRA II and its use to set IFRA standards for each fragrance material. This should cover both the selection of the IFRA standard, the anticipated uses of the fragrance (including uses other than as a fragrance) and necessary procedures for frequent feedback on experiences in the clinics with patients using products containing the fragrance material.

A further aspect is to ensure that member companies of IFRA apply QRA consistently and appropriately to their products and ensure compliance with the IFRA standards. It was proposed that an inter-company quality control scheme should be introduced to maximise the value and confidence in its use of QRA II.

G. Follow-up and priorities for further work

The development of the RIFM / Creme aggregate exposure model represents the most significant advance since the RIFM QRA I was first published in 2008.

Additional challenge in the development of QRA II is to ensure that inter-individual differences among consumers in the potential for the initiation of induction by any fragrance material is taken into account but not unnecessarily over compensated for. Key requirements to achieve this are:

- the judicious selection and use of hazard characterisation tests;
- the selection of appropriate SAFs;
- a robust procedure(s) for the validation of the QRA process

The target of a revised QRA being available by the end of June 2014 for submission to the JRC requires prioritisation into short term (2 months only) and longer term tasks (deliverables).

G.1. The main short term tasks

These may be identified as:

i) Guidance on how to apply the RIFM / Creme aggregate exposure model for the risk assessment of individual exposures;

ii) Specification of the values to be assigned to allow for uncertainty and extrinsic and methodological uncertainty. Along with guidance on specific circumstances where difference SAFs ought to be applied;

iii) Selected case histories to demonstrate the appropriate application of QRA II

iv) Establish feedback mechanism so that clinical experience with a fragrance allergen results in evaluation of the assumptions within QRA.

G.2. Longer term tasks

Theses have been identified as:

i) Further progress on databases to enable the development of (Q)SAR tools for inducers. Use of these SARs to develop cumulative exposure models.

ii) A protocol to enable identification and testing of pre-haptens based on structural considerations for each fragrance (see pre and pro hapten workshop findings)

iii) Laboratory studies to identify the ability of the hazard characterisation tests to convert pro-haptens to haptens;

iv) Development of exposure assessment models for professional exposure to fragrances;

v) Identification of how to phase the regulatory imposed shift from animal based hazard assessment to *in vitro* and *in silico* based hazard assessment;

vi) Continuation of effective dialogue among the key stakeholders coupled with effective actions to improve the utility of the QRA in order to ensure protection of consumers and others.

H. References

- Api, A.-M. *et al.* (2008). Special Issue: Dermal Sensitization Quantitative Risk Assessment for Fragrance Ingredients. Regulatory Toxicology and Pharmacology, **52**(1), 1-73.
- Monika R. Upadhye, Howard I. Maibach (1992). Influence of area of application of allergen on sensitization in contact dermatitis. *Contact dermatitis*. ***27*****:** 281-286.
- Kligman AM. (1966)' The identification of contact allergens by human assay. II. Factors influencing the induction and measurement of allergic contact dermatitis. *J Invest Dermatol.* ***47***(5):375-92.

Professor Jim Bridges
Workshop Rapporteur

Appendix 1 – Workshop Participants:

- European Commission and European Scientific Committees: Dr. Gaetano Castaldo (EU Commission, DG Sanco B2 Unit), Dr. Federica De Gaetano (EU Commission, DG Sanco B2 Unit), Prof. David Gawkrodger (Royal Hallamshire Hospital and Vice-chairman of the SCCS), Ms. Izabela Taborska (EU Commission, DG Sanco B2 Unit).
- Academic community and national Authorities: Dr. David Basketter (Consultant), Prof. Donald Belsito (Columbia University Medical Center and RIFM Expert Panel Member), Prof. Magnus Bruze (Lunds Universiteit and RIFM Expert Panel Member), Prof. Thomas Diepgen (Ruprecht-Karls University), Dr. Janine Ezendam (RIVM), Dr. Peter Friedmann (University of Southampton), Dr. Christine Lafforgue (Université Paris sud 11), Dr. Cronan McNamara (Crème Global), Prof. David Roberts (Liverpool John Moores University), Prof. Vera Rogiers (Vrije Universiteit Brussel), Dr. Bob Safford (Consultant), Dr. Joanne Salverda (RIVM), Prof. Axel Schnuch (IVDK / University of Göttingen), Dr. Ian White (Guy's & St Thomas' NHS Hospitals).
- Industry: Dr. Jay Ansell (PCPC), Dr. Eric Antignac (L'Oréal), Dr. Anne Marie Api (RIFM), Dr. Dagmar Bury (L'Oréal), Dr. Peter Cadby (Chanel), Dr. Nicola Gilmour (Unilever), Dr. Peter Griem (Symrise), Dr. Etje Hulzebos (I.F.F.), Dr. Petra Kern (Procter & Gamble), Dr. Christeine Lally (Procter & Gamble), Dr. Sylvie Lemoine (A.I.S.E.), Dr. Andreas Natsch (Givaudan), Dr. Florian Schellauf (Cosmetics Europe), Dr. Scott Schneider (Firmenich).
- IDEA Staff: Dr. Hans-J. Bender (Moderator), Dr. Fred Lebreux (IFRA), Dr. Matthias Vey (IFRA).
- Supervisory Group members: Prof. Jim Bridges (Rapporteur).

IDEA
International Dialogue for the Evaluation of Allergens

Key conclusions of the IDEA Workshop

Validity of the QRA Methodology & Possibilities of Further Refinement

March 13th, 2014 – La Hulpe

The workshop participants identified a set of elements that should be taken into consideration for the development of a QRA 2.0.

The starting point of the QRA is the NESIL which is defined as the threshold known not to induce skin sensitization, considering all available hazard data in a weight of evidence approach, under the specific exposure conditions of a standard protocol HRIPT.

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  - The variation in individual human susceptibility to skin sensitization is substantial. The biological basis of this variability is largely unknown, with ethnicity, gender, age (including infants), genetics each making only a minor contribution.
  - Regarding skin diseases / conditions:
    - Atopic dermatitis, psoriasis and dry skin have probably no impact on skin sensitization.
    - Irritant dermatitis is known to promote skin sensitization.
  - The inter-individual variability not accommodated in the NESIL is reflected by a SAF of 10.

- Considerations related to Products:
  - The impact of product use factors such as degree of occlusion, frequency / duration of product use and the product matrix itself are reflected in SAFs that range between 0.3 and 3.
  - o The role of skin condition / site is determined by a stepwise consideration of pre-existing inflammation, irritation by product, and penetration / permeation of product and is reflected in SAFs each between 1 and 3.

In conclusion, the assumptions for the SAFs underpinning QRA 1.0 have been reviewed: QRA 2.0 represents a more detailed and transparent assessment with regard to aggregate exposure, skin condition, product type and site of application.

The participants

Attachment: Table of new proposed product use SAF values

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

www.ideaproject.info

Attachment: Table of new proposed product use SAF values

Factor	Consideration	Influence	New proposed SAF values
Occlusion	Some areas of skin are semi-occluded by clothing, or product with moisturising agents may lead to semi-occlusion.	Semi-occluded = Non-occluded ↓	1 0.5
Product matrix	Role of vehicle	Delivery	0.3 or 1 or 3
Frequency / duration of product use	Products may be used over extended periods of time resulting in bio-accumulation	↑	1 or 2
Skin condition / site	Pre-existing inflammation Irritation by product Penetration / permeation of product	Increase of induction susceptibility	1 or 3 1 or 3 1 or 3

IDEA
International Dialogue for the Evaluation of Allergens

IDEA WORKSHOP

Validity of the QRA Methodology & Possibilities of Further Refinement

May 13-15th, 2014

1. Program
2. Report on the IDEA Workshop
3. Key conclusions of the IDEA Workshop

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

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IDEA
International Dialogue for the Evaluation of Allergens

IDEA Workshop
Validity of the QRA Methodology & Possibilities of Further Refinement

May 13-15th, 2014

Martin's Klooster
Onze-Lieve-Vrouwstraat 18
3000 Leuven, Belgium
Tel: +32 (0)16 21 31 41, Fax: +32 (0)16 22 31 44

Program

Tuesday, May 13th – Welcoming

4:00 - 6:30 pm	Welcome and registration
5:00 - 6:30	Sightseeing tour of Leuven (meeting in the lobby of the hotel Martin's Klooster) – cobblestones streets => good walking shoes recommended!)
6:30 - 9:30	Standing buffet (Martin's Klooster, Morillon room)

Wednesday, May 14th (8:45 am to 6:00 pm) – Day 1 (Dominicanen meeting room)

8:45 - 9:00 am	Workshop opening – *Hans Bender and Matthias Vey*

First session – Rapid presentation of QRA 1.0 and of the first IDEA events dedicated to QRA 2.0

9:15 - 9:30	Brief review of the 2008 publications on QRA 1.0 and how SAF proposed at that time were assigned to specific product categories *Speaker: Anne Marie Api*
9:30 - 09:45	Outcome of QRA Workshop #1 (March 2013) and #2 (March 2014) with focus on revision of SAF *Speaker: David Basketter*
9:45 - 10:15	Questions and Discussion

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10:15 - 10:30 Coffee break

Second session – Presentation of the latest developments on aggregate exposure and SAF

10:30 - 11:00 Review of new SAF and agreement on values for product categories
Speaker: Anne Marie Api

11:00-11:30 Presentation of suitable case studies
Speaker: Graham Ellis

11:30-12:30 Questions and discussion

12:30 - 1:00 Summary of the aggregate exposure model and presentation of a proposal to incorporate aggregate exposure into the QRA categories
Speaker: Cronan McNamara

1:00 – 1:45 Lunch

1:45- 2:15 Presentation of application of aggregate exposure in a case study
Speaker: Bob Safford

2:15-2:45 Questions and discussion

Third session – Gaps in the current QRA 2.0 and plans to bridge them in the short / medium-term

2:45 - 3:00 Coffee break

3:00 - 3:30 What is/is not already addressed in the current QRA?
Speaker: David Basketter

3:30 - 4:00 Questions followed by a moderated discussion on potential other gaps to address

Fourth session – Measure of the QRA method effectiveness

4:00 - 4:30 Discussion of the main parameters to take into consideration for the development of meaningful prospective studies
Speaker: Anne Marie Api

4:30 - 5:30 Questions and discussion

Fifth session – Conclusions of Day I

5:30 - 6:00	Preliminary progress report *Speaker: Rapporteur of the workshop (Prof. Jim Bridges)*
6:15-6:30	Transfer to the Brewery by bus (meeting in the hotel lobby)
6:30 - 8:00	Visit of AB InBev (world's largest brewer) and beer-tasting
8:15 - 10:00	Dinner (restaurant D'Artagnan, Naamsestraat 72 - B, 3000 Leuven)

Thursday, May 15th (9:00 am to 4:30 pm) – Day 2

9:00 - 9:15 am	Adoption of the agenda and wrap-up of Day 1

First session – Transition to a world without animal testing

9:15 - 10:00	Read across, in silico, in vitro and human testing for skin sensitizer identification and potency determination: current state of knowledge and thought starter *Speaker: Graham Ellis*
10:00 - 11:00	Questions and discussion
11:00 - 11:15	Coffee break

Second session – Working groups discussion

11:15 - 3:00 pm	The participants will be subdivided into two working groups:
Meeting Room	*Theme*
Dominicanen	Working group 1 – Theme and participants to be agreed at the end of Day 1 *Working group Rapporteur: to be determined*
Franciscanen	Working group 2 – Theme and participants to be agreed at the end of Day 1 *Working group Rapporteur: to be determined*
12:30 - 1:15	Lunch
3:00 - 4:00 pm	Presentation of the conclusions / recommendations of the working groups
3:15 - 4:30	Conclusions of the workshop and next steps
4:30 pm	End of Day 2 and workshop closing

List of participants (37):

Dr.	Anne Marie	Api	RIFM, USA
Dr.	David	Basketter	RIFM Consultant, UK
Prof.	Donald	Belsito	Columbia University Medical Center and REXPAN Member, USA
Dr.	Hans	Bender	Consultant *(Moderator of the Workshop)*, Germany
Dr.	Christophe	Brault	LVMH, France
Prof.	James	Bridges	Chairman of the IDEA Supervisory Group *(Rapporteur of the Workshop)*, UK
Prof.	Magnus	Bruze	Lunds Universiteit and REXPAN Member, Sweden
Dr.	Dagmar	Bury	L'Oréal, France
Dr.	Peter	Cadby	Chanel, France
Dr.	Gaetano	Castaldo	EU Commission – DG Sanco – Risk Management Unit, Belgium
Prof.	Pieter-Jan	Coenraads	SCCS Member, The Netherlands
Dr.	Federica	de Gaetano	EU Commission – DG Sanco – Risk Management Unit, Belgium
Prof.	Thomas	Diepgen	Ruprecht-Karls University, Germany
Prof.	Jeanne	Duus Johansen	University of Copenhagen, Denmark
Mr.	Graham	Ellis	Givaudan, Switzerland
Dr.	Janine	Ezendam	RIVM, The Netherlands
Dr.	Nicola	Gilmour	Unilever, UK
Dr.	Margarida	Goncàlo	University of Coimbra, Portugal
Dr.	Peter	Griem	Symrise, Germany
Dr.	Etje	Hulzebos	I.F.F., The Netherlands
Dr.	Petra	Kern	Procter & Gamble, China
Dr.	Maya	Krasteva	L'Oréal, France
Dr.	Christine	Lafforgue	Université Paris sud 11, France
Dr.	Christeine	Lally	Procter & Gamble, Belgium
Dr.	Fred	Lebreux	IFRA *(IDEA Management Team)*, Belgium
Dr.	Linda	Loretz	PCPC *(Observer)*, USA
Dr.	Cronan	McNamara	Creme Global, Ireland
Prof.	David	Roberts	Liverpool John Moores University, UK
Prof.	Vera	Rogiers	Vrije Universiteit Brussel, Belgium
Dr.	Bob	Safford	RIFM Consultant, UK
Dr.	Joanne	Salverda	RIVM, The Netherlands
Dr.	Florian	Schellauf	Cosmetics Europe *(Observer)*, Belgium
Prof.	Axel	Schnuch	IVDK / University of Göttingen, Germany
Dr.	Ben	Smith	Firmenich, Switzerland
Ms.	Izabela	Taborska	EU Commission – DG Sanco – Risk Management Unit, Belgium
Dr.	Matthias	Vey	IFRA *(IDEA Management Team)*, Belgium
Dr.	Ian	White	Guy's & St Thomas' NHS Hospitals, UK

IDEA
International Dialogue for the Evaluation of Allergens

Report on the IDEA Workshop on

Validity of the QRA Methodology & Possibilities of Further Refinement

May 13-15, 2014

Martin's Klooster
Onze-Lieve-Vrouwstraat 18
3000 Leuven, Belgium

1. Background information regarding the International Dialogue for the Evaluation of Allergens (IDEA):

Fragrance Allergy is a topic of high interest for the fragrance industry, its customers and the Authorities as expressed through the 2012 SCCS Opinion on Fragrance Allergens. The fragrance industry is determined to address this issue and provide solutions supported by a broad, multi-stakeholder approach.

To fulfil this objective, a work plan (att.01) was developed in the course of 2012 and submitted to DG Sanco Risk Assessment Unit for scrutiny. All comments and suggestions were taken into consideration and the final document, having received the Commission's support, is a clear roadmap intended to deliver positive outcomes for the consumers, the Authorities and the industry. This work plan has now moved into its execution phase and the International Dialogue for the Evaluation of Allergens (IDEA) represents its transposition into concrete actions and investments. Through the organization of experts' workshops and the planning of scientific studies, IDEA aims at providing an agreed and transparent framework for assessing fragrance sensitizers in a prospective way and, ultimately, to find optimal solutions to the issue of fragrance induced skin allergies.

The objective of this workshop was to improve the current Dermal Sensitization Quantitative Risk Assessment methodology (QRA) and to understand how far it can already be commonly agreed for application to fragrance allergens as a risk management tool. To reach this objective, the participants of this workshop were mandated to review the methodology as used today by the fragrance industry in view to identify the areas of further refinements. This event was the opportunity to review and discuss the status of action items recommended by experts who participated in the first two workshops on QRA, held on March 19-20, 2013 and March 11-13, 2014.

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2. Report of the Rapporteur :

Aim of the workshop

The intention of this workshop was to build on the work carried out at, or following on from the two previous workshops on QRA.

Its main objective was to identify, in detail, the components necessary for a reliable, easy to use, consistent to apply and transparent methodology (termed QRA II), which is based on current scientific understanding and expectation to suggest a safe level of exposure for each fragrance material assessed. A safe use level is defined in this context as one that will not induce skin sensitisation (contact allergy) in consumers. Where this cannot be achieved fully at the workshop, to agree a work plan to complete QRA II, bearing in mind the deadline of the 20th of June 2014 for its submission via DG SANCO to the JRC.

Aspects identified for discussion

a) Form of the submission of the QRA

Two options for the submission were considered:

i) Provision of QRA I (see special issue of Regulatory Toxicology and Pharmacology (2008) Vol 52, no 1) along with documentation where changes have been made to it.

ii) A stand-alone document.

b) *Exposure assessment*

Reliable assessment of human exposure is commonly the weaker part of the risk assessment of chemicals. This has also been the case for fragrance substances. Consequently, a focus in the development of QRA II has been to develop an aggregate exposure model that enables the estimation of exposure to individual fragrance substances through the use of a wide range of cosmetic products.

c) Justification for data extrapolation

Various extrapolation factors (safety assessment factors, SAFs) were introduced in the RIFM QRA I method. It was agreed at the two previous workshops that the values assigned to these factors needed to be reconsidered in the light of the available scientific evidence.

d) *Hazard characterization*

Inevitably, because of the nature of the research required, substantial advances in the tests used for hazard characterisation (including reliable demonstration of thresholds relevant to human exposure) has been slow. The ban on animal testing makes this aspect of the development of the QRA a priority and a particularly challenging one. However, it was agreed at the previous workshop, that a revision of the guidance on animal testing was a very major task, and therefore couldn't be included in time for the submission of QRA II. It was agreed instead that it should be a central component of a subsequent development of QRA II (QRA III).

e) *Evaluation of the effectiveness of the QRA to protect consumer health*.

It was agreed that it was important to determine the effectiveness of the introduction of QRA I and QRA II in reducing contact allergy to fragrance substances.

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A. PROPOSED CHANGES IN QRA I FOR QRA II

1. Form of the QRA II submission to JRC

This was discussed in a breakout group. The JRC submission date is 20th June. This means that a draft has to be available for internal evaluation by June 6th.

It was agreed that it would be a stand-alone document using a stick and paste of QRA I as the core. In terms of the SAFs these would need to be justified scientifically based on the recent commentary by Basketter and Safford (provided as a draft at the workshop).

The QRA dossier will be set out as follows:

i. Introduction

- A summary of key features developed in the last few years (and the reasons they have been prioritised i.e. SAFs, aggregate exposure).
- Explanation of the underlying science (induction *vs* elicitation and mode of action).

ii. The QRA methodology

- Hazard characterisation (deriving the NESIL, use of WoE)
- Aggregate exposure assessment (including exposure tables)
- Use of SAFs and modified SAFs for standard setting
- Plans for the Assessment of the effectiveness of the QRA (existing and new chemicals)

iii. Priorities for future development of QRA II

- An outline of the potential for alternative hazard characterisation models.
- Approach for the assessment of pre- and pro- haptens.
- Occupational/professional exposures.

iv. Case histories to demonstrate the use of the QRA.

v. Appendices

- References Including EU references.
- Background to the development of QRA II (workshops etc).
- An updated version of Basketter and Safford providing the scientific rationale for each SAF value.

2. Specific aspects of exposure assessment

i. Features

The major new aspect, in terms of exposure, is the introduction of the RIFM/Creme aggregate exposure assessment model. This enables the total exposure of consumers to a fragrance material from all product

sources to be estimated instead of estimates of exposure to individual products. The model is proposed to be used for both retrospective and prospective use. Particular feature are:

- It is based on extensive database of consumer responses to questionnaires on their use of products containing fragrance materials and information on quantity of each fragrance material in each product type.
- The 95th percentile of worst case and worst day use for each product is assumed. This was described as extreme worst case.
- It is assumed that each product incorporates the maximum RIFM level.
- Body site SAFs are integrated.

ii. Case histories to support the introduction of the Creme model

Two products were considered: Benzaldehyde and BMHCA. Using the proposed QRA II model in conjunction with RIFM/Creme aggregate exposure model it was found that, in contrast to the QRA II without the aggregate exposure consideration, the RIFM/Creme model gave CEL/AEL values above 1 for certain exposure sites. In such circumstances the product use at such sites needs to be reduced. This indicates a useful application of the model however the calculation relies on the appropriateness of the SAF values.

iii. Current exclusions from QRA II for exposure

The following aspects are not proposed to be covered in QRA II:

- Occupational/professional exposures.
- Co-exposure to other chemicals with a common mode of action (showing cross reactivity and/or combination effects i.e. cumulative exposure).
- Consumer exposure to so called natural products (i.e. consumer exposure outside the control of the fragrance industry e.g. aromatherapy).
- A number of other consumer products that are also not considered in terms of consumer exposure (food, drugs, etc.).

3. Specific aspects of the application of SAF values

i. The application of SAFs

In addition to the SAF for inter-individual variability (to allow for age, genetic differences, gender, etc.) for which a standard factor of 10 is used SAFs relating to exposure were introduced in QRA I to address uncertainties and inherent variability in the following:

- Product formulation.
- Consumer use (nature of application and frequency).
- The state of the skin e.g. inflammation
- Differences between skin sites.

ii. Proposed SAFs (See Table below)

The following values[2] were proposed):

Factor	Consideration	Influence	New proposed SAFs	Comments (comparison of the experimental condition with the product use condition)
Inter-Individual	There can be large inter-individual differences in response to a chemical exposure due to several different parameters.	Increase of induction susceptibility	10	The inter-individual variability not accommodated in the NESIL is reflected by a SAF of 10.
Product	Role of vehicle/matrix	Delivery	0.3 or 1 or 3	The predicted effect of product formulation versus the experimental conditions; 0.3 (inert objects with no direct contact, e.g. candles or detergent pods or no vehicle/matrix) or 1 (most products) or 3 (penetration enhancers greater than anticipated from the experimental condition)
	Irritation by product	Increase of induction susceptibility	0.3 or 1 or 3	Can the product cause irritation related to repeated normal conditions of use? Ingredients that are added to mitigate any types of irritation
Frequency / duration of product use	Products may be used over extended periods resulting in bio-accumulation	↑	1 or 2	Products may be used frequently over extended periods of time resulting in accumulation (chemical or biological accumulation) or reservoir effect
Occlusion	Some areas of skin are semi-occluded by clothing, or product with moisturising agents may lead to semi-occlusion.	Semi-occluded = Non-occluded ↓	1 0.5	To assure consistency, it was concluded that the occlusion factor should be 1 for all consumer products since at some time all body parts could be covered by

[2] Nota bene:
(1) Each value needs to be cross-references to the key statement in Basketter and Safford or elsewhere and to the publications supporting it.
(2) It is noted that QRA II appears to be largely in line with other methodologies for the risk assessment of chemicals.

	Includes occlusion by body part, clothing or product.			clothing.
Skin condition/ site	Pre-existing inflammation	Increase of induction susceptibility	1 or 3	Pre-existing inflammation for body site: body areas that are specifically prone to increased level of inflammation – hands, underarms, any shaved area, under a diaper, peri-anal and peri-ocular regions

Body Site	**Additional definition for this study**	**Skin Site**		**Total Body Site SAF**
		Occlusion	**Inflammation**	
Scalp		1	1	1
Face*	Does not include: Eyes, Lips, Mouth, Behind Ears	1	3	3
Peri-ocular	The eyelid and surrounding skin.	1	3	3
Lips		1	3	3
Peri-oral	"Buccal" / "Inside Cheek" Does not include: Lips	1	3	3
Neck	Does not include: BehindEars	1	3	3
Behind Ears		1	1	1
Chest	Does not include: Underarms, Stomach	1	1	1
Abdomen		1	1	1
Back	Does not include: Underarms	1	1	1
Axillae		1	3	3
Arms	Does include: Shoulder, Forearm, Upper arm Does not include: Wrists, Hands, Palms, Underarms	1	1	1
Wrists		1	3	3
Back of Hand	Does not include: Palms, Wrists	1	3	3
Palms		1	3	3
Ano-genital		1	3	3
Legs	Does include: Bottom, Thighs, Calves Does not include: Feet	1	3	3
Feet		1	3	3

4. Evaluation of the QRA

Assuming that adequate interventions have arisen as a consequence of QRA I it should be expected that there would be a reduction in the levels of sensitisation, albeit these changes might not be major as skin sensitisation

involves a life-long change in immune response. The importance of high quality patch testing in providing this relevant data was emphasised. There is a rich source of information from regularly recording baseline studies in various academic publications. The academic support from such studies may not last beyond a few years and this is a very strong reason to use these databases now. This was agreed. A breakout group examined this aspect in more depth and arrived at the following conclusions.

i. *Retrospective studies*

First step is to check the quality of the data. In principle, since the QRA was implemented for a fragrance substance there should be a reduction in incidence of sensitisation to the specific substance. Preference should be for data from initial patch tests and for the results of consecutive testing. Expertise is required in the interpretation of data. In principle the analysis of the available data and its interpretation could be available in half a year.

ii. *Prospective studies*

- Using standards

Involve clinics across Europe and the USA with a minimum contribution per centre pre-identified (say, a minimum of 500 consecutive tests per clinic per year. Below this may cause selection and other bias) Questionnaire used to gain relevant information about patient behavior and exposure. Patch test methods have to be standardised using selected standard test materials (FMI and FMII and their 14 individual ingredients). Location of sensitisation and age and sex of patients should be recorded.

- New fragrance substances

Early information for the dermatological community regarding consumer exposure to new fragrance substances is needed. Each new substance needs to be available to the clinics.

B. NO CHANGE PROPOSED FOR QRA II

1. Degree of public protection

In QRA I the extent, if any, of public protection is not defined further although the aim is clear, namely to reduce the burden of contact allergy. The extent of the reduction that can be achieved through the application of QRA II is to be determined.

2. Hazard characterisation and threshold setting

i. *Use of animal testing*

Identification of an appropriate NESIL is the critical decision in the QRA. It is derived from a weight of evidence approach including animal tests (LLNA in mice, maximisation test in guinea pigs, historic human data and typically a confirmatory HRIPT). Although, as a result of an EU regulatory decision these tests will not be available for use in Europe, it was decided at an earlier workshop that there was insufficient time to include it as a central part of QRA II.

In regard to the use of the animal tests, the favoured current approach in QRA is to use the LLNA to identify an EC3 value which is equivalent to a NOEL in humans. It is stated that the LLNA provides a reliable assessment of the potency likely to be experienced in man. However, and although there are a number of studies to show that

this is the case, this critical assumption has not been justified fully in QRA I. It is very important for QRA II that this assumption is backed by appropriate published literature.

ii. Use of HRIPT

The EC3 value for each fragrance in the LLNA is converted to a human exposure concentration per cm^2 of skin. Based on this value a likely lower (safe) dose is estimated and this is usually applied as the sole dose level in the HRIPT test in human volunteers. The assumption is made that this is the 'gold standard' for identifying a safe level in man (NB It is very important for QRA II that this assumption is backed by appropriate published literature).

C. BEYOND QRA II

In view of the short time to submission there are several areas that, while very important will not achieve significantly progressed in time for the submission of QRA II. The identification and prioritisation of these areas was given as a remit to a breakout group.

- **Chemical considerations.** It was discussed whether structural alerts. (Q) SAR for induction could be better developed. The use of (Q) SAR for the identification of potential pre-haptens and /or pro-haptens was also considered to be a viable approach. It was agreed to ask the IDEA pre-& pro-hapten group to develop this recommendation.

- **Kinetics of absorption and persistence in the skin.** Better use of physicochemical data, such as volatility, might aid in the understanding of the influence of concentration and retention on potency.

- **Modes of action studies** with particular focus on the main drivers of potency was recognised as very important in the development of non-animal tests.

- **Effects of combinations of fragrance substances.** This is generally considered under the topic of cumulative exposure. Development in this area is dependent on progress on SAR and mode(s) of action.

- **Replacement of animal tests**

Some data will continue to be developed for REACH purposes using LLNA. However although it is an important source of data for the NESIL determination the LLNA should not be regarded as a gold standard for the purpose of future research into non-animal tests.

The likelihood in the near future, for at least some materials is that animal tests will not be available. The available list of validated non–animal models is very limited and this situation is unlikely to change rapidly. It was proposed to map out the strengths and weakness/uncertainties of each.

One approach is to use regression analysis based on an existing LLNA data base and other relevant data. The Direct Peptide Reactivity Assay (DPRA) based on the peptide binding rate seems to be the strongest contributor to potency assessment. To date use of physical chemistry data such as log P not found to be useful for the potency estimation of skin sensitisers.

For the future, the development of a framework based on the use judiciously chosen combinations of tests (termed *integrated testing strategies. (ITS))* is likely to prove the best way forward.
Tests may be designed to represent parts of the adverse outcome pathway beginning with structural alerts. Tests for reactivity with proteins, irritancy metabolic fate etc. may also be included in the series. Data may be presented as a probability of particular potency assignment computer software. It is an ongoing development with tests for other parts of the mode of action sequence being introduced progressively.

- **Occupational/professional exposure**

- This is a strong confounder of testing consumers for dermal sensitisation. However it falls under different legislation from that of consumer exposure. It can provide a valuable early warning of potential allergens.

D. CONCLUDING REMARK

Substantial progress was made at the Workshop. The next month will be a very challenging one and the help of the workshop participants will be needed at various stages in completing a strongly science based document. A time table will be drawn up and circulated to all *asap*. Everyone should identify how they can contribute.

Professor Jim Bridges
Workshop Rapporteur

Appendix 1 – Workshop Participants:

- European Commission and European Scientific Committees: Dr. Gaetano Castaldo (EU Commission, DG Sanco B2 Unit), Dr. Federica De Gaetano (EU Commission, DG Sanco B2 Unit), Prof. Pieter-Jan Coenraads (University Medical Centre Groningen and member of the SCCS).

- Academic community and national Authorities: Dr. David Basketter (Consultant), Prof. Donald Belsito (Columbia University Medical Center and RIFM Expert Panel Member), Prof. Magnus Bruze (Lunds Universiteit and RIFM Expert Panel Member), Prof. Thomas Diepgen (Ruprecht-Karls University), Prof. Jeanne Duus Johansen (University of Copenhagen), Dr. Janine Ezendam (RIVM), Prof. Margarida Goncàlo (University of Coimbra), Dr. Christine Lafforgue (Université Paris sud 11), Dr. Cronan McNamara (Crème Global), Prof. David Roberts (Liverpool John Moores University), Dr. Bob Safford (Consultant), Dr. Joanne Salverda (RIVM), Prof. Axel Schnuch (IVDK / University of Göttingen).

- Industry: Dr. Anne Marie Api (RIFM), Dr. Christophe Brault (LVMH), Dr. Dagmar Bury (L'Oréal), Dr. Peter Cadby (Chanel), Mr. Graham Ellis (Givaudan), Dr. Nicola Gilmour (Unilever), Dr. Peter Griem (Symrise), Dr. Etje Hulzebos (I.F.F.), Dr. Petra Kern (Procter & Gamble), Dr. Maya Krasteva (L'Oréal), Dr. Christeine Lally (Procter & Gamble), Dr. Florian Schellauf (Cosmetics Europe), Dr. Benjamin Smith (Firmenich).

- IDEA Staff: Dr. Hans-J. Bender (Moderator), Dr. Fred Lebreux (IFRA), Dr. Matthias Vey (IFRA).

- Supervisory Group members: Prof. Jim Bridges (Rapporteur), Dr. Ian White (Guy's & St Thomas' NHS Hospitals).

IDEA
International Dialogue for the Evaluation of Allergens

IDEA WORKSHOP

Characterization and Categorization of Fragrance Allergens

September 23-25th, 2014

1. Program
2. Report on the IDEA Workshop
3. Key conclusions of the IDEA Workshop

IDEA Management Team
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Fax: +32-2 214 20 69

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IDEA Workshop

Characterization and Categorization of Fragrance Allergens

September 23-25th, 2014

Château du Lac
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1332 Genval, Belgium
Tel: +32 (0)2 655 71 11, Fax: +32 (0)2 655 74 44

Program

Tuesday, September 23 – Welcoming

16:00 - 18:30 Welcome and registration

18:30 - 21:30 Standing buffet (Château du Lac, Grand Salon du Lac)

Wednesday, September 24 (9:00 am to 6:00 pm) – Day 1 (Geneviève plenary meeting room)

9:00 - 9:15 Workshop opening – *Hans Bender and Matthias Vey*

<u>First session – Relationship between contact allergy and the diagnosis of allergic contact dermatitis</u>

9:15 - 9:45 The usefulness of clinical data and the concept of clinical relevance
Speaker: Jeanne Duus Johansen

9:45 - 10:15 Understanding the link between contact allergy and allergic contact dermatitis, definition of a concept of clinical relevance
Speaker: Thomas Diepgen

10.15 – 11.00 Moderated discussion

11:00 - 11:15 Coffee break

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11:15 - 11:45	How to design meaningful studies to improve data collection (by reducing uncertainties associated with patch testing, including false positives and negatives), to feed the risk assessment and management process and provide information about the effectiveness of risk management interventions *Speaker: Magnus Bruze*
11:45 - 12:30	Moderated discussion
12:30 - 13:15	Lunch

Second session – Fundamental data basis for characterization and categorization of allergens

13:15 - 14:00	Identification of an allergen by non-clinical pre-tests (historical animal and human data and existing and future tools of alternatives to animal testing) for the characterization of allergens *Speaker: Graham Ellis*
14:00 - 14:35	Possible genetic controls of differing susceptibility to skin sensitization - experimental evidence. *Speaker: Peter Friedmann*
14:35 – 15:15	Identification of an allergen and identification of possible genetic predispositions by clinical data *Speaker: Axel Schnuch*
15.15 – 15.30	Coffee break
15:30 - 16:00	Understanding the differences of prevalence of skin sensitization which might be caused by consumer habits (e.g. in US vs. Europe) *Speaker: Don Belsito*
16:00 - 17:00	Moderated discussion

Conclusions of Day I

17:00 – 17:30	Preliminary progress report *Speaker: Rapporteur of the workshop (Ian White)*
	End of day One
19:00 - 22:00	Diner (Château du Lac, Grand Salon du Lac)

Thursday, September 25 (9:00 am to 4:30 pm) – Day 2 (Geneviève plenary meeting room)

9:00 - 9:15 Wrap-up of Day 1 and confirmation of WGs for day 2

Third session – Improve the dialogue between the Industry and the Dermatology Community

9:15 - 9:30 Feedback from the Communication TF and outlook into the future
Speaker: Peter Griem and Nicola Gilmour

9:30 - 9:45 Moderated discussion

Fourth session – Characterization and categorization of allergens

9:45- 10:15 Toward a meaningful system for the characterization and the categorization of allergens
Speaker: David Basketter

10:15 - 10:45 Moderated discussion

10:45 – 11:00 Coffee break

Fifth session – Working groups discussions

11:00 - 13:00 The participants will be subdivided into up to three working groups:

Meeting Room	*Theme*
Geneviève	Working group 1 – Theme and participants to be agreed at the end of Day 1 *Working group Rapporteur: to be determined*
Boardroom B	Working group 2 – Theme and participants to be agreed at the end of Day 1 *Working group Rapporteur: to be determined*
Boardroom C	Working group 3 – Theme and participants to be agreed at the end of Day 1 *Working group Rapporteur: to be determined*

13:00 - 13:45 Lunch

13:45 - 15:00 Presentation of the conclusions / recommendations of the working groups

15:00 - 15:15 Coffee break

15:15 - 16:30 Conclusions of the workshop and next steps

16:30 End of Day 2 and workshop closing

List of participants:

Prof. Klaus Andersen	Odense University Hospital, Denmark
Dr. Anne Marie Api	RIFM
Dr. David Basketter	Consultant in toxicology
Prof. Donald Belsito	Columbia University Medical Center and RIFM Expert Panel Member
Dr. Hans Bender	Consultant (Moderator of the IDEA Workshop)
Prof. James Bridges	University of Surrey and SCENIHR Chair
Prof. Magnus Bruze	Lunds Universiteit and RIFM Expert Panel Member
Dr. Peter Cadby	Chanel
Dr. Gaetano Castaldo	EU Commission – DG Sanco – Risk Management Unit
Prof. Pieter-Jan Coenraads	University Medical Centre Groningen
Dr. Federica de Gaetano	EU Commission – DG Sanco – Risk Management Unit
Prof. Thomas Diepgen	Ruprecht-Karls University
Prof. Jeanne Duus Johansen	University of Copenhagen and Member of the SCCS WG on Fragrance Allergens
Mr. Graham Ellis	Givaudan
Prof. Peter Friedmann	University of Southampton
Prof. Tony Gaspari	University of Maryland, US
Prof. David Gawkrodger	Former SCCS member
Dr. Nicola Gilmour	Unilever
Dr. Cécile González	International Fragrance Association
Dr. Peter Griem	Symrise
Dr. Etje Hulzebos	IFF
Dr. Petra Kern	Procter & Gamble
Dr. Fred Lebreux	International Fragrance Association
Dr. Sylvie Lemoine	AISE
Dr. Linda Loretz	PCPC
Dr. David Lovell	University of Surrey
Prof. Stefan Martin	University of Freiburg, Germany
Prof. Hans Merk	Universitätsklinikum Aachen
Prof. Jean-François Nicolas	University of Lyon, France
Prof. Marc Pallardy	Université Paris-Sud, France
Dr. Florian Schellauf	Cosmetics Europe
Dr. Scott Schneider	Firmenich
Prof. Axel Schnuch	IVDK / University of Göttingen
Dr. Matthias Vey	International Fragrance Association
Dr. Ian White	Guy's & St Thomas' NHS Hospitals and SCCS Chair

IDEA
International Dialogue for the Evaluation of Allergens

Report on the IDEA Workshop on

Characterization and Categorization of Fragrance Allergens

September 23-25th, 2014

Château du Lac
Avenue du Lac, 87
1332 Genval, Belgium

This report is based on the formal presentations and discussions that took place. It is intended to be a balanced report of what took place. Bias in the selection of speakers and interests of the other workshop participants affect the proceedings. The rapporteur (Ian R. White) had copies of the presentations and comprehensive notes taken during the meeting when preparing this report. Participants had the opportunity of commenting on the draft report. **Only items headed 'Agreed Conclusions' are such.**

1. Objective of Workshop

"To lay the foundation for an allergen characterization and categorization procedure which feeds risk management steps towards reduction of allergic contact dermatitis and which can be subject to continuous review, correlation, and improvement."

2. Definition of a Contact Allergen (Workshop Aug 27-29, 2013) for the purposes of IDEA

"A contact allergen is a substance that is capable of inducing delayed type sensitization in humans, which may manifest as allergic contact dermatitis.
The elicitation of allergic contact dermatitis requires sufficient exposure and is subject to significant inter-individual variability".

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

www.ideaproject.info

3. Relationship between contact allergy and allergic contact dermatitis

Contact allergy may be induced by skin contact with low molecular weight haptens and may evolve to allergic contact dermatitis if the exposure exceeds the individual elicitation threshold in sensitized individuals.

Contact allergy is an altered immune status induced by a specific substance; it is demonstrated by a positive patch test and identifies the population at risk of developing allergic contact dermatitis.

Once sensitised (induction has occurred), allergic contact dermatitis occurs when the exposure to the allergen exceeds the individual threshold of elicitation. When exposure to an allergen is causing/has caused clinical symptoms (disease) of dermatitis (allergic contact dermatitis) the allergen is considered to be of current/old relevance, respectively. It may be the case that there is no obvious history of exposure or dermatitis relevant to the allergen and in such circumstances the individual's allergy is considered to be of unknown relevance. However, should sensitised individuals have appropriate exposure at some time in the future they will be at risk of developing allergic contact dermatitis. In this respect, contact allergy can have life-long implications for the individual.

Most knowledge about contact dermatitis is derived from clinical case reports, clinical studies of in- and out-patient groups, statistical compilations of patch test reports, and from studies of small outbreaks of dermatitis.

Dose-response thresholds are important to consider in both the induction of contact allergy and its expression in the elicitation of allergic contact dermatitis. In general, more individuals will become sensitised with higher doses or repeated lower doses (exposure) of the allergen and similarly for the elicitation of reactions.

Dinitrochlorobenzene (DNCB) has been used as an experimental model to show the effects of dose on induction. Repeated open application tests (ROAT) with a number of fragrance allergens and preservatives illustrate the important of frequency of applications for the elicitation of allergic contact dermatitis in the clinical setting. A ROAT may mimic consumer exposures.

Patch testing (performed according to the International Contact Dermatitis Research Group (ICDRG) guidelines) is the gold standard to determine the presence of contact allergy.

Patch test concentrations should cause a minimum of irritant/doubtful and a maximum of allergic reactions and are determined accordingly (the highest non-irritant concentration that will cause the fewest false-negative reactions). The clinical technique, allergen preparation, application, reading and

interpretation is presently under review by the European Society of Contact Dermatitis (ESCD) who are writing a guideline. Considering fragrance allergens, however, they should be applied to test chambers immediately before application to the skin to reduce evaporation which could lower the dose.

For fragrance substances there are now two mixes of fragrance allergens (**fragrance mix I** containing *Evernia prunastri* (Oak moss abs.), isoeugenol, cinnamal, cinnamyl alcohol, eugenol, hydroxycitronellal, geraniol and α-amyl cinnamal; **fragrance mix II** containing hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), citral, farnesol, citronellol, hexyl cinnamal and coumarin) and **Balsam of Peru** (*Myroxylon pereirae*) used in routine diagnostic patch testing as indicators (screening agents) with varying specificity and sensitivity regarding contact allergy to fragrances.

Current data from the National Allergy Research Centre in Denmark show that (*circa*) 8% of eczema patients undergoing patch testing have contact allergy to fragrance mix I, 5% to fragrance mix II, 4% to Balsam of Peru and 2% to the specific fragrance chemical HICC. Of females tested, some 14.5% of women have contact allergy to the fragrance markers and 10% of men with an overall rate of 13% in the tested population. In the years 2005 to 2008 the prevalence of fragrance mix I in Germany was 6.58% (standardized for age and sex) (Uter W et al. Contact Dermatitis 2010: 63; 254-261). In 2010: 7.4% ; in 2011 : 8.1% ; in 2012: 9.1% (all standardised) (Mahler V, Geier J, Schnuch A. Deutsche Dermatologische Gesellshaft. DOI: 10.111/ddg.12371; 2014). For 2013 (not yet published) 8.8% (Schnuch, personal communication). There are temporal variations but the current overall trend appears to be upwards.

Determining clinical relevance of a positive patch test reaction can be difficult and time-consuming. In essence it depends on:

a) History of the patient (including information on exposure and (subsequent) rashes/eczema);

b) Re-exposures with the suspected allergen patch test preparation and, if needed, patch testing with own products and use testing with a suspected product;

c) Exposure analysis which involves the expert knowledge of the investigating dermatologist, review of product ingredient labels, material safety data sheets (MSDS) and (when available) chemical analysis and, if available, information from the manufacturer of the consumer product.

The reading of patch test reactions is a standardised (?+, +, ++, +++) system to show the 'severity' of the reaction (allergic contact dermatitis) elicited by the standardised allergen preparation. Weak (+), strong (++), and extreme (+++) reactions, classified according to the respective morphology are considered as positive reactions. At least a (+) reaction is considered as a proxy for contact allergy.

The industry-sponsored 'EDEN' study (Diepgen et al) has shown good reproducibility of fragrance mix patch test results for ++ and +++ reactions but poorer reproducibility of former patch test results for + reactions and excellent specificity for negative subjects.

In general, individuals who show stronger reactions will experience elicitation reactions with lower concentrations of the allergen. Studies have shown that up to 100% of patients with +++ reactions to fragrance markers have a positive history of fragrance intolerance but only a quarter of those with ?+ reactions. (Frosch PJ et al. Contact Derm 1995:32; Johansen JD et al. Acta Derm Venereol 1997:77).

For repeated exposures, as in the ROAT, smaller concentrations are sufficient for elicitation as compared to patch testing. The number of days (exposures) until elicitation occurs depends on the exposure concentration. This is illustrated with isoeugenol where for 0.2%, 7 days of exposure (median) was required and for 0.05%, 15 days of exposure (Andersen KE et al. Toxicol Appl Pharmacol 2001:170:166-171). The individual's threshold dose needed for elicitation in patch testing affects the time required for elicitation in a ROAT (as sensitivity increases (the threshold dose decreases) the time until a positive ROAT decreases). Two applications per day for 14 days is recommended (Johansen JD, Frosch PJ, Svedman C, Andersen KE, Bruze M, Pirker C, Menné T. Contact Dermatitis 2003:48:310-316). When doing such elicitation tests it is important to appreciate that sensitivity depends on anatomical region: axilla > arm; face=neck> arm; upper back > lower back.

Perfumes for women were shown to have a mean content of 12 fragrance allergens (of the 26 required to be labelled) (Buckley DA.Br J Dermatol. 2007 :157; 295-30) as determined by examination of product labels. In the Uter et al study (Contact Dermatitis 2013: 69; 335-341) the median number of fragrance allergens labelled in products varied between categories, ranging up to 9 in perfumes. Such mixtures ('cocktails') of allergens reflect normal consumer exposure. In animal experiments it has been shown that mixtures enhance induction and elicitation (Bonefeld C et al. Contact Dermatitis 2011: 65; 336-42).

For 1790 patients with diagnosed fragrance allergy, the contact allergy was relevant in at least 60% of cases and in 753 (42.1%) a cosmetic product was identified as the cause of the dermatitis (Heisterberg M on behalf of DCDG, Contact Dermatitis 2011: 64; 258-64). Deodorants, scented lotions, fine fragrances, shampoos and liquid soaps and aftershaves were particularly responsible.

Clinical relevance provides information for the patient with a dermatitis (whether the allergen is causing or contributes to the dermatitis, or is of old relevance). Assessment is complicated and resource demanding and (usually) does not provide information about what induced the contact allergy. Information about presence of individual chemicals is critical.

Patch test data provides the first indication that sensitisation is occurring. Data from larger patch test populations may indicate that sensitisation is occurring in the general population (or specific subgroups), which is therefore of concern.

Although the dose required for induction of contact allergy is (usually) higher than required for the elicitation of an allergic reaction, regulations do restrict exposure based on elicitation concentration rather

than induction concentration if the frequency of contact allergy is high in the general population. Examples of this are nickel and chromium (cement, leather). Clinical epidemiological data illustrate the benefits of this approach. Clinical epidemiological data has also been used as evidence of concern leading to ban (legal prohibition) allergens from the market to prevent any further exposure to the consumer. Clearly, consumer exposure to allergens should be such as to prevent the induction of contact allergy in the first place (primary prevention) and thereby prevent a proportion of the population from having to be protected from elicitation reactions (secondary prevention). To date, the only available method to achieve this has been by restrictions based on elicitation data. This has direct relevance for humans and provides safe levels for both induction and elicitation. In the future, a scientifically valid and applied Quantitative Risk Assessment (QRA) may be utilised.

4. Differences in prevalence of skin sensitisation

Provided that patch testing has been done in a standardized way following the pertinent guidelines (to reduce uncertainties associated with patch testing due to e.g., non-standardised patch test material or inadequately trained personnel), regional variations in the prevalence of contact allergy to a particular allergen may be due to:

1) variation in product usage and. allergen exposure,
2) differences in proportion of occupational cases seen,
3) inter-individual variations in patch test readings and
4) access to care / patch testing.

Data from the United States of America (USA) show differences in prevalence which could be due to variations in product use and patterns, access to patch testing and the way patch test reading takes place. Interpretation of data is difficult as there is a huge geographical area with relatively few numbers (clinical data) from individual centres. There might also be selection bias based on health insurance. Further, the TRUE Test® is less sensitive than petrolatum-based allergens for fragrance mix I (Mortz CG, Andersen KA. Contact Dermatitis 2010: 63; 248-53).

Data from Europe also show geographical differences (Uter et al. Contact Dermatitis 2012: 67; 9-19 and Schnuch et al. Contact Dermatitis 1997: 37; 200-209).

An allergen may be rarely reported simply because it is not tested.

Agreed Conclusions

Properly conducted patch tests are the ‘gold standard’ for the clinical detection of contact allergy.

-Positive patch tests are the indication that exposure to a substance is causing contact allergy with a risk of allergic contact dermatitis and should trigger a re-evaluation of the risk.

-Epidemiological evaluation of patch test results allow a comparison of the relative importance of contact allergens in terms of frequency of reaction and indicate contact allergy trends over time.

-Positive patch test data represent the relevant endpoint in humans and are core data which assist in making decisions for preventive strategies in public health.

Proposal for additional conclusion, provided by Johansen and Diepgen on request of the workshop participants but not discussed or agreed at the Workshop

-Exposure information is crucial for diagnosing contact allergy and allergic contact dermatitis, for advising patients and for prevention. The most important source of exposure information concerning cosmetic products is ingredient labelling.

5. Data basis for characterisation and categorisation of allergens

Methods to determine sensitisation potential of a substance include:

- OECD[3] 429: Local lymph node assay (LLNA);
- OECD 406: Guinea pig maximisation test (GPMT), Buehler occluded patch test.

However, these are no longer permitted in Europe for new cosmetic ingredients where the information generated would be used solely for the purposes of risk assessment in the sector. Historical data, created before the legislative cut-off, can be used.

In silico tools (Weight of Evidence) with read-across and structural considerations (alerts) are utilised.

Human non-clinical studies (in that they are done on normal individuals and not as part of the investigation of a disease process) include human maximisation test (considered as unethical in Europe) and the human repeat insult patch test (to show that the substance does not induce contact allergy under the test condition).

Now, a series of *in vitro/ in chemico* methods are under varying degrees of development and for some (Direct Peptide Reactivity Assay (DPRA), keratinocyte activation (KeratinoSens), human cell-line activation test (h-CLAT)) – OECD guidelines are expected to be published. For these, however, they provide

[3] Organisation for Economic Cooperation and Development

information on whether the substance is a sensitiser or not but not the relative potency. Additionally, they provide no or very limited capability to identify pro-haptens. These methods are not developed as stand-alone assays to replace the animal assays, but are meant to be used in combination under a testing strategy scheme.[4]

Allergen classification for labelling and packaging (CLP) legislation originally has been developed for handling of substances in the workplace. There is scepticism among the dermatological community and others that it is of use for the prevention of contact allergy or the development of allergic contact dermatitis in the consumer.

An OECD guidance document under development aims to describe an Integrated Approach to Testing and Assessment (IATA) as a structured approach used for hazard identification (potential), hazard characterisation (potency) and/or safety assessment (potential/potency and exposure) of a chemical or group of chemicals, which strategically integrates and weights all relevant data. This approach considers metabolism, biological availability, covalent binding, cellular response, organ response (T cell proliferation), outcome (clinical, challenge) applied in a matrix to inform weight of evidence. This general framework guidance for skin sensitization:

1) anticipates sufficient flexibility in the use of the individual information sources to cover multiple regulatory needs within OECD member countries;
2) provides generic guidance on the evaluation and application of IATA;
3) provides consistent description of the information sources that can be used within an IATA for skin sensitisation and
4) includes a template for describing IATA so that the same documentation format for describing and evaluating IATA can be used by member countries.

Although significant progress has been made on *in vitro* methods for hazard identification, the challenge remains potency assessment. Additionally, identification of weaker allergens remains a problem. A Weight of Evidence approach to No Expected Sensitisation Induction Level (NESIL) needs to be developed.

Agreed Conclusion

[2] If protein reactivity (DPRA) and keratinocyte activation (KeratinoSens) are both negative this is highly sensitive to predict that the substance is a non-sensitiser. If there is dendritic cell activation (e.g. h-CLAT) then this is highly sensitive to predict the substance is a sensitiser.
The so-called 'gold list' of substances spanning a range of sensitising potencies developed from LLNA and other data should be used with caution as original data may not be accessible and errors are known to be present.

Non-clinical methods including non-animal approaches (e.g. those with OECD guidelines) have the potential to allow for the identification of a contact allergen. However non-animal test systems require further refinement for characterization and categorization.

6. Characterisation and categorisation of allergens

For allergic hazard potential of substances, the 'sensitivity' is:

- Clinical diagnostic capability > limit of predictive toxicology > regulatory limits

After a hazard has been identified, the next step is to examine the dose response and use it to characterise the relative potency of the substance. For the local lymph node assay (LLNA), this is well recognised as the EC3[5] value, now widely used as a potency marker. For *in vitro* methods, some methods or IATA may provide some information on potency, but they do not achieve the graded response of the LLNA. Human data can play a role.

For nearly 50 years, there have been two categories: sensitiser/not classified. Recent "progress" advanced this to three: strong sensitiser/moderate sensitiser/not classified. The European Chemicals Agency (ECHA) Guidelines have taken a step further: extreme/strong/moderate/not classified. The Scientific Committee for Consumer Safety (SCCS) have also made category suggestions. A recent proposal has proposed 6 categories:

- Extreme/strong/moderate/weak/very weak/non-sensitiser.

Regulatory classification: human

Human evidence for sub-category 1A (under the CLP system, differentiating very strong and strong skin sensitisers in 1A and 1B) can include:

1) positive responses at ≤ 500 µg/cm2 (human repeat insult patch test (HRIPT), human maximisation test (HMT) – induction threshold);
2) diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure;
3) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.

[5] The EC3 value, interpolated from the dose response curve, is the effective concentration of the test substance required to produce a three-fold increase in the stimulation index compared to vehicle-treated controls.

Human evidence for sub-category 1B can include:

1) positive responses at > 500 µg/cm^2 (HRIPT, HMT – induction threshold);
2) diagnostic patch test data where there is a relatively low but substantial incidence of reactions in a defined population in relation to relatively high exposure;
3) other epidemiological evidence where there is a relatively low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure.

The United Nations Globally Harmonized System of Classification and Labelling of Chemicals (GHS) may be used to split the classification of allergens as Extreme, Strong, Moderate, Weak, Very Weak, Non-sensitiser (Basketter et al, 2014; Dermatitis 25; 11-21) and could help by associating each category with a default NESIL and existing substances placed into these six categories could assist in the evaluation of *in vitro* methods for potency prediction.

Fragrance ingredients, as ordinary chemicals, are covered by chemical regulations and use of > 1 tonne per annum puts them within REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals).

To ensure that any actions (classification, exposure) are meaningful for prevention of contact allergy there must be measurement focused on consumers and workers.

7. Genetic factors

For certain drugs there is very clear and strong evidence of genetic determination of susceptibility to sensitisation. For certain contact allergens genetic linkage has been shown controlling reactivity to various metals, dinitrofluorobenzene (DNFB) and other allergens in various strains of mice. Relevant linkage is almost all within H2 and Ia regions (Homologues of human HLA Class I and II). Most mice cannot be sensitised to nickel because of a lack of key histidine residues in the toll-like receptor (TLR)-4– nickel binds to histidine, hence in humans, TLR-4 is activated. Guinea pigs of strain II can be made allergic to dichromate and beryllium but not mercury. Guinea pigs of strain XIII are the reverse (Polak, Barnes & Turk (1968) Immunology, 14: 707-711).

The role of TLR-4 in sensitisation to nickel in mice was recently challenged. The allergic response to nickel following epicutaneous exposure is MYD88-dependent (an element of the innate immune system) and interleukin (IL)-1 receptor dependent, but independent of TLR-4 (Vennegaard et al. Contact Dermatitis 2014: 71; 224-231).

In considering the situation in man, we may consider 1) genetic control of general susceptibility to sensitisation by anything – non-specific susceptibility (high/low responders) and 2) specific susceptibility to sensitisation by the allergen(s) of interest where single gene products may be critical – HLA molecules, TCR, specific proteins that get haptenated etc.– as in drug allergy. Susceptibility may be acquired.

In general, there is a normal (Gaussian) distribution of reactivity in humans. Polysensitised individuals have a stronger response on challenge, i.e., a lower elicitation threshold. (Moss C, Friedmann PS, et al. Clin Exp Immunol 1985; 61: 232-4; Schnuch A, Westphal G, et al. Contact Dermatitis 2011; 64:2-23). Polysensitisation can be regarded as a clinical sign of increased susceptibility.

It was presented that genetics/polymorphisms may play a role in sensitization to moderate/weak allergens or in lower exposure conditions in combination with further risk factors.

The HRIPT enrols 'normal' individuals. Testing 'at risk' populations would increase sensitivity. Increasing age appears to be a risk factor for polysensitisation.

Whatever the influence of genetic susceptibility on sensitisation, the relative influence is considerably lower than exposure (dose) and sensitising potency of an allergen. In general, exposure is critical, not susceptibility. However, in cases of contact allergy, where the chemical is i) a very rare sensitiser and ii) a very weak sensitiser, susceptibility could be the driving force compared to the above 'normal' situation.

Agreed Conclusion

The role of genetic factors in susceptibility to contact allergy is yet to be defined.

8. Improving Dialogue between Industry and the Dermatology Community

There is a complex communication interchange between the dermatologist – patient – industry with regards to information on the presence of an allergen, availability to test the substance and mechanisms for the patient (consumer) to avoid exposure.

An industry-led task force has been mandated to establish a process for obtaining diagnostic data.

1) Working process to identify (fragrance) allergens that is well-publicized to both industry and dermatology communities (global).
2) Easy way to identify individual(s) in consumer product companies for the dermatologist to contact on a worldwide basis.
3) Standardized method of supplying properly identified samples to dermatologist.
4) Formal mechanism for obtaining results from the dermatologist.
5) Agreement on information needed to help improve the risk assessment.
6) Formal mechanism to review data on (fragrance) allergens.

7) Identifying potential pro-active surveillance fragrance materials for dermatologists to test.

It is central that feedback be established so that:

- Industry → Dermatologists: provide reference materials to help the diagnosis of contact dermatitis
- Dermatologists → Industry: provide results of clinical testing as feedback into risk assessment/management process

Full ingredient labelling is seen as essential by the dermatological community. However, in the absence (at present) of full ingredient labelling of fragrance substances, there is a requirement to develop a strategy to inform the consumer of the presence of non-labelled fragrance substances to which they have a contact allergy. Additionally, there should be a single point of contact.

Agreed Conclusion

Readily accessible product ingredient information including labelling is critical for evaluating exposure, reliable diagnosis and prevention.

9. Break out reports

9.1. Studies

Retrospective studies are problematic as data from different centres may involve different samples, methods, readings etc. as well as competence of local dermatologists.

For new materials early studies are of dubious benefit as it can take time before consumer exposure to the material is established.

However, there is a need for accurate baseline data for prevalence to assess the effectiveness of QRA and to develop a procedure for dealing with clinical alerts.

A common protocol for patch testing, with a high degree of standardization and calibration for the preparation, application, reading and interpretation of the test material(s) is critical for the establishment of baseline data from different clinics.

Fragrance mixes I and II and the 14 individual ingredients should be monitored, together with *Evernia furfuracea* (Tree moss) and oxidised linalool and limonene. For oxidised linalool and limonene they must be adequately standardised as patch test ingredients. The relevance assessment of these oxidation products is taking place in the context of the IDEA workshop on pre- and pro-haptens.

For other substances, routine testing of groups of substances over blocks of time would provide information on the prevalence and relative importance of them as allergens (information on consumer exposure is required).

Synchronous application of patch ingredients and on consecutive patients is required from a range of dermatology centres with the necessary competences and clinic loads.

Use of a detailed questionnaire is required to obtain quantitative and qualitative information on exposures (to fragrance allergens), occupation, consumer habits, past and present topical drugs used, product types presented by the patient, body site of initial and present dermatitis, etc.

Primary readout is the prevalence of contact allergy (endpoint of concern) and the secondary readout is the prevalence of allergic contact dermatitis.

The studies should be overseen by an independent organization (e.g., European Commission services/Joint Research Centre (JRC) of the European Commission).

9.2. Suggested criteria for ranking the relative concern of fragrance allergens

Although many reactive chemicals will qualify as a 'contact allergen', this does not necessarily mean that adverse reactions will occur in practice. Therefore, an appropriate question is what are the criteria that qualify a substance as contact allergen of concern?
It is important to consider allergens with human data. *In vitro* / *in silico* / animal data are helpful but by themselves insufficient.

Some substances are assumed to be contact allergens only in a specific context. Mixture effects, presence of skin penetration enhancers and patch test concentration may have importance in the elicitation process.

In clinical practice, the routine surveillance of contact allergy to fragrance substances covers only a few such substances (those in fragrances mixes I and II, *Myroxylon pereirae* and, from some centres, those fragrance allergens required to be labelled in the European Union (EU)); this is insufficient.

Concerns result from the multiplication of several factors, the most important being: individual cases of allergic contact dermatitis, clinical epidemiology demonstrating contact allergy (including data from

cosmetovigilance networks) and population-based studies of contact allergy, including occupational subgroups.

Exposure assessment may be difficult where there is a lack of appropriate information. Presently, the presence of only 26 fragrance allergens is required on the ingredient labels of cosmetic products and household detergents. No other meaningful labelling or consumer information tool exists currently.

At least some indication of the exposure levels to all suspect substances in the general population is essential.

It is suggested that the relative concern regarding fragrance allergens could be considered as:

Major concern

•Many reported cases (at least 100) of contact allergy or,
•Few reported cases (at least 10) where there is low and/or infrequent exposure or,
•Some cases of very severe allergic contact dermatitis.

Potentially major concern

•There are cases but there is no existing epidemiological survey to confirm the frequency in the general population or in a subgroup.
•Non-clinical data (*in vitro*, *in silico*, animal) indicates a risk, but there is no clinical or epidemiological data to confirm it.

Moderate concern

•More than minor but does not fit criteria for major.
•*Definitio per exclusionem*.

Minor concern

•Isolated sporadic case reports where there is large and/or frequent exposure and,
•Large epidemiological data demonstrates/confirms rarity of contact allergy.

No current concern[6]

(This remains to be formally discussed and fully considered).

9.3. Communication

[6] This was not fully discussed at the IDEA meeting but a suggestion post-meeting was: "Many people have been extensively exposed to the substance over a long time (a minimum of 7 years), but where the chemical has been sufficiently tested, and in particular surveyed by an epidemiological surveillance system, contact allergy has been shown to be extremely rare."

Ideally, samples for patch testing should be diluted according to de Groot. If not listed in de Groot, the raw material (with Certificate of analysis of all ingredients) should be provided.

For larger companies there is usually no problem with this, but this may not be so for small and medium sized enterprises (SMEs).

On line resources are needed that provide information to dermatologists (e.g. guidelines for sample preparation/who to contact, etc.) to help diagnosis.

Diagnosis allows identification of causative agents and a means to avoid. Full ingredient labelling is central to providing the consumer (patient) a means to avoid future exposures that are detrimental to their health (elicitation of allergic contact dermatitis). The construction and maintenance of lists of products that do not contain the material of concern and list of safe alternatives would be helpful for the consumer.

Ingredient information must be available at the time of assessment. Although full product ingredient labelling is central to this and fragrance substances are no different than other chemicals/substances), 'apps' and similar digital resources are considered important supportive systems.

The key to monitoring the safety of a cosmetic ingredient, including a fragrance substance, is good feedback form clinician/patient and industry. Stakeholder meetings to discuss new and emerging allergens are necessary.

10. Overall Discussion and Conclusions:[7]

Risks to human health presented by contact allergens must be rigorously assessed and properly managed.

Patch testing performed by appropriately trained individuals (necessary competencies with frequent and direct patient involvement) fits the criteria for which the testing has been designed, to be sensitive and specific as a diagnostic tool. The relevance of a positive patch test for an individual (patient or consumer) is a matter for the trained dermatologist investigating the patient.

A positive patch test (demonstrating contact allergy) is the first indication that exposure to a substance is causing allergy in the population. Data from individual clinics and regions may be used as a means of comparing the relative importance of contact allergens in terms of the frequency of reactions and allows contact allergy trends to be followed over time.

A positive patch test reaction does not:

[7] These are produced by the rapporteur.

- prove what exposures caused the induction of contact allergy;
- give any dose-response information for the causal exposure;
- inform on what types of exposure may be tolerated, either for induction or elicitation.

Some non-experts may believe that a positive patch test result is not relevant for "real life" exposures. This is a fallacy, based on the failure to understand that the elicitation of contact allergy under diagnostic patch test conditions is intended to show only one thing, whether an individual patient has contact allergy to a substance. Those real life exposures have culminated in an adaptive immune response. A test material may not represent the "labelled allergen" but rather the "actual allergen" to which the consumer (or worker) is exposed (e.g. linalool, oxidised linalool). Thus, pre- /pro-hapten activities must be considered.

Positive patch test data should inform those who produce and/or use the substance that:

- it is a skin sensitiser;
- consequently, a potential cause of contact allergy….
- and, therefore, of allergic contact dermatitis.

Exposure information is crucial for diagnosing contact allergy and allergic contact dermatitis, for advising patients and for prevention. To date and in practice, the most important source of exposure information concerning cosmetic products is ingredient labelling.[8]

QRA must be evaluated by its impacts in minimising the frequency of contact allergy to fragrance substances in the population (eczema patients undergoing routine patch testing may be considered an at risk group and, therefore, suitable for study). However, it is also critical to the evaluation that sources of exposure to the substance can be easily identified. It is accepted by dermatologists[9] that full ingredient labelling is pivotal to this; on-line and other resources should be considered a desirable addition and not a substitute for ingredient labelling.[10]

[8] The 6th Amendment of the Cosmetics Directive (93/35/EEC, June 1993) introduced full ingredient labelling apart from fragrance substances. The preamble to the Directive stated that labelling would allow consumers with an identified contact allergy to avoid exposures harmful to them. The 7th Amendment introduced labelling (with pragmatic limits of 10 ppm and 100 ppm for leave-on and rinse-off cosmetic products, respectively, determined by the European Parliament) of 26 fragrance substances identified in the 1999 Opinion of the SCC-NFP (SCCNFP/0017/98 Final). The 2012 Opinion of the SCCS (SCCS/1459/11) on contact allergy to fragrance substances identified 54 simple chemicals (12 high risk) and 28 natural extracts (8 high risk) that are established contact allergens in man. The consumer is presently unaware of the presence of many fragrance substances identified as allergens.

[9] This has been stated by national associations (dermatology) in Europe and the ESCD.

[10] In the agreed Conclusion of the first IDEA meeting on QRA, March 2013, it is stated "Labeling and Provision of information on ingredients as an important complement to QRA and in-market validation."

Classification and potency sub-categorisation of allergens may be useful in prioritising work on consumer protection only. They are not substitutes for primary and secondary preventive strategies.

In order to progress the IDEA project, studies are now required to examine the effectiveness of QRA and the frequency of contact allergy to fragrance substances in eczema patients (as a proxy for the general population). As well as monitoring the frequencies of contact allergy to the substances present in Fragrance mixes I and II, oxidised limonene and oxidised linalool are a good starting point for the other SCCS-identified materials to be assessed. These lists are, however, indicative and not exhaustive and other substances identified as potential allergens in humans from *in vitro* or *in silico* methods should be monitored for contact allergy.

Such studies will permit feedback into the QRA model as a tool to prevent induction of contact allergy (primary prevention).

Protocols for the necessary studies should be drawn up independently of industry or its advisers. Although the Joint Research Centre (JRC) of the European Commission could be involved, a suggestion is that the IDEA Supervisory Group takes on the responsibility. Monitoring and evaluation should also be independent.

Priorities for other activities to progress the IDEA project also need to be identified and an action plan established to enable them.

Dr. Ian R. White
Workshop Rapporteur

Appendix 1 – Workshop Participants:

- European Commission and European Scientific Committees: Dr. Gaetano Castaldo (EU Commission, DG Sanco B2 Unit), Dr. Federica De Gaetano (EU Commission, DG Sanco B2 Unit), Prof. Pieter-Jan Coenraads (University Medical Centre Groningen and member of the SCCS).

- Academic community and national Authorities: Prof. Klaus Andersen (Odense University Hospital), Dr. David Basketter (Consultant), Prof. Donald Belsito (Columbia University Medical Center and RIFM Expert Panel Member), Prof. Magnus Bruze (Lunds Universiteit and RIFM Expert Panel

Member), Prof. Thomas Diepgen (Ruprecht-Karls University), Prof. Jeanne Duus Johansen (University of Copenhagen), Prof. Peter Friedmann (University of Southampton), Prof. Tony Gaspari (University of Maryland), Prof. David Gawkrodger (University of Sheffield, former SCCS member), Dr. David Lovell (University of Surrey), Prof. Stefan Martin (University of Freiburg), Prof. Hans Merk (Universitätsklinikum Aachen), Prof. Jean-François Nicolas (University of Lyon), Prof. Marc Pallardy (Université Paris-Sud), Prof. Axel Schnuch (IVDK / University of Göttingen).

- Industry: Dr. Anne Marie Api (RIFM), Dr. Peter Cadby (Chanel), Mr. Graham Ellis (Givaudan), Dr. Nicola Gilmour (Unilever), Dr. Peter Griem (Symrise), Dr. Etje Hulzebos (I.F.F.), Dr. Petra Kern (Procter & Gamble), Dr. Sylvie Lemoine (AISE), Dr. Linda Loretz (PCPC), Dr. Florian Schellauf (Cosmetics Europe), Dr. Scott Schneider (Firmenich).

- IDEA Staff: Dr. Hans-J. Bender (Moderator), Dr. Cécile González (IFRA), Dr. Fred Lebreux (IFRA), Dr. Matthias Vey (IFRA).

- Supervisory Group members: Prof. Jim Bridges (University of Surrey), Dr. Ian R. White (Guy's & St Thomas' NHS Hospitals, Rapporteur)

IDEA
International Dialogue for the Evaluation of Allergens

Key conclusions of the IDEA Workshop

Characterization and Categorization of Fragrance Allergens

September 23-25th, 2014

- Properly conducted patch tests are the gold standard for the clinical detection of contact allergy.
- Positive patch tests are the indication that exposure to a substance is causing contact allergy with a risk of allergic contact dermatitis and should trigger a reevaluation of the risk.
- Epidemiologic evaluation of patch test results allow a comparison of the relative importance of contact allergens in terms of frequency of reaction and indicate contact allergy trends over time.
- Patch test data represent the relevant endpoint in humans and are core data which assist in making decisions for preventive strategies in public health.
- Non-clinical methods including non-animal approaches (e.g. those with OECD guidelines) have the potential to allow for the identification of a contact allergen. However non-animal test systems require further refinement for characterization and categorization.
- The role of genetic factors in susceptibility to contact allergy is yet to be defined.
- Readily accessible product ingredient information including labelling is critical for evaluating exposure, reliable diagnosis and prevention.

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

www.ideaproject.info

IDEA
International Dialogue for the Evaluation of Allergens

IDEA WORKING GROUPS

1. Hydroperoxide Task Force
2. Categorization Task Force
3. Communication Task Force

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

www.ideaproject.info

IDEA
International Dialogue for the Evaluation of Allergens

IDEA MEETING

Hydroperoxides Task Force

March 24th, 2014

1. Agenda
2. Final minutes of the IDEA meeting
   - Attachment 1 to the minutes
   - Attachment 2 to the minutes

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

www.ideaproject.info

IDEA
International Dialogue for the Evaluation of Allergens

IDEA Meeting of the

Hydroperoxides Task Force

March 24th, 2014 from 2:00pm to 6:00pm

IFRA-IOFI Offices
Avenue des Arts, 6
B-1210 Brussels, Belgium
Tel: +32 (0)2 214 20 61, Fax: +32 (0)2 214 20 69

Program

1. Adoption of the agenda
2. Key objectives of this group: presentation and discussion
3. Hydroperoxides of concern:
    - From which terpenes?
    - Which isomers?
4. The synthesis of hydroperoxides
    - Background science
    - Approach to adopt and establishment of criteria to select a contract research lab
    - Specific questions (hazardous chemicals transporter, stability upon storage)
    - Potential research labs
5. The quantification of hydroperoxides
    - Background science
    - Approach to adopt
    - Establishment of criteria to select a contract analytical lab
6. Definition of needs for further analytical studies (e.g. stability studies)
7. Potential applications for the methods still to be developed
8. Next meeting

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

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Final Minutes

Participants: Jean-Marie Aubry (Lille university), Hans Bender (IDEA), Anna Börje (Gothenburg university), Hugues Brevard (Robertet), Alain Chaintreau (Firmenich), Elena Gimenez (Strasbourg university), Fred Lebreux (IDEA), Andreas Natsch (Givaudan), Ulrika Nilsson (Stockholm university), Neil Owen (Givaudan), Véronique Rataj (Lille university), David Roberts (Liverpool university), Clémentine Marteau (I.F.F.), Matthias Vey (IDEA).

1. Adoption of the agenda

As a result of the election conducted in March, Alain Chaintreau was appointed chairman of the IDEA Hydroperoxides TF. An informal agreement was taken between the two candidates who applied for the chairman position: Alain Chaintreau will lead the group until completion of the chemical part, then Andreas Natsch will take care of the follow-up application of developed methods to risk assessment.

The chairman opened the meeting at 2:00pm by welcoming the participants and organized a tour de table. The agenda was adopted such as provided. The Chairman's general presentation is attached to the minutes (att.01).

2. Antitrust statement

The Chairman reminded the constraints of the antitrust law to the participants. All agreed that there shall be no discussions of agreements or concerted actions that may restrain competition. This prohibition includes the exchange of information concerning individual prices, rates, coverages, market practices,

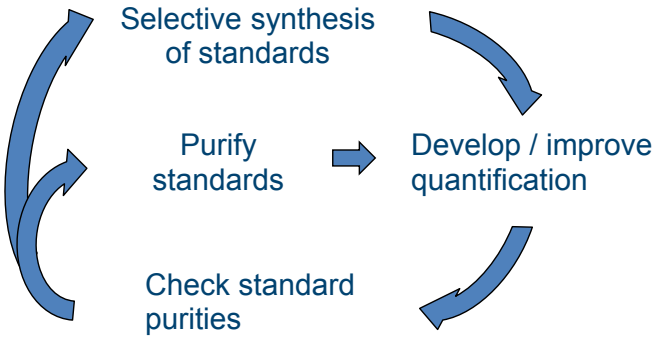
claims settlement practices, or any other competitive aspect of an individual company's operation. Each participant is obligated to speak up immediately for the purpose of preventing any discussion falling outside these bounds.

3. Key objectives of this group: presentation and discussion

The key objectives of this group were summarized as follows:

- Select and ensure the general availability of a suitable range of pure references resulting from abiotic transformation of fragrance ingredients; this step implies the development of procedures to prepare and purify haptens currently not commercially available. Furthermore, and because some products of abiotic transformation may be unstable (i.e. hydroperoxides), the half-life of these chemicals as well as any other parameters related to their conservation should also be investigated.
- Use these references to develop new analytical methods for the detection and the quantification of chemically-defined haptens, resulting from abiotic transformations, in fragranced products. These methods should be sensitive, specific, with target limits of quantification below the estimated induction levels and limits of detection below the estimated elicitation levels.
- Make all relevant haptens resulting from the abiotic transformation of fragrance ingredients readily available for patch-testing. In case of success, these new patch-testing references will be presented to the dermatology community and potentially introduced in patch test baseline series.

The participants agreed that the hydroperoxides issue can only be solved via an iterative approach as pure hydroperoxides are necessary to develop a reliable quantification method and a reliable quantification method is necessary to assess the purity of hydroperoxides.



4. Hydroperoxides of concern

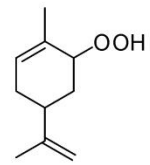
- Terpenes:

  The group agreed that hydroperoxides resulting from limonene, linalool and linalyl acetate oxidation are the most important ones and should be studied in priority. This choice is justified by several elements including the consumer exposure, the oxidation potential, the existing knowledge already collected on these allergens and the great difference of skin sensitization potency with parent materials. Citronellol

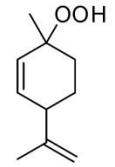
hydroperoxides was added to the list because its synthesis is simpler (one double bond vs two double bonds in geraniol), well controlled and because the skin sensitization potency of citronellol is limited compared to its oxidized form. Other hydroperoxides could be considered in the future once light is shed on the ones outlined above.

- Isomers:

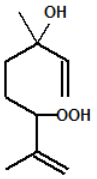
  The group agreed that the research should stay limited to a few isomers: limonene-1-OOH, limonene-2-OOH, linalool-6-OOH and linalool-7-OOH are the major isomers resulting from limonene / linalool autoxidation and seem to have the strongest skin sensitization potency.



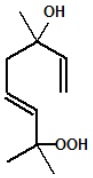
cis/trans-
Limonene-2-OOH
EC3 = 0.83%



cis/trans-
Limonene-1-OOH
EC3 = 0.33%



Linalool-6-OOH



Linalool-7-OOH

EC3 of 5:3 mixture = 1.6%

5. The synthesis of hydroperoxides

- Background science:

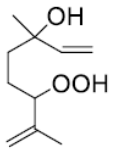
  The chemistry of hydroperoxides has been studied and several reactions can be used to selectively synthesize some of the substances of interest (limonene-1-OOH, limonene-2-OOH, linalool-6-OOH, linalool-7-OOH and citronellol hydroperoxides). One of the most common reactions to produce organic hydroperoxides is the Schenck reaction[11].

  Except for very hydrophobic substrates, the use of microemulsions was regarded as useless and even counterproductive. This complex system should be avoided for the synthesis of terpenes hydroperoxides and replaced, for instance, by methanol.

  The main shortcomings of all existing methods are the limited yields and the difficulty to purify hydroperoxides.

[11] Singlet oxygen ($^1O_2$), the oxidative specie, is made *in situ* by peroxymolybdate-catalyzed (MoO_4^{2-}) disproportionation of hydrogen peroxide (H_2O_2). In theory, singlet oxygen is only necessary to initiate the reaction, then a radical propagation starts. A careful adjustment of hydrogen peroxide and peroxymolybdate is therefore necessary to optimize reaction's kinetic.

Elena Gimenez gave a short presentation highlighting the merits of derivatization (via peroxysilane formation) to separate isomers and enhance their purity (att.02). Her group can selectively synthesize limonene-2-OOH from carveol (one step, overall yield of 48%) and linalool-7-OOH from linalool (3 steps, overall yield of 31%).



The group remarked that the form of linalool-6-OOH not reacting with one equivalent of TBDPSCl (reported at the left) was not recovered. The recovery of this material might lead to another source of pure hydroperoxides and therefore should be investigated. Elena Gimenez agreed to check with the trainee who developed this methodology. She mentioned that the student will leave the laboratory in June therefore a rapid confirmation is necessary.

ACTION: Elena Gimenez will check with her student whether or not the unreacted linalool hydroperoxide isomer can be recovered.

Andreas Natsch's group has developed a method to synthesize a mixture 5:3 of linalool-7-OOH and linalool-6-OOH. The isomers of this mixture are very difficult to separate (at least in GC-MS conditions) but the synthesis is efficient and Givaudan could provide this reference sample to the group if needed.

Anna Börje and Ulrika Nilsson developed conditions to efficiently synthesize limonene-1-OOH.

ACTION: The participants will share articles focusing on the synthesis of selected hydroperoxides with the task force.

The question was asked if the isomers separation is really needed as the objective is to understand what happens in raw materials and consumer products (where the hydroperoxides formation is mainly not selective). Furthermore, it was mentioned that cross-reactivity between several (if not all) forms of hydroperoxides cannot be excluded. If this is the case, there would be no reason to separate isomers. The group agreed that this needs to be verified but, at least for the analytical development, isolated isomers need to be available.

The Chairman asked if correlations could be made between bond dissociation energies (BDE) and chemical reactivity, allergenic activity or stability. Regarding allergenic activity there is limited interest because all hydroperoxides have a comparable EC3 (between 0 and 2). Rather than BDE, Jean-Marie Aubry suggested to calculate charge densities.

- <u>Approach to adopt and establishment of criteria to select a contract research laboratory:</u>
  The Chairman asked to the participants who should take the lead on this project and summarized the specifications that the ideal synthesis lab should meet:

1. Selective synthesis of isomers (without taking the chirality into account). Alternatively, a preparative isolation from a mixture of isomers could be considered, if the resulting quantities and timeframe comply with items 4 and 6 reported below.
2. Structural confirmation of the compound: To be checked, notably by NMR (^{1}H and ^{13}C).
3. Purity: the highest possible purity of each isomer (>90%)
4. Quantities to be delivered: at least 10 g / isomer to be shared between the laboratories developing the quantification.
5. Stability: it should be checked in the course of the development
6. If the stability of some isomers in pure state is too low, alternatives should be investigated so that the analytical laboratories receive samples at known concentrations.
7. Maintain the availability of most frequent standards during all the project.
8. Timeframe: 6 months
9. Partnership: The synthesis lab should work in partnership with (the) analytical lab(s).

The fragrance industry does not have the resources and expertise to entirely manage it. The academic laboratories around the table explained that this work requires an important manpower and none of the universities have engineers who could work on it. Ideally, this should be a Ph.D. thesis subject but some participants felt that the technical difficulties inherent to this project and the limited opportunities to publish are prone to discourage candidates. The name of a well-known company specialized in the manufacturing of hydroperoxides-containing patch-test devices was mentioned. The group felt that it might be a solution for the access to hydroperoxides mixtures but probably not to pure chemically-defined hydroperoxides.

ACTION: The participants will send to the FL the contact details of laboratories which could take care of the synthesis part of this project.

- <u>Specific questions (hazardous chemicals transporter, stability upon storage):</u>

The group confirmed that the common belief that hydroperoxides are unstable is mainly wrong. Most of hydroperoxides resulting from terpenes oxidation do not degrade below 80°C. The rule saying that "organic hydroperoxides with more than 10 carbons do not explode and are even pretty stable" is almost always verified. Terpenes are just at the limit but, based on researchers' experience, it can already be considered as stable.

The Chairman found contact details of a consultant who might take care of hydroperoxides transportation. Although the group did not regard it as necessary, this consultant is able to ship materials at -180°C and -90°C.
Hazard classification needs to be determined to transport materials by airways. However the consultant explained that this can be done by reading-across of other hydroperoxides.

The bibliography indicates that the exchange of hydroperoxides between research laboratories is already something usual and the transportation issue was not regarded as a real problem.

6. The quantification of hydroperoxides

- Background science:

  Several analytical methods (HPLC-MS/MS, HPLC-CL, TMS+GC-MS, PPh_3+GC-MS, LC-MS) have been published and led to relatively accurate results in well-controlled conditions (given hydroperoxides, given matrices, etc.) However, the group agreed that there is no general / ideal method: the existing ones are complementary and still need to be optimized / validated. This optimization / validation work cannot be achieved until pure reference materials become available.

  The group agreed that the ideal method should not require sample pre-treatment or chemical reactions, be specific and sensitive and avoid hydroperoxides degradation during the analysis.

  It was mentioned that the iodometric titration, although non-specific (dosage of all hydroperoxides), can provide useful information on the general oxidation state of mixtures. This method might become very useful in case cross-reactivity between all hydroperoxides is proved.

- Establishment of criteria to select a contract analytical laboratory:

  The Chairman summarized the specifications that should be met by a contract research laboratory in charge of developing the analytical method:

  1. Selectivity towards the hydroperoxides, or convenient means to locate hydroperoxides in a chromatogram.
  2. When the calibration of hydroperoxides has been achieved once, use of recorded (relative) responses to avoid the further use of standards.
  3. Alternatively, if these two criteria cannot be met by a single method, several methods would be developed if each of them meets one of these criteria.
  4. Methods based on a spectrometric detection should comply with the state-of-the-art practices. Notably, the identity of quantified peaks should be checked to avoid analyte confusion and detect coelutions.
  5. Purity and stability of standards: in partnership with the synthesis laboratory, the purity and stability of standards as a function of time will be checked, to determine possible storage conditions and shelf-life.
  6. The proposed method should be submitted to a pre-validation (intermediate precision) by its author.
  7. Method delivery one year after the beginning of the synthesis project. The quantification development should start before the availability of pure standards, to support the synthesis project in the purity determination of standards.
  8. Partnership: The analytical laboratory should work in partnership with the synthesis laboratory.

The group briefly discussed the financial aspects of this project and it was recommended that the industry applies for EU funds (e.g. Horizon 2020). Elena Gimenez knows the process quite well and is ready to participate in a small group to determine whether or not the hydroperoxides project has the potential to be EU-funded. In case the group decides to opt for this strategy, a rapid preparation is necessary. In general it is a two-step selection process for all the calls. The first step is a pre-proposition (short) and if selected then one month is granted for the second-step which consists in submitting a full proposition. Elena Gimenez recommended that the task force looks at the calls for 2015 and explained that the participation of IFRA (fragrance industry) as co-founder might be important. A consultant would have to do the administrate part of this preparation and this is quite a big project to set up therefore it was agreed to determine first whether or not hydroperoxides are considered a public health priority by the Commission.

ACTION: A small group will be formed to determine whether or not the hydroperoxides project has the potential to be EU-funded.

- Next steps:

  It was regarded as appropriate to first evaluate the existing methods via a kind of ring-test (identical samples would be sent to all participant laboratories for analysis of hydroperoxides content). Orange oil was considered an excellent matrix to quantify limonene-1-OOH and limonene-2-OOH. Shiu oil will be used to quantify linalool-6-OOH and linalool-7-OOH. Robertet agreed to provide both essential oils to the participants. Givaudan agreed to spike Shiu oil with a mixture of linalool-6-OOH and linalool-7-OOH and also to provide the reference material to all participants. The IDEA Management Team still has to find a reliable source of limonene hydroperoxides. Andreas Natsch will investigate internally. At a later stage, and based on first ring-test's results, hydroalcoholic products could be investigated too.

  ACTION: Andreas Natsch to check whether or not Givaudan can provide limonene hydroperoxides. If not, the IDEA Management Team will look for alternative sources.

  ACTION: Hugues Brevard to provide Orange oil and Shiu Oil to the laboratories responsible for spiking and distribution (to be confirmed for Orange oil).

  ACTION: IDEA Management Team to coordinate the ring-test to come.

  As a second step, it was suggested that labelled hydroperoxides (^{2}D or ^{13}C) be synthesized to facilitate their analysis. The group agreed that it might be a good idea.

  ACTION: As per Jean-Marie Aubry's request, Givaudan, Firmenich and Robertet will check if qualities of limonene without BHT are commercially available. Such qualities would facilitate the research on antioxidants.

FL reminded that hydroperoxides degradation products are always less potent sensitizers than the parent hydroperoxides. Beyond the usual risk management measures that can be derived from better analytical tools, catalysts might then be developed to promote the degradation of hydroperoxides once formed. This “scavenger” would act in tandem with antioxidants and allow the global reduction of hydroperoxide-content in consumer products. The group agreed that this point is worthy of consideration and it might the object of future Hydroperoxides TF meetings along with other topics such as the chemistry of antioxidants.

Preparation, 28/03/2014
F. Lebreux
IDEA Management Team

First Review, 09/04/2014
A. Chaintreau
Chairman of the IDEA Hydroperoxides TF

Final Review, 23/04/2014
IDEA Hydroperoxides TF

Attachments:
IDEA Hydroperoxides TF meeting (att.01) Presentation of the Chairman
IDEA Hydroperoxides TF meeting (att.02) Presentation of Elena Giménez Arnau

Firmenich

IDEA
Hydroperoxide task force

Brussels, March 24th 2014

A. Chaintreau

Agenda

- Antitrust statement
  - No discussions of agreements or concerted actions that may restrain competition
- Adoption of the agenda

Composition of the ROOH T-F

Name	Email	Affiliation
Jean-Marie Aubry	Jean-Marie.Aubry@univ-lille1.fr;	U.Lille
Anna Börje	aborje@chem.gu.se	U. Gothenburg
Hugues Brevard	Hugues.Brevard@robertet.com	Robertet, IFRA-AWG
Michael Calandra	Michael.Calandra@firmenich.com	Firmenich
Alain Chaintreau	Alain.Chaintreau@firmenich.com	Firmenich; IFRA-AWG
Elena Gimenez	egimenez@unistra.fr	U. Strasbourg
Ann-Therese Karlberg	karlberg@chem.gu.se	U. Gothenburg
Frédéric Lebreux	flebreux@ifraorg.org	IFRA
Clémentine Marteau	clementine.marteau@iff.com	IFF
Andreas Natsch	andreas.natsch@givaudan.com	Givaudan
Ulrika Nilsson	ulrika.nilsson@anchem.su.se	U. Stockholm
Neil Owen	Neil.Owen@givaudan.com	Givaudan, IFRA-AWG
Veronique Rataj	Veronique.Rataj@univ-lille1.fr	U. Lille
David W. Roberts	D.W.Roberts@ljmu.ac.u	U. Liverpool
Matthias Vey	mvey@ifraorg.org	IFRA

Objectives

- Debates in the current literature:
  - Real kinetics of ROOH formation ?
  - Potential role of fragrances in the population allergy ?
- Vicious cycle:
  - No reliable method to assess ROOH purities
  - No (commercial) source of pure standards to calibrate the instruments
- Priorities
  - Synthesis/purification of standards
    - Ensure their availability to all teams
  - Developing/improving reliable quantitative methods

01 Synthesis

Exchanging standards: an issue

- Transportation of dangerous materials is regulated
  - Stability of pure ROOH : unknown
    - Some ROOHs commercially available at high concentration → delivered by usual transportation means
    - Standards to be sent from the synthesis lab to all partners
      - Terrestrial means can be used
      - Restrictions for air transportation

  → Are ROOH stable enough for a slow delivery system ? Under which conditions ?

- A consultant in chemical transportation has been identified
  - Address sent to Fred
  - Issue to be solved before deciding on the synthesis of standards

Hydroperoxides of concern

- All ROOHs cannot be considered
  - Too long for the IDEA time frame
  - Would require an endless budget

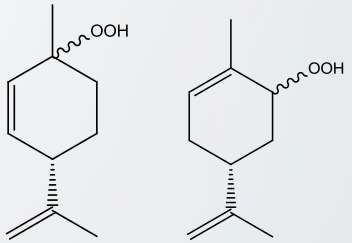
  ⇨ Priorities to be defined

- Most frequently investigated ROOH
  - Limonene
  - Linalool
  - (Linalyl acetate)
  - Others ?

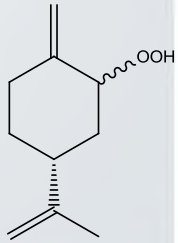
- Isomers . . . . . → next slide

Isomers of concern (I)?

- Isomers differ in allergenic activity
  - "Limonene hydroperoxide analogues differ in allergenic activity", Christensson et al, *Contact Dermatitis*, **59, 344-52**
  - "Limonene hydroperoxide analogues show specific patch test reactions"", Christensson et al, *Contact Dermatitis*, in press
- Detector response
  - Differs in MS
  - Unknown for CL
- Limonene
  - Limonene 1- and 2-hydroperoxide
    - Main ROOH in citrus oils
    - Specific synthesis only for lim-1-OOH
    - Lim-1-OOH more allergenic

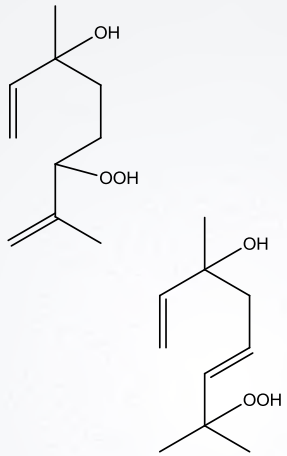


  - 2-hydroperoxy-1-methylene-4-(prop-1-en-2-yl)cyclohexane
    - Absent/minor isomer in autooxidized EO
    - Generated in presence of a photosesitizer
      - P.Shieberle, HRC, 1987, *10* ,588-593



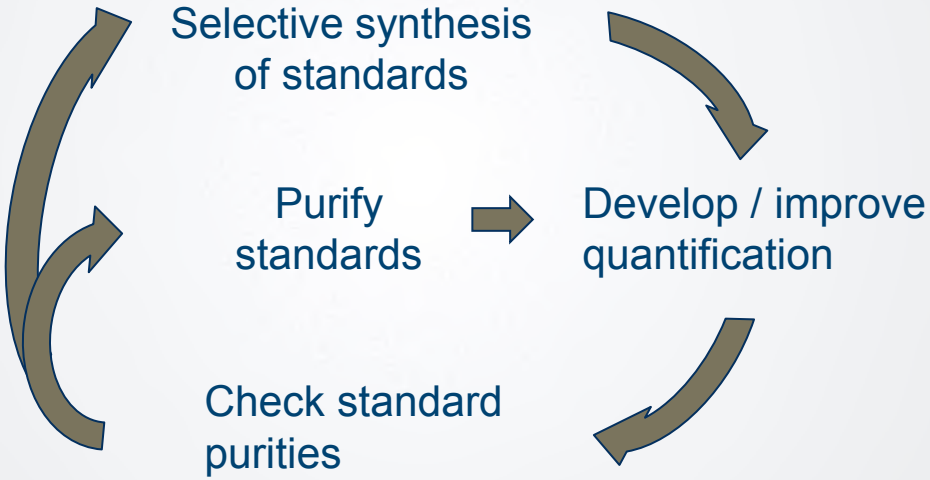
Isomers of concern (II)?

- Linalool
  - Lin-6-OOH
    - Minor
  - Lin-7-OOH
    - Major

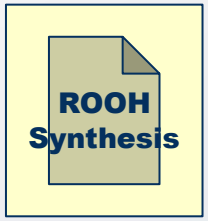


Synthesis routes

› Preparing pure standards → an iterative process



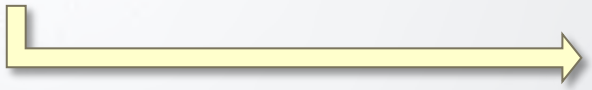
› Possible routes →by Elena



Firmenich

To which lab ?

- Too small niche for the fragrance industry
- University ?
  - Manpower, large scale (> 10 g), stock, certification ?
- Contract lab ?
  - Specifications to be matched



Specifications for the synthesis lab

1. Selective synthesis of isomers (without taking the chirality into account). Alternatively, a preparative isolation from a mixture of isomers could be considered, if the resulting quantities and time frame comply with items 4.and 6.
2. Structural confirmation of the compound: To be checked, notably by NMR (^{1}H and ^{13}C).
3. Purity: the highest possible purity of each isomer (>90%)
4. Quantities to be delivered: at least 10 g / isomer to be shared between the laboratories developing the quantification.
5. Stability: it should be checked in the course of the development
   a. Either by NMR
   b. And/or in partnership with a laboratory in charge of the analytical development for IDEA
6. If the stability of some isomers in pure state is too low, alternatives should be investigated so that the analytical laboratories receive samples at known concentrations.
7. Maintain the availability of most frequent standards within a reasonable time frame
8. Time frame: 6 months

The synthesis lab should work in partnership with (the) analytical lab(s)

Bond Dissociation Energies

- To be calculated for a later correlation attempt with
  - Chemical reactivity
  - Allergenic activity
  - Stability

02 Quantifications methods

Quantification methods

- All methods are very recent:
  - HPLC-MS/MS (AT Karlberg, U. Göteborg, 2013)
    - *J. Sep. Sci. 2013, 36, 1370–1378*
  - HPLC-Chemiluminescence (M. Calandra, Firmenich)
    - Not yet published
  - GC-MS (AT Karlberg, U. Göteborg, 2013)
    - J.Sep.Sci, 2014, in press
  - $P\Phi_3$ reduction and LC-MS quantification
    - A. Natsch, submitted
  - + Another method in development (Firmenich)

Method overview

	HPLC-MS/MS	HPLC-CL	TMS+GC-MS	$P\Phi_3$ +LC-MS
Needs standards	Y	Y	Y	Y/N
Specificity to all ROOHs	N	Y Only way to detect all and only ROOHs	N	N
Specificity to known analytes	Y/Y	Y	Y/Y	Y/Y
Analyte identification	Y	n.a.	Difficult	Exact mass
Tested by spiking	Y (in EOs)	N	N	Y
Others	• Insufficient specificity in complex mixtures (Natsch)		• Structure of linalool-TMS t.b.d.	• Reduction yield t.b.d. • Pb if endogenous reduction product

No ideal method → complementary
None of these methods is really validated
→Need to be further optimized before being applicable
→ Depends on the availability of pure isomers as standards

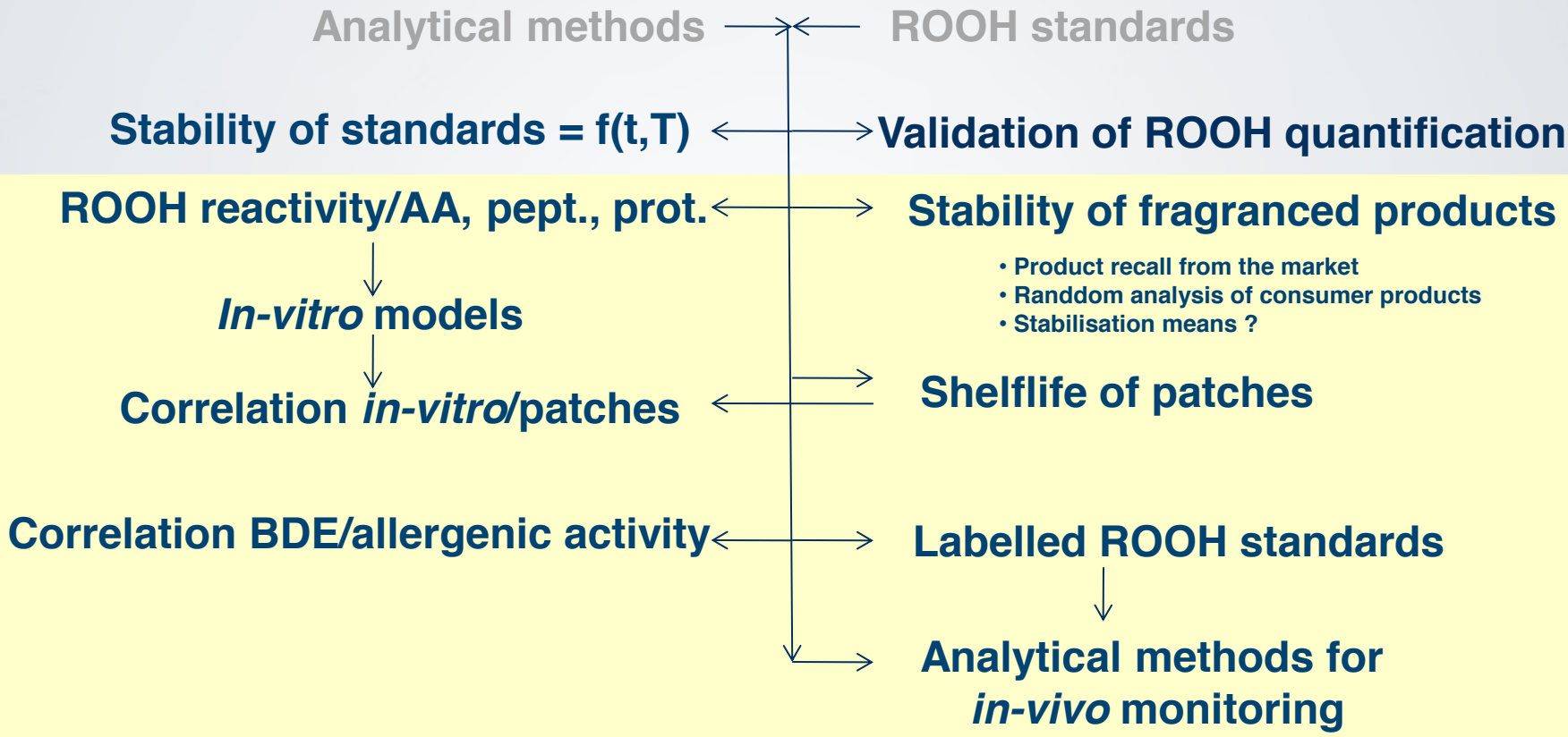
Specification for the analytical labs

- Development/improvement of a quantitative method with the following characteristics:
  - Selectivity towards the hydroperoxides, or convenient means to locate hydroperoxides in an chromatogram.
  - When the calibration of hydroperoxides has been achieved once, use of recorded (relative) responses to avoid the further use of standards
- Alternatively, if these two criteria cannot be met by a single method, several methods would be developed if each of them meets one of these criteria.
- Methods based on a spectrometric detection should comply with the state-of-the-art practices. Notably, the identity of quantified peaks should be checked to avoid analyte confusion and detect co-elutions.
- Purity and stability of standards: in partnership with the synthesis laboratory, the purity and stability of standards as a function of time will be checked, to determine possible storage conditions and selflifes.
- The proposed method should be submitted to a prevalidation (intermediate precision) by its author.
- Method delivery one year after the beginning of the synthesis project. The quantification development should start before the availability of pure standards, to support the synthesis project in the purity determination of standards.

The analytical labs should work in partnership with synthesis

03 Outlooks

Application for Horizon 2020 funding ?



Firmenich

Firmenich

inspiring!

INNOVATIVE CRAFTSMANSHIP IN FRAGRANCES AND FLAVORS SINCE 1895

Synthesis of linalool and limonene sensitizing hydroperoxides

E Giménez-Arnau

Laboratoire de Dermatochimie

Institut de Chimie de Strasbourg
Université de Strasbourg (CNRS-UMR 7177)
Strasbourg, France

Methods to prepare hydroperoxides

Autoxidation of unsaturated compounds

General mechanism

Initiation $RH \longrightarrow R^{\bullet}$

Propagation $R^{\bullet} + {}^3O_2 \rightleftharpoons ROO^{\bullet}$ fast

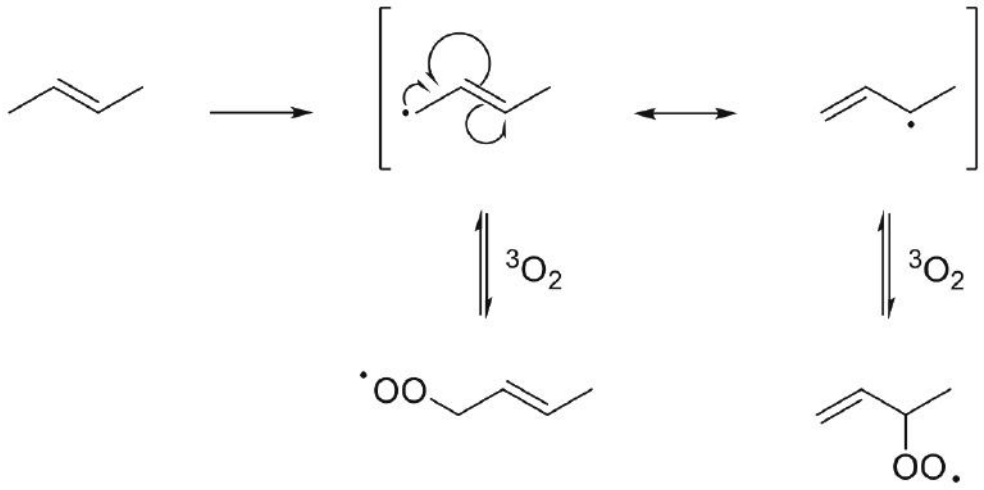
$ROO^{\bullet} + RH \longrightarrow ROOH + R^{\bullet}$ slow

Termination $2\ R^{\bullet} \longrightarrow$

$R^{\bullet} + ROO^{\bullet} \longrightarrow$ } non-radical products

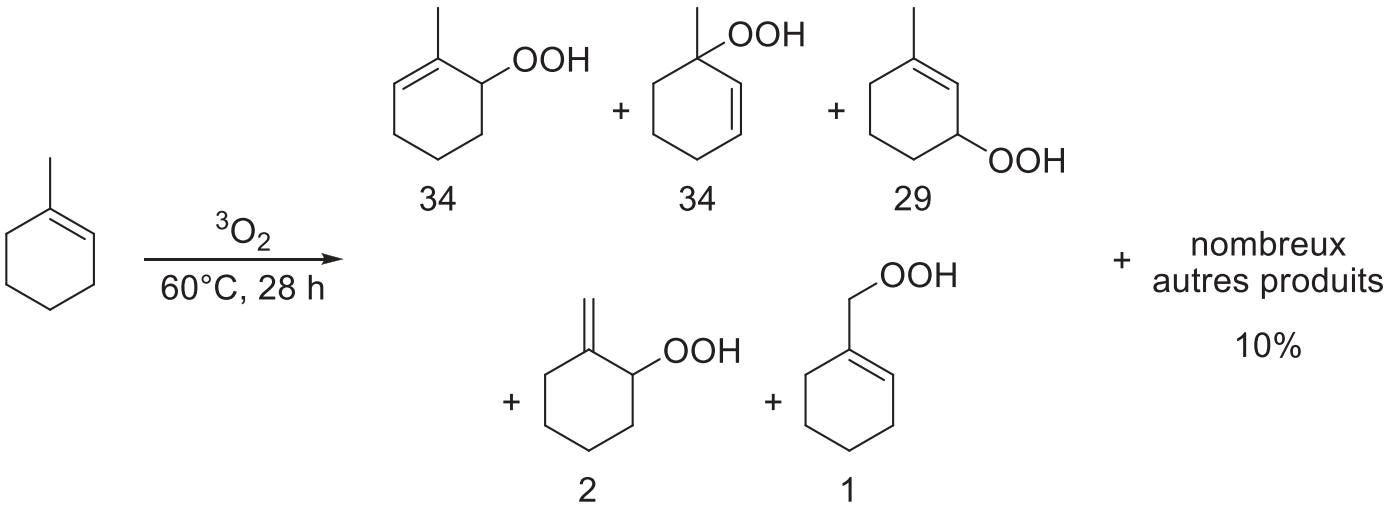
$2\ ROO^{\bullet} \longrightarrow$

For unsaturated compounds



Methods to prepare hydroperoxides

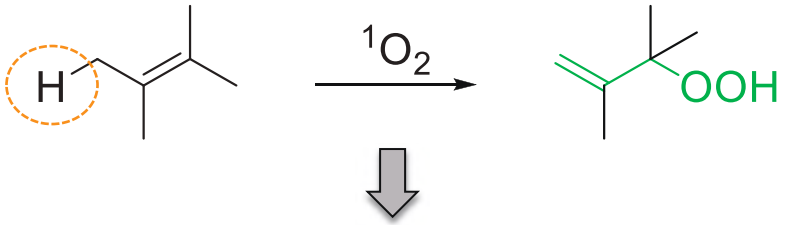
Non-selective, multitude of oxidation products …



Courtneidge JL, Bush M. *J Chem Soc, Chem Comm* 1989, 17,1227

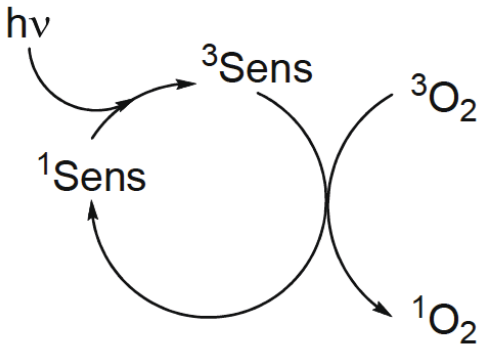
Methods to prepare hydroperoxides

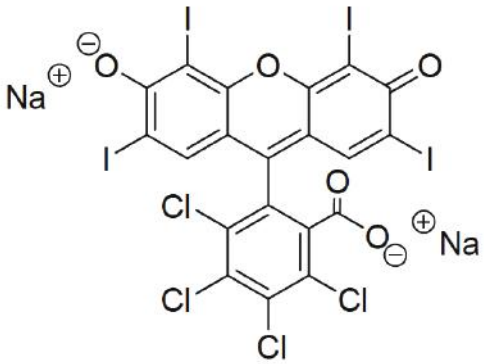
Singlet oxygen ene reaction – Schenck reaction



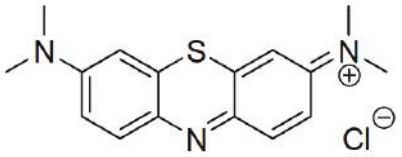
production of singlet oxygen

Photochemical methods : mostly employed





Bengal Rose



Methylene Blue

Methods to prepare hydroperoxides

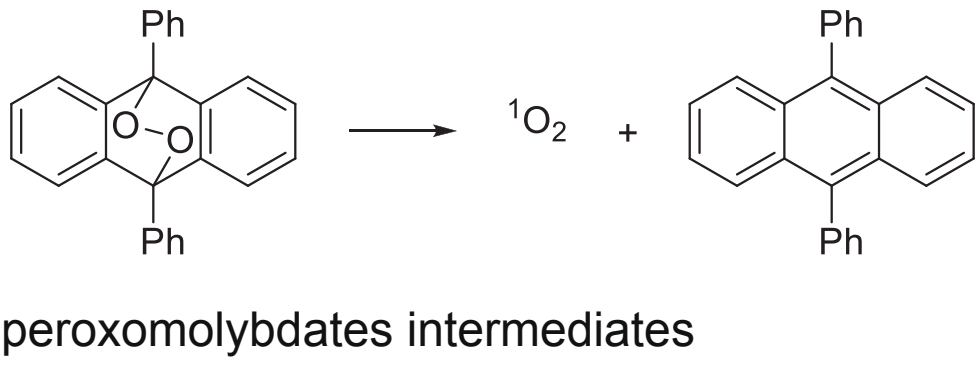
Singlet oxygen ene reaction – Schenck reaction

Chemical methods:

$H_2O_2 + NaOCl \longrightarrow {}^1O_2 + H_2O + NaCl$

$(PhO)_3PO_3 \longrightarrow {}^1O_2 + (PhO)_3PO$

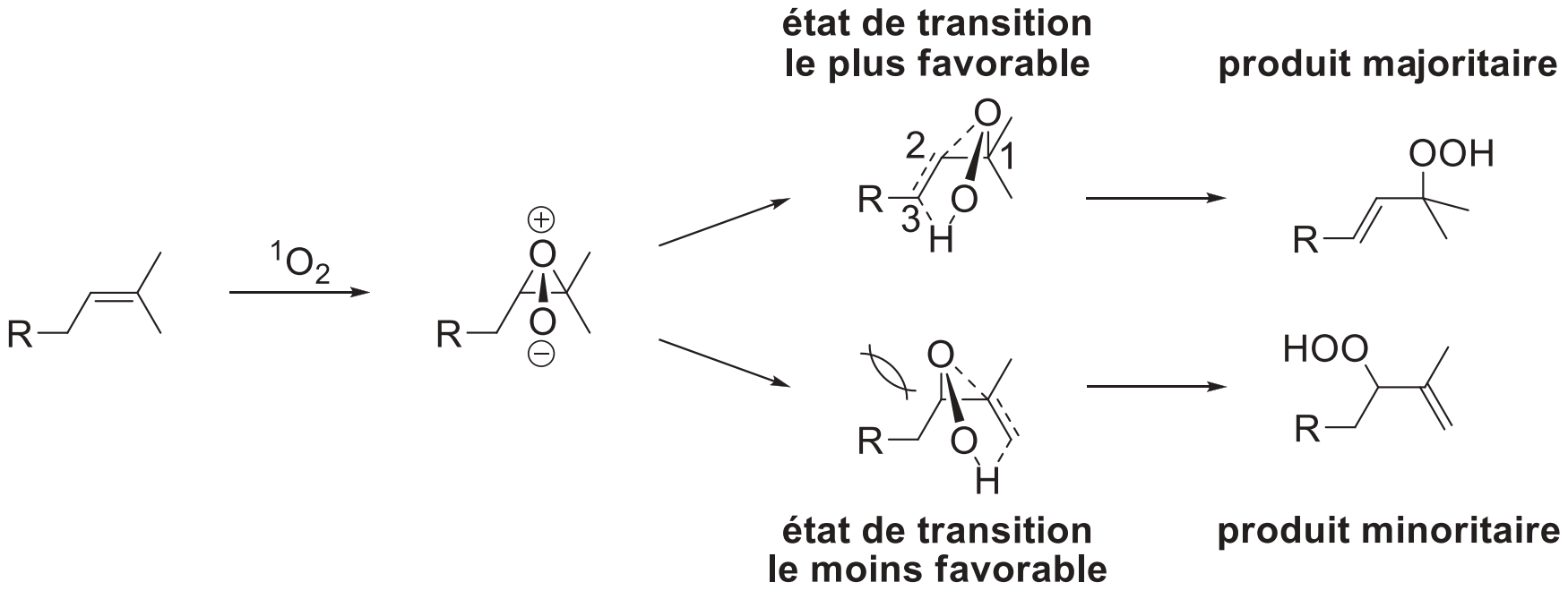
$MoO_6^{2-} \longrightarrow {}^1O_2 + MoO_4^{2-}$



Methods to prepare hydroperoxides

Schenck reaction on trisubstituted olefins

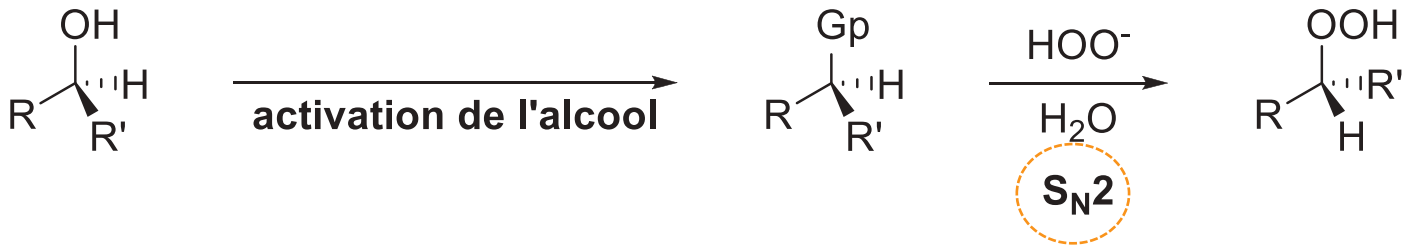
regioselectivity and stereoselectivity

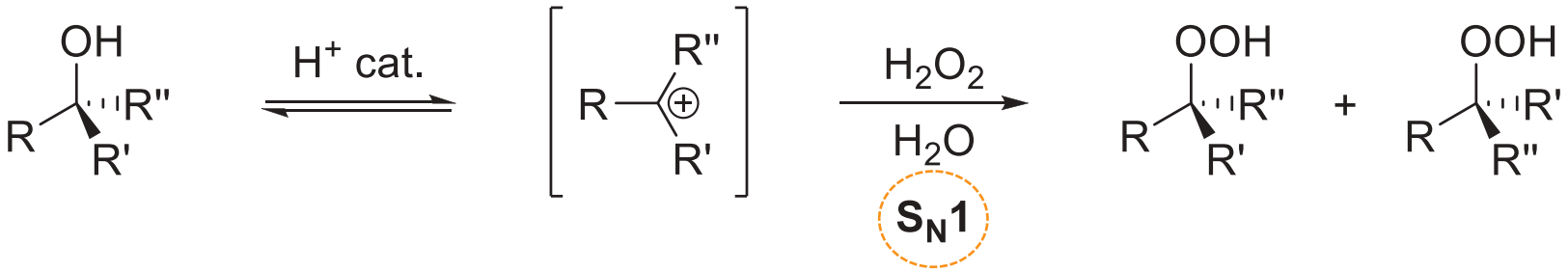


Stratakis M, Orfanopoulos M, *Tetrahedron* 2000, 56, 1595

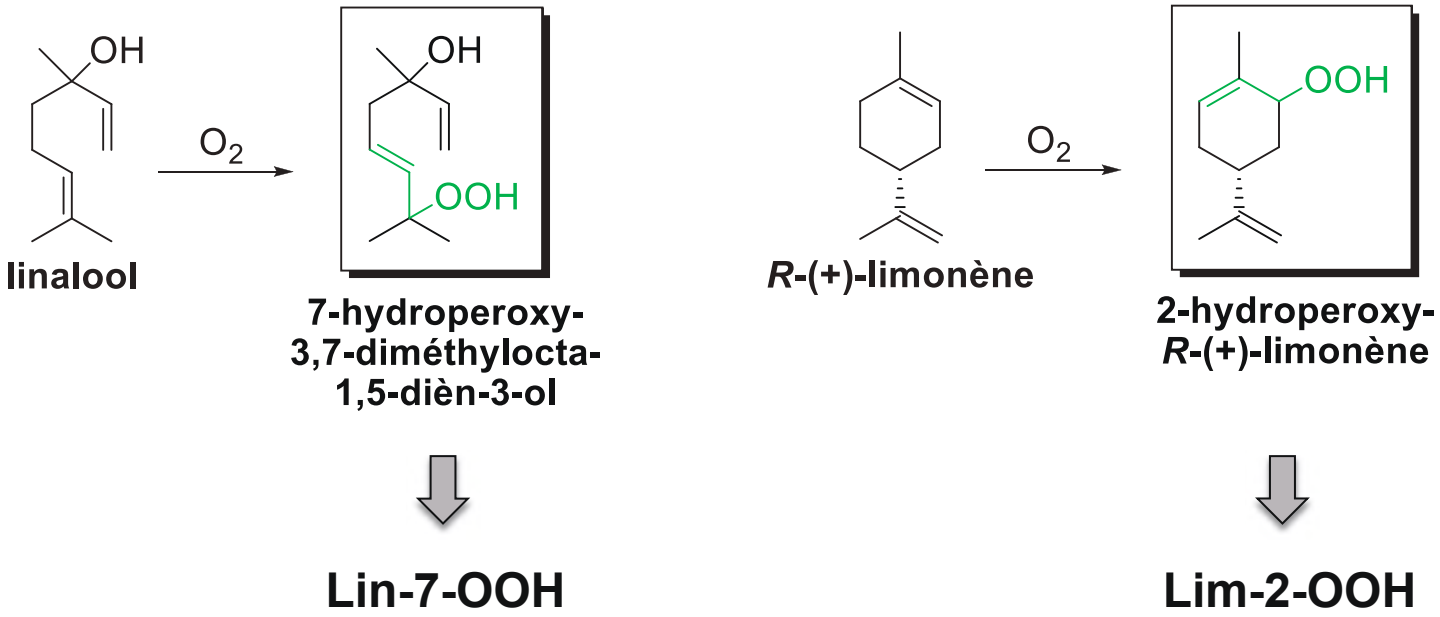
Methods to prepare hydroperoxides

Nucleophilic substitution on allylic alcohols





Hydroperoxides of our concern



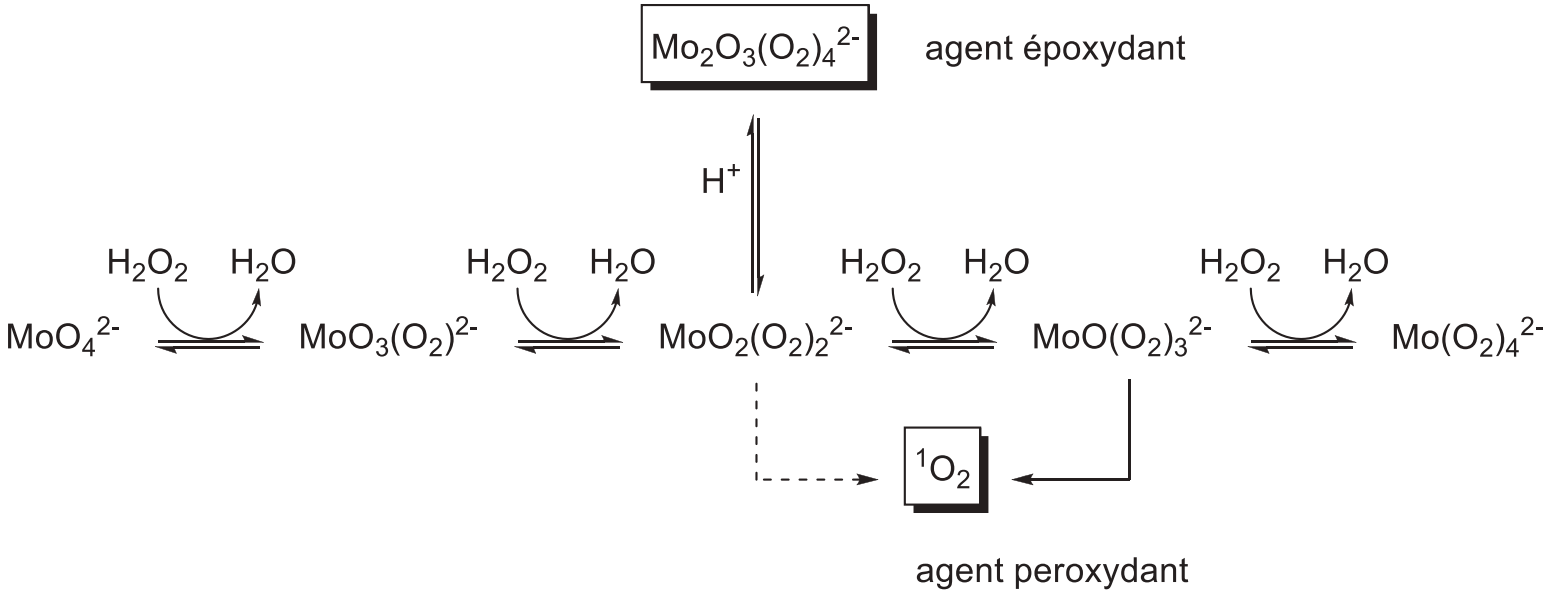
Synthesis of Lin-7-OOH

Schenck reaction on trisubstituted olefin

Experimental conditions : obtention of $^1O_2$

$$2\ H_2O_2 \xrightarrow[\text{pH 9-12}]{MoO_4^{2-}\ \text{cat.}} {}^1O_2 + 2\ H_2O$$

100%

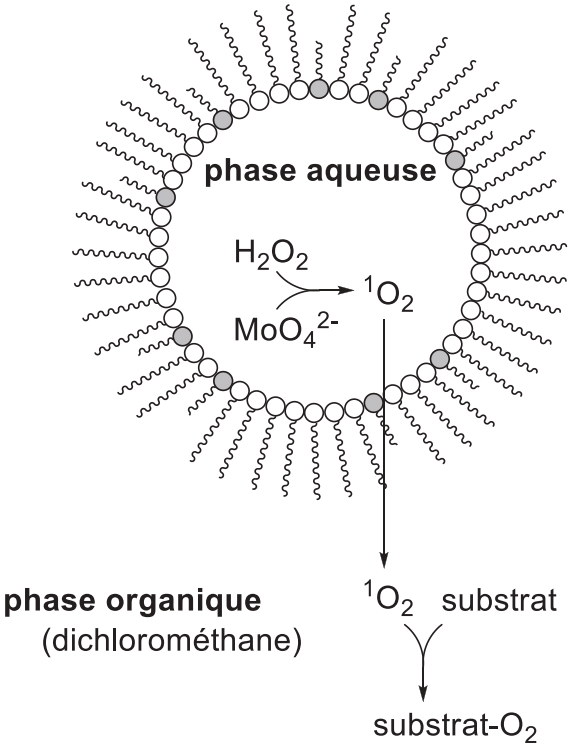


Aubry J-M *et al.*, *Tetrahedron* 2006, 62, 10753

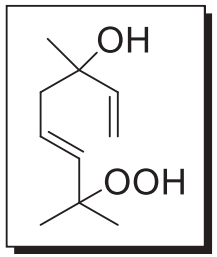
Synthesis of Lin-7-OOH

Schenck reaction on trisubstituted olefin

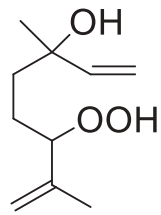
Experimental conditions : microemulsion



H_2O_2, MoO_4^{2-} cat.
microémulsion, t.a.
réaction de Schenck
80%



+

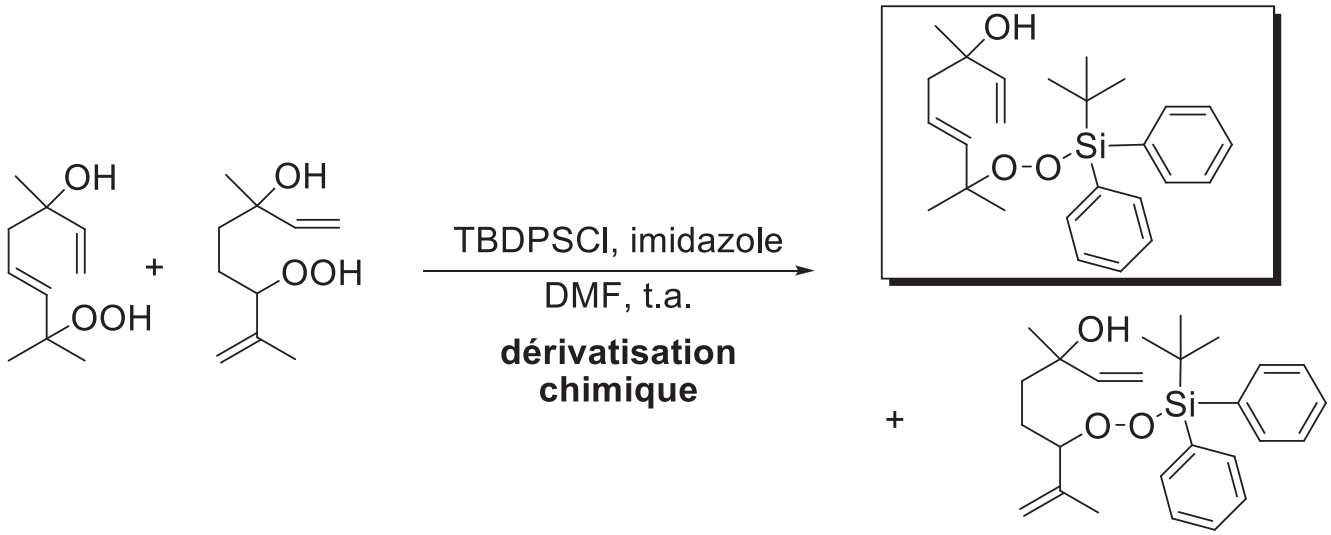


32% **48%**

rapport 4:6

Synthesis of Lin-7-OOH

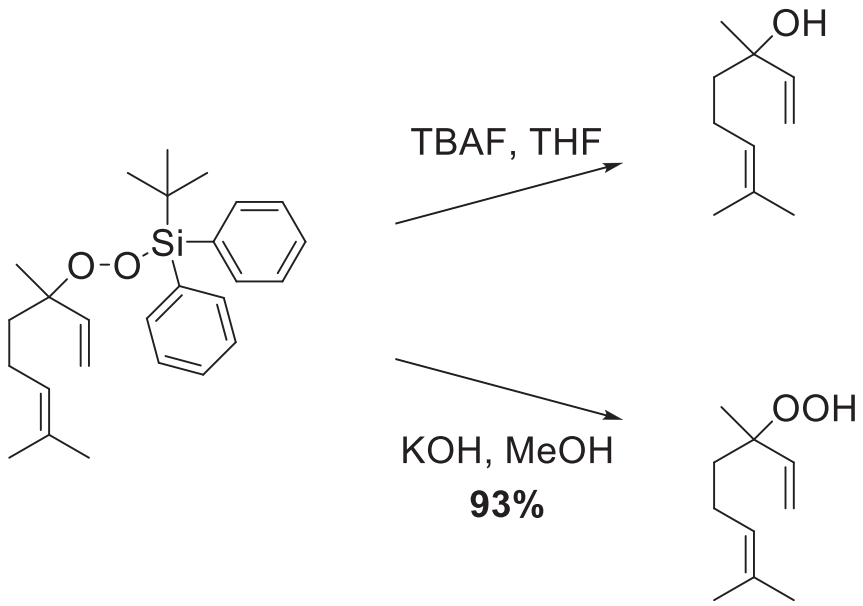
Chemical derivatization (silylization) of the hydroperoxides

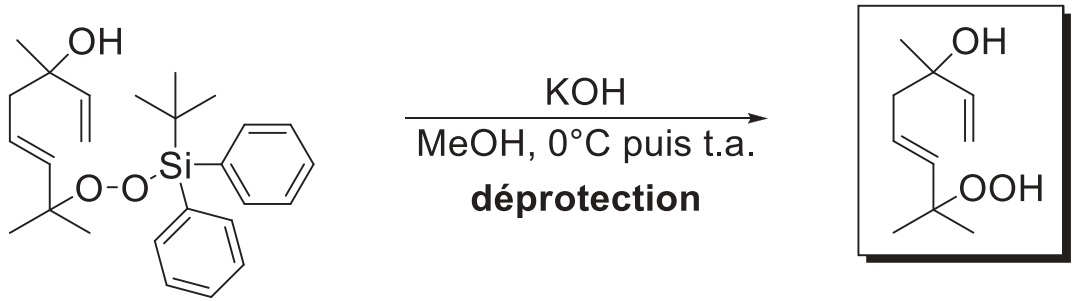


Mixture of hydroperoxides	TBDPSCl	Imidazole	DMF	
391 mg	1,2 éq.	2 éq.	8,5 mL	Two isomers protected
200 mg	1,2 éq.	2 éq.	8,5 mL	One single isomer protected

Synthesis of Lin-7-OOH

Deprotection of the peroxysilane





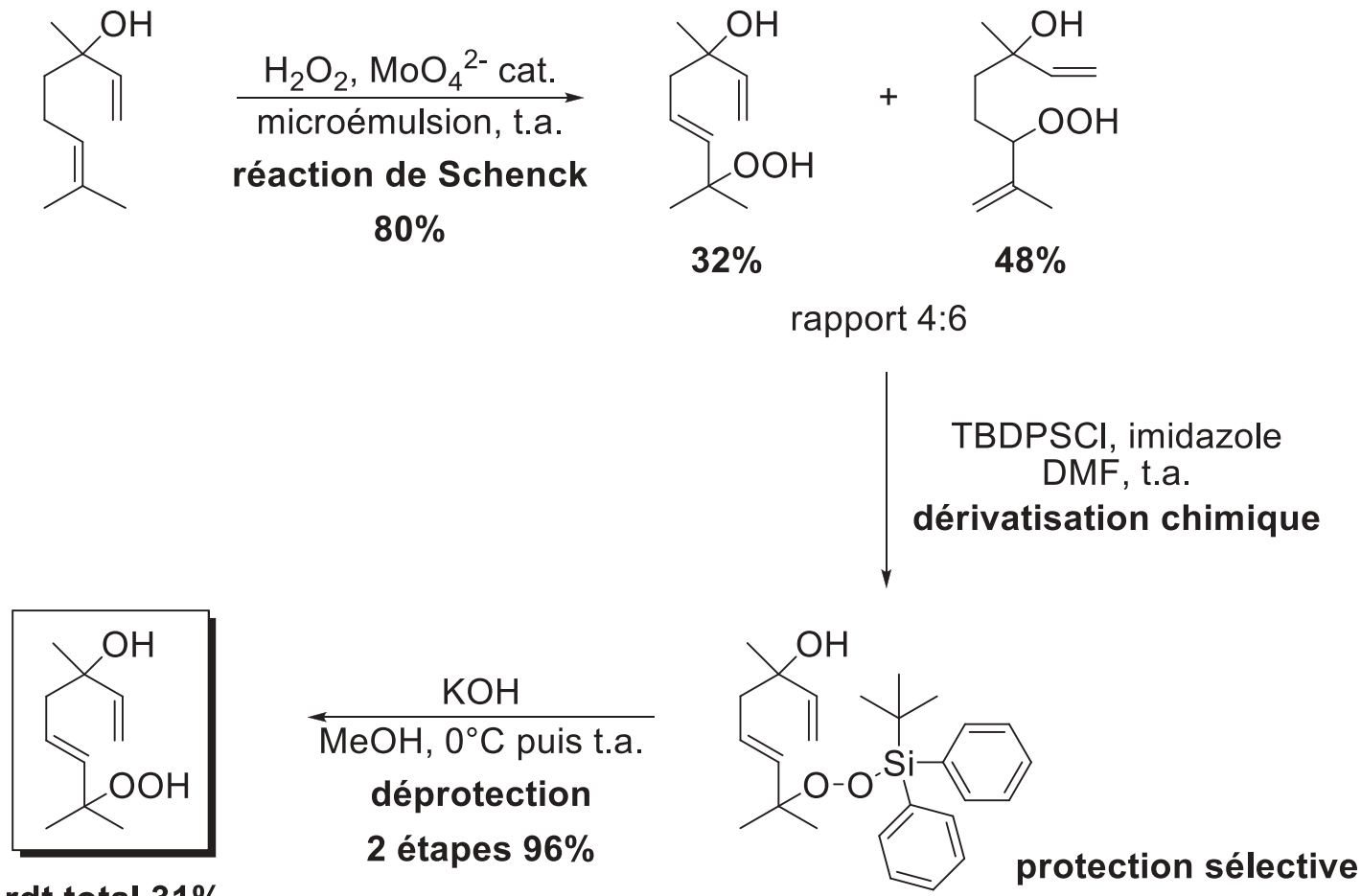
Synthesis of Lin-7-OOH

Derivatization/Deprotection optimization

Weight mixture hydroperoxides	Concentration mixture hydroperoxides	Reaction time	Yield on the last two steps
200 mg	0,13 mol.L^{-1}	2 days	13%
200 mg	0,11 mol.L^{-1}	10 days	61%
200 mg	0,14 mol.L^{-1}	10 days	59%
200 mg	0,21 mol.L^{-1}	10 days	96%
1 g	0,21 mol.L^{-1}	10 days	9%

Synthesis of Lin-7-OOH

Summary

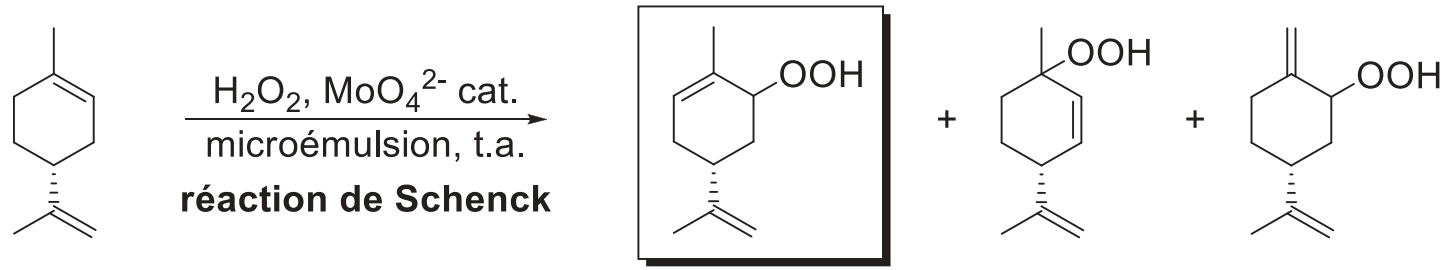


Kao D *et al.*, *J Org Chem,* 2011, 76, 6188

Synthesis of Lim-2-OOH

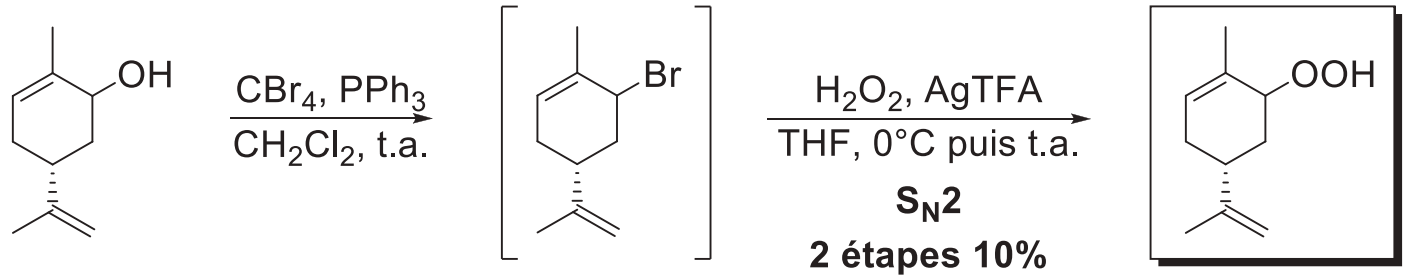
First tests

Schenck reaction



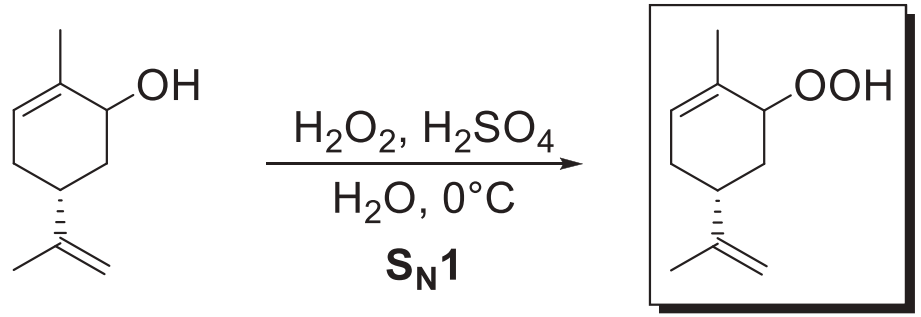
produit minoritaire

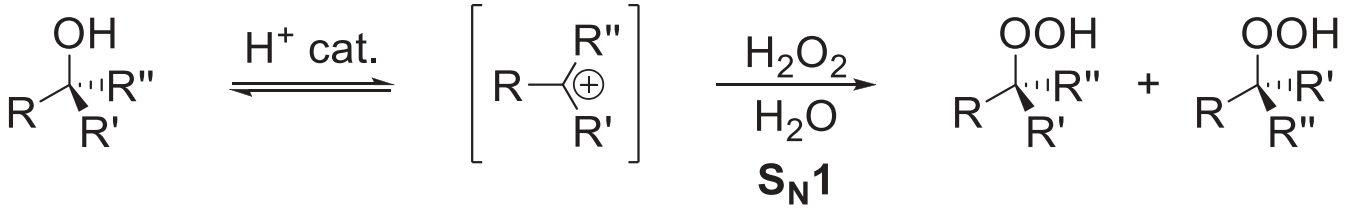
S_N2 nucleophilic substitution



Synthesis of Lim-2-OOH

S_N1 nucleophilic substitution





Kao D *et al.*, *J Org Chem,* 2011, 76, 6188

IDEA WEBMINAR

Categorization Task Force

April 28th, 2014

1. Agenda
2. Final minutes of the IDEA webminar

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

www.ideaproject.info

IDEA
International Dialogue for the Evaluation of Allergens

IDEA Webminar of the

Categorization Task Force

Monday, April 28th, 2014 from 3:00pm to 5:00pm (Brussels Time)

Tel: +32 (0)2 404 03 05, Participant PIN: 46340660#

Agenda

1. Adoption of the agenda
2. **Objective**: Arrive at a commonly accepted characterization for fragrance allergens, which enables further categorization and builds the basis for effective and proportionate risk management procedures.
3. **Characterization** ("Yes/No"):
    - Overview of existing approaches for characterization: SAR's, in vitro, animal, human.
    - Discussion of hierarchy of approaches
    - "How to" guidance for Characterization
4. **Categorization** ("From low to high"):
    - Needs for categorization
    - Overview of existing approaches : SCCS, general toxicology principles, CLP regulation
    - Applications (LLNA, in vitro, epidemiology, cosmetovigilence, other)
    - "How to" guidance for Categorization
5. **Opportunities for improvement**:
    - In science, methodology,
    - In use
6. **Summary**: Brief description of current approach, opportunities for improvement, recommendations, way forward.
7. Next meeting

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

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IDEA
International Dialogue for the Evaluation of Allergens

IDEA Webinar of the

Categorization Task Force

Monday, April 28th, 2014 from 3:00pm to 5:00pm (Brussels Time)

Minutes

Participants: Klaus Andersen (Odense University Hospital, University of Southern Denmark), Anne Marie Api (RIFM), David Basketter (Toxicology consultant), Hans Bender (Chairman), Peter Cadby (Chanel), Graham Ellis (Givaudan), Helmut Greim (IDEA Supervisory Group), Peter Griem (Symrise), Maya Krasteva (L'Oréal), Fred Lebreux (IDEA Management Team), Scott Schneider (Firmenich), Theodor Schumacher (Smart Practice), Benjamin Smith (Firmenich), Matthias Vey (IDEA Management Team).

1. Adoption of the agenda

The chairman welcomed the participants and went through the agenda, which was adopted such as provided.

2. Antitrust statement

The Chairman reminded the constraints of the antitrust law to the participants. All agreed that there shall be no discussions of agreements or concerted actions that may restrain competition. This prohibition includes the exchange of information concerning individual prices, rates, coverages, market practices, claims settlement practices, or any other competitive aspect of an individual company's operation. Each participant is obligated to speak up immediately for the purpose of preventing any discussion falling outside these bounds.

3. Objective

The group agreed that the remit of this task force is to arrive at a commonly accepted framework for the fragrance allergens characterization, which enables further categorization. This framework could be the basis for future effective and proportionate risk management procedures.

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

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4. Characterization of allergens ("Yes/No")

The participants agreed that the ECHA guidance on the application of the CLP criteria (att.01[1], section 3.4 from page 348 to 378) is an excellent basis for the characterization of allergens. This guidance describes which human and animal testing can be used but also how it should be interpreted to determine whether or not a substance is a skin sensitizer.

ACTION: The participants will review the ECHA guidance and provide feedback.

It was stressed that positive human data, and in particular the clinical experience resulting from patients examination, should take precedence over other negative data sources. The case of Methylisothiazolinone was reported as an illustration of toxicological studies refuted by post-marketing clinical data. A participant confirmed that human data (and it relative importance compared to other data sources) is comprehensively detailed in the ECHA guidance. However, only the substances already placed on the market can benefit of this clinical data and QSAR, in-vitro and animal data (although the regulatory context tends to discourage the latter) remains the basis for the characterization of newly introduced allergens. In effect, human testing such as HRIPT can only be conducted at concentrations not supposed to induce skin sensitization (tolerance studies) and are therefore of no help for the characterization of allergens.

The ranking of data by quality order was discussed as, for instance, a poorly conducted HRIPT (or conducted at too low level) cannot override a properly done LLNA. It was confirmed that all pieces of information should be considered and combined according to a well-thought weight of evidence approach. However, it was remarked that the weight of evidence approach is relatively subjective, like any other activities where expert judgment is engaged.

After consideration, it appeared difficult to define an objective and systematic process that non-experts could use to characterize allergens based on all available data. It was agreed that a workable solution in that case is to refer to the examples offered in the ECHA guidance. These examples ranging from elementary to complex help the decision-making process and allow non-experts to transpose usual weight of evidence techniques into their own cases.

The only drawback of the examples provided by ECHA is that they all lead to the substance classification while actually most of the reviewed substances do not qualify as skin sensitizer. Therefore the group recommended that these examples be complemented with a few cases where the data analysis leads to no classification.

[1] http://echa.europa.eu/documents/10162/13562/clp_en.pdf

However, these examples do not pretend to eradicate the subjectivity of the weight of evidence approach and it was recognized that two toxicologists analyzing the same data could potentially end up with 3 different conclusions. This difference of data interpretation can result from the complexity of cases (contradiction of testing data) and from biases inherent to toxicologists' organization (industry, regulators).

5. Categorization ("From low to high")

D. Basketter presented an article recently published in Dermatitis and titled "Categorization of Chemicals According to Their Relative Human Skin Sensitizing Potency". The article, co-written by D.A. Basketter, N. Alépée, T. Ashikaga, J. Barroso, N. Gilmour, C. Goebel, J. Hibatallah, S. Hoffmann, P. Kern, S. Martinozzi-Teissier, G. Maxwell, K. Reisinger, H. Sakaguchi, A. Schepky, M. Tailhardat and M. Templier, proposes a new categorization system of skin sensitizers based on human data only.

The main objective of this article was to help the development of in vitro methods by optimizing their use for the definition of skin sensitizers' potency. In effect, current in vitro testing are more and more predictive for the characterization of allergens but remain of limited use for the determination of allergens potency or, at least, do not have the same predictability accuracy as traditional tools such as the LLNA. As of today, in vitro alternatives can qualitatively predict the potency category of an allergen ranging from non-sensitizing to extreme sensitizer.

Based on this observation, the authors created six categories (see Table 1) that result from the subdivision of the three GHS categories: SS 1A (strong sensitizer) led to categories 1 and 2, SS 1B (weak sensitizer) to categories 3 and 4 and no classification to categories 5 and 6. These categories were then populated with the main allergens found in commerce based on all existing human data (epidemiologic studies, clinical data, NOEL, results of HRIPT, etc.). The exposure criterion was also accounted in a qualitative way (expert judgment of substances used at low level and no very often vs. substances used very widely and in big quantities).

TABLE 1. Criteria for Categorization

Human Category*	Clinical Data (Benchmark Substances)	Human Test Data and NOEL
1	Extensive evidence of contact allergy in relation to degree of exposure and size of exposed population (MCI/MI, DNCB, *p*-phenylenediamine)	Where data were available, a best estimation has been made of the "NOEL" for the induction of skin sensitization in a HRIPT
2	A frequent cause of contact allergy, but of less significance compared with category 1 (formaldehyde, isoeugenol, methyldibromo glutaronitrile)	
3	A common cause of contact allergy, perhaps requiring higher exposure compared with category 2 (abietic acid, eugenol, imidazolidinyl urea)	Where a substance was nonsensitizing, this in indicated by "NS"
4	Infrequent cause of contact allergy in relation to level of exposure (benzocaine, hydroxycitronellal, resorcinol)	Where insufficient data were available, this is indicated as "ND".
5	A rare cause of contact allergy except perhaps in special circumstances, eg, use in topical medicaments (hexylcinnamal, isopropanol, parabens)	Key references are indicated for each substance
6	Essentially absent, with at least no systematic convincing evidence of contact allergy (xylene, glycerol, sodium lauryl sulfate)	

Although expert judgment took an important place in the assignment of known allergens to categories (which could therefore lack objectivity), the result of this categorization is expected to help toxicologists convert in vitro testing data into a qualitative determination of skin sensitizers' potency. Motivated by the necessity to adapt risk management measures to allergens' potency, D. Basketter explained that default NESIL values could be attributed to each category. By doing so, in vitro testing data could feed the Dermal Sensitization QRA methodology and avoid resorting to other data sources. Furthermore, existing allergens should also be categorized within this new system to systematize the application of other types of risk management measures such as consumer information (although some participants felt that consumer information should not be conditioned by the categorization process but ensured for all types of sensitizers).

Most of the group agreed that this 6-category based approach is compatible with the recommendations made at the last IDEA workshop on fragrance allergens characterization. The work achieved through this article was regarded as a useful starting point and the recycling of GHS categories considered appropriate as it reflects current regulatory toxicology.
The group was not aware of any other sophisticated categorization approach that could compete with or be opposed to the article presented by D. Basketter. This work is apparently the first tentative to categorize 100+ allergens based on human data.
However the participants recommended that the model be further improved in light of the following information:

- The sensitization exposure quotient (SEQ), calculated as the quotient of the relative frequency of sensitization and the relative frequency of use. This concept developed by A. Schnuch is thoroughly described in the article "Risk of sensitization to preservatives estimated on the basis of patch test data and exposure, according to a sample of 3541 leave-on products", A. Schnuch, G. Mildau, E.-M. Kratz and W. Uter, 2011, Contact Dermatitis, 65, 167-174. However, it was remarked by the group that the relative frequency of use is not always easily accessible.

- The criteria published by the MAK Commission in the article "When should a substance be designated as sensitizing for the skin ('Sh') or for the airways ('Sa')?", A. Schnuch, H. Lessmann, K.-H. Schulz, D. Becker, T. Diepgen, H. Drexler, S. Erdmann, M. Fartasch, H. Greim, P. Kricke-Helling, R. Merget, H. Merk, D. Nowak, A. Rothe, G. Stropp, W. Uter and G. Wallenstein, 2002, Human & Experimental Toxicology, 21, 439-444. This article indicates when there are sufficient evidences, probable evidences or insufficiently documented evidences of an allergenic effect based on clinical and experimental data.

- The above quoted ECHA guidance which describes how human data should be analyzed, including in relation to potency determination. This ECHA guidance also proposes a categorization system in

four categories (three grades of skin sensitization potency and one category for non-sensitizing substances) which might be considered in the context of this development.

- The categorization system proposed by the SCCS in its opinion on fragrance allergens (SCCS/1459/11). The group agreed that it should be well understood how the SCCS established the relative importance of human fragrance allergens.

- More generally, the inclusion of all available information (including QSAR results, in vitro and animal testing data) was recommended. This is not a usual approach in toxicology to exclude non-human data and toxicologists usually try to collect all available information in order to make an informed decision. Such an improvement would make the system more robust and allow its use with new substances covered by little (or no) human data. It was mentioned that the LLNA predicts the NOEL in humans for about 90% of substances. For the ones it does not, the LLNA underestimates the NOEL in humans in the majority of cases. It confirms that the use of non-human data is important and should be included whenever this is available.

ACTION: The participants will read in detail the article of D. Basketter et Al. and make improvement proposals in line with the outlined above suggestions.

Additionally, it was stressed that the categorization of an allergen should be revisited every time new data (and in particular clinical data) become available.

It is noteworthy that a concern was raised about the categorization approach in general. Clinical reports show that some individuals tend to overreact to some very weak sensitizers either because they are particularly sensitive or due to an overexposure to the allergen. There was agreement by the participants that the way an individual reacts would not be the best descriptor for the property of an allergen. A strong reaction by one individual could happen to a weak sensitizer and a relatively weak reaction by another to a potent one. The group therefore agreed that the intrinsic sensitizing properties of a substance should not be confounded with the expression of the disease in an individual. Therefore, the categorization process should not be affected by this element of the contact allergy.

6. Next meeting

The group agreed to schedule a physical meeting end of June, potentially in Munich, Germany (to be confirmed). The IDEA Management Team will send a doodle poll to the participants in the next days.

Preparation, 09/05/2014 (F. Lebreux, IDEA Management Team)
First Review, 09/05/2014 (H. Bender, Chairman of the IDEA Categorization TF)
Final Review, 26/05/2014 (IDEA Categorization TF)

IDEA CONFERENCE CALL

Communication Task Force

April 28th, 2014

1. Agenda
2. Final minutes of the IDEA conference call

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

www.ideaproject.info

IDEA
International Dialogue for the Evaluation of Allergens

IDEA Conference call of the

Communication Task Force

Wednesday, June 4th, 2014 from 3:00pm to 5:00pm (Brussels Time)

Tel: +32 (0)2 404 03 05, Participant PIN: 46340660#

Agenda

1. Adoption of the agenda
2. **Objective**: Arrive at a commonly accepted information exchange procedure, which enables an improved communication between the industry and the dermatology community. This communication would be two-sided:
    - **From the industry to the dermatologists**: provide pure reference materials and fractions of fragrances in order to facilitate the diagnosis of contact dermatitis
    - **From the dermatologists to the industry:** provide the result of clinical testing in order to feed the risk management process.
3. Identification of the causes of an allergic reaction to a fragranced consumer product (sharing input samples)
    - Process description
    - Guidance on preparation of fractions of the fragrance
4. Communication of the causes of an allergic reaction to a fragranced consumer product (sharing output clinical data)
5. Practical implementation
    - Development of appropriate documentation (standardized forms, protocols, etc.)
    - Development of appropriate tools to optimize exchanges (IT platform, helpdesk, etc.)
    - Development of data storage capacities (publication in journals or website, database maintenance, etc.)
6. Next meeting

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

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IDEA
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IDEA Conference Call of the

Communication Task Force

Wednesday, June 4th, 2014 from 3:00pm to 5:00pm (Brussels Time)

Minutes

Participants: Hans Bender (Chairman), Michèle Elbaz (Chanel), Peter Griem (Symrise), Maya Krasteva (L'Oréal), Fred Lebreux (IDEA Management Team), Florian Schellauf (Cosmetics Europe), Scott Schneider (Firmenich), Matthias Vey (IDEA Management Team).

1. Adoption of the agenda

The IDEA Management Team welcomed the participants and went through the agenda, which was adopted such as provided.

No dermatologists could join this call and the group recognized that the conclusions drawn during this call might be inadequate. Therefore, the minutes of this call will be shared with dermatologists for review and feedback.

2. Antitrust statement

The IDEA Management Team reminded the constraints of the antitrust law to the participants. All agreed that there shall be no discussions of agreements or concerted actions that may restrain competition. This prohibition includes the exchange of information concerning individual prices, rates, coverages, market practices, claims settlement practices, or any other competitive aspect of an individual company's operation. Each participant is obligated to speak up immediately for the purpose of preventing any discussion falling outside these bounds.

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

www.ideaproject.info

3. Objective

The participants agreed that the main objective of this group is to arrive at a commonly accepted information exchange procedure, which enables an improved communication between the industry and the dermatology community. This communication would be two-sided:

- **From the industry to the dermatologists**: provide pure reference materials and fractions of fragrances in order to facilitate the diagnosis of contact dermatitis
- **From the dermatologists to the industry:** provide the result of clinical testing in order to feed the risk management process.

An important other objective of this group is, via the establishment of meaningful communication procedures, to hopefully prevent fragrance allergens issues from becoming public health problems as it happened with HICC. If information can be exchanged quickly and efficiently then suitable corrective risk management measures can be implemented before a fragrance allergen really becomes a problem.

4. Identification of the causes of an allergic reaction to a fragranced consumer product (sharing input samples)

A process describing how samples should be requested by dermatologists and provided by the industry has already been established and is published in the Flavour and Fragrance Journal[1]. This article also gives guidance on how the industry should prepare fractions of analyzed fragrances.

The group regarded this document as well written but too general and proposed to make it more specific in order to better match industry's needs. For instance, the document should explain in details how fractions should be prepared.

ACTION: The article will be reviewed and made more specific where this is needed. Then it will be given for review to the dermatologists who are involved in the IDEA project and resubmitted to Contact Dermatitis.

The biggest issue that the industry has to face is the quasi-absence of sample requests from the dermatology community. The group agreed that dermatologists are not sufficiently aware of this procedure, partly because the article is published in a journal not read by the dermatologists (Contact Dermatitis was approached but they refused to publish this article). There was a consensus that more efforts should be done by the industry to advertise the procedure and its benefits. However, and beyond this communication aspect, the group feared that most of dermatologists do not get involved in follow-up testing by lack of time or experience and simply recommend the avoidance of perfumed products when patients react to FMI and/or FMII2.

[1] Identification of the causes of an allergic reaction to a fragranced consumer product, P. Cadby, G. Ellis, B. Hall, C. Surot and M. Vey, *Flavour Fragr. J.*, **2011**, *26*, 2-6.

[2] FMI = Fragrance Mix I (α-Amyl cinnamaldehyde, Cinnamaldehyde, Cinnamic alcohol, Eugenol, Geraniol, Hydroxycitronellal, Isoeugenol, Oak moss), FMII = Fragrance Mix II (Citral, Citronellol, Coumarin, α-Hexyl cinnamaldehyde, Farnesol, Lyral).

Most patch test results are obtained by testing FMI, FMII and individual allergens and consumer products are not always tested and, when tested, the patch test results are frequently negative. To do a follow-up testing, a product used by the consumer must be patch test positive. Only in this case can the ingredients of the product be requested from the respective company. Some clinics in Europe conduct follow-up clinical investigations with common individual fragrance allergens (26 fragrance allergens that have to be labelled when used in cosmetics in Europe) and a very few numbers of European clinics exchange with the industry and can then patch-test a broad range of individual fragrance allergens but most do not. The reasons might be numerous as this follow-up testing is usually time-consuming, costly and unpleasant/cumbersome for the patient*. The patient may need to come 12 or 15 times to the dermatologist before a perfume ingredient is identified as causal. Additionally, it was pointed out that the teams of dermatologists in hospitals are usually quite limited compared to the daily number of patients to examine and most of dermatologists have no time for follow-up activities (which imply a lot of administrative tasks).

A relevant remark was that the procedure is too long and this could explain why the cosmetic industry only receives a limited number of requests. In effect, the patient has to await several months to figure out to which allergic he/she is allergic and he/she may get out of patience before the end of the procedure.

Dermatologists associations should be approached on that matter and events like the ESCD congress might be appropriate venues to inform the dermatology community about the benefits of testing individual fragrance ingredients.

Additionally, it was reminded that this initiative aims to protect consumers and therefore consumers should get more involved in the process. The patient has a right to know to which substances he/she is allergic and grass-rooting campaigns could be useful to raise consumers' awareness. A website may be developed to this end and, why not, a section of the IDEA website. The EU Commission is used to this kind of initiatives (e.g. "ex-smokers are unstoppable") and might want to play an active role on this issue.

5. Communication of the causes of an allergic reaction to a fragranced consumer product (sharing output clinical data)

The industry needs to get early feedback on clinical investigations carried out by the dermatologists with provided samples. A rapid understanding of a problem would indeed help to take corrective actions on time and then avoid the potential spread of an issue. Consequently, the group agreed that the article discussed above should be reviewed in the light of this two-sided dialogue and the new article should be made of four parts:

- A process description of how samples should be requested by dermatologists and prepared by the industry.

- A guidance of how dermatologists should contact the industry to get its support.
- A procedure on how the result of clinical investigation should be shared with the industry.
- A process description of how risk management measures should be taken and implemented to correct problematic situations.

6. Practical implementation

The number of dermatologists who really do patch-test being relatively small, it was suggested that dermatologists are informed about this initiative on a one-to-one basis.

Technological means (website, blog, Twitter account, etc.) should also be developed to ensure that dermatologists can easily obtain up-to-date technical but also contact information on follow-up testing of fragranced products.

7. Next meeting

An open call for interest will be resent to dermatologists who are involved in the IDEA project along with the minutes of this call. Then a follow-up conference call or a meeting will be scheduled.

Preparation, 16/06/2014 (F. Lebreux, IDEA Management Team)

Review, 07/07/2014 (IDEA Communication TF)

* Example of patch testing for fragrance allergy

1. Patch testing of standard series, additional series + two patch test readings
2. Product testing + 2 patch test readings (may be done during step 1)
3. If the product is positive: Request of product ingredients and ingredient patch testing + 2 patch test readings
4. If the perfume is positive: Request of perfume ingredients and perfume fractions patch testing + 2 patch test readings
5. If a fraction is positive: Request of fraction ingredients and further patch testing + 2 patch test readings

Step 5 may be repeated several times.

IDEA
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ANNEX

Annex I to all IDEA Workshops Progress Reports

Modus Operandi

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

www.ideaproject.info

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Annex I to all IDEA Workshops Progress Reports
Modus Operandi

Fragrance Allergy is a topic of high interest for the fragrance industry, its customers and the Authorities as expressed through the 2012 SCCS Opinion on Fragrance Allergens. The fragrance industry is determined to address this issue and provide solutions supported by a broad, multi-stakeholder approach.

To fulfill this objective, a work plan was developed in the course of 2012 and submitted to DG Sanco Risk Assessment Unit for scrutiny. All comments and suggestions were taken into consideration and the final document, having received the Commission's support, is a clear roadmap intended to deliver positive outcomes for the consumers, the Authorities and the industry. This work plan has now moved into its execution phase and the International Dialogue for the Evaluation of Allergens (IDEA) represents its transposition into concrete actions and investments. Through the organization of experts' workshops and the planning of scientific studies, IDEA aims at providing an agreed and transparent framework for assessing fragrance sensitizers in a prospective way and, ultimately, to find optimal solutions to the issue of fragrance induced skin allergies.

The protocol reported below will apply to all IDEA workshops:

- Antitrust statement: The workshops participants are systematically reminded before the workshops opening about the constraints of the antitrust law. All have to agree that there shall be no discussions of agreements or concerted actions that may restrain competition. This prohibition includes but is not limited to the exchange of information concerning individual prices, rates, coverage, market practices, claims settlement practices, or any other competitive aspect of an individual company's operation. Each participant is obligated to speak up immediately for the purpose of preventing any discussion falling outside these bounds.

- Chatham House rule: The workshops participants are free to use information received and are encouraged to openly express their point of view but neither the identity nor the affiliation of the speakers, nor that of any other participant, will be revealed.

  The meetings will be recorded but only to ensure the appropriate preparation of the meeting report.

- IDEA Supervisory Group: In order to secure the optimal governance of the project, a Supervisory Group (SG) has been nominated for the entire IDEA project length. Its mission consists in overseeing the process and ensuring the scientific integrity and the full transparency of the overall project. The IDEA SG is composed of about 4 members with no vested interests in Industry activities and jointly nominated by the EU Commission and IFRA.

IDEA Management Team
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 61
Fax: +32-2 214 20 69

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The remits of this group is to scrutinize all aspects of the work plan implementation in order to guarantee the neutrality of scientific debates and experts' selection procedures. The IDEA SG reviews and approves the draft agenda of all IDEA workshops and also the list of participants. Furthermore, and for all IDEA workshops, the IDEA SG nominates a rapporteur amongst its members to write the progress report and summarize the key elements at the end of each event.

The progress reports are validated by the entire IDEA SG, distributed to the workshop participants for review and adoption. An EU Commission review will be organized at the end of every year to communicate the outcome of the workshops to all relevant stakeholders. The progress reports of the year are presented at this occasion by the respective workshop rapporteurs.
The IDEA SG members are compensated in line with normal practices to prepare the workshops and the reports as well as the Annual Review.
The list of the IDEA Supervisory Group members and their affiliations is public and will be provided by the IDEA Management Team on request.

- Moderator: All IDEA workshops are moderated by a person holding a senior expertise in mediation and a scientific background. The Moderator cannot be an employee of the industry at the moment where the workshops take place. Moderator's mission is to ensure at all time that the debate does not deviate from the agenda and to keep the participants focused on the objectives set during the workshops.
The name and the CV of the current moderator are public and will be provided by the IDEA Management Team on request.

- Organization: The workshops are 2-day events usually divided into two parts:

  The first day is dedicated to formal presentations intended to present the state of the art, describe the main issues and collect the points of agreement and disagreement from the participants. A moderated debate takes place at the end of the first day to summarize the outcome of the session and prepare the ground for the second day.

  The second day is devoted to a moderated debate focusing on specific points identified the day before as being of special importance. The speakers of the first day co-moderate the debates and chair working groups when the agenda foresee panel sessions. The key conclusions of each workshop are drawn up during the meeting, endorsed by the participants at the workshop closing and reported as the executive summary of the respective progress reports.

- Transparency: The workshops participants (including the speakers) are not compensated for their attendance except the Moderator and the Rapporteur who, due to their official role in helping run the workshop, receive a fixed compensation in line with normal practices.
CV's of the speakers will be requested and made available to the participants of the workshop. At the beginning of the workshop, when the participants will be introduced, they will be asked to declare potential conflicts of interest due to co-operation projects with the industry, governmental groups, etc.

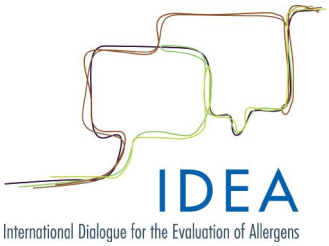
Regarding the reimbursement of travel expenses, the following was agreed:

- Representatives of the industry and representatives of national agencies do not receive any form of reimbursement for their travel and accommodation expenses.

- Representatives of the academic community are reimbursed by IFRA for all their travel expenses in line with the IFRA Travel Policy (1st class for train tickets, business class for flights exceeding 6 hours and economy class for flights otherwise). The taxi fares are reimbursed. Accommodation is paid by IFRA at the venue and at the dates where the workshops take place.

- Representatives of the EU Commission or members of the EU Scientific Committees delegation do not receive any form of reimbursement for their travel and accommodation expenses. The EU Commission and IFRA agreed that IFRA might provide a shuttle service to the EU Scientific Committees delegation if the workshops are organized in a remote area where there is no obvious public transportation possibility.

- Access to the progress reports: The progress reports prepared by the workshop Rapporteurs are not confidential and will be made publicly available to all interested stakeholders by the IDEA Management Team. However, before becoming public, the progress reports have to be reviewed by the workshop participants and validated by the Supervisory Group. More details on the status of the draft progress reports can be provided by the IDEA Management Team on request.



International Dialogue for the Evaluation of Allergens (IDEA)

Avenue des Arts, 6, 1210 Brussels, Belgium
Tel: +32 (0) 2 214 2067 - Fax: +32 (0) 2 214 2069

www.ideaproject.info