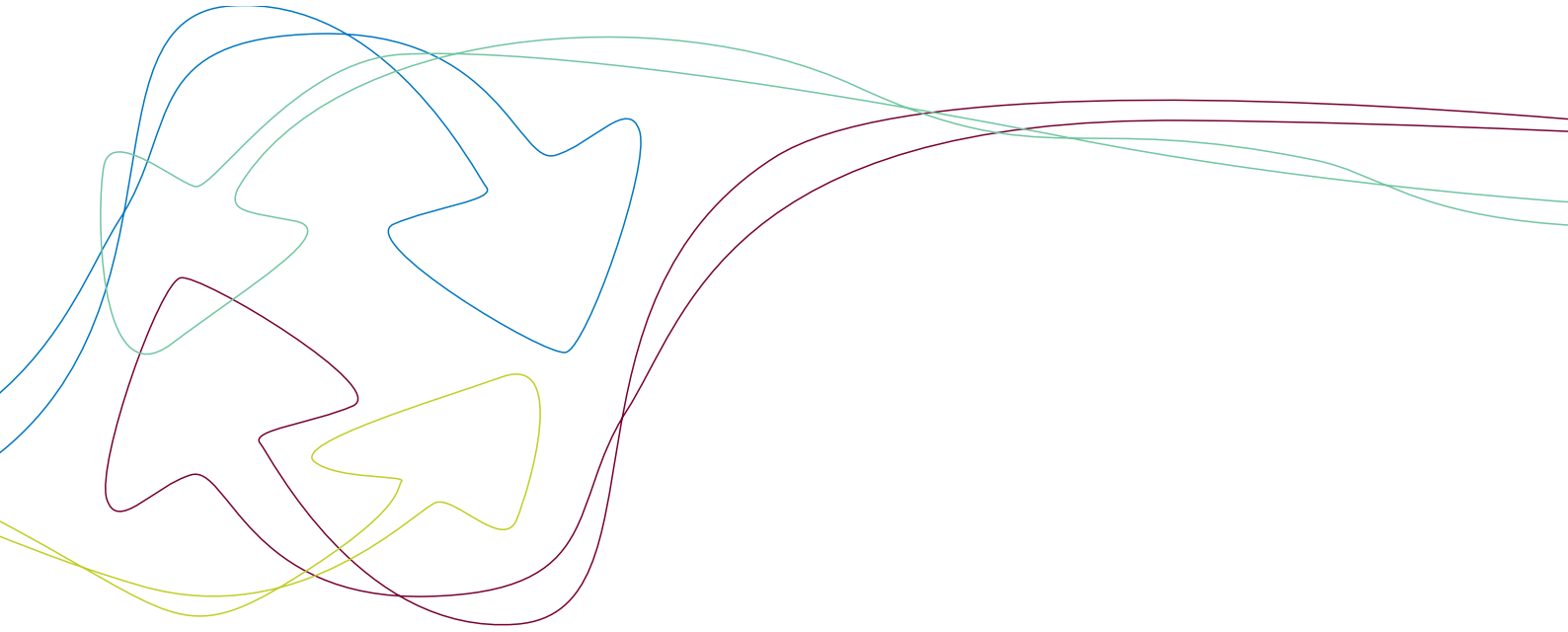
IDEA

International Dialogue for the Evaluation of Allergens

SCIENTIFIC WORK PLAN ON ALLERGENS (IDEA PROJECT)

ANNUAL REVIEW: PROGRESS MONITORING

December 13th, 2013



IDEA
International Dialogue for the Evaluation of Allergens

Introduction

The 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 prevent induction and consequently skin sensitisation of all consumers and others who may be exposed'. This is no easy task and will inevitably take some considerable time to achieve however it is one where significant progress can be anticipated.

It is recognised that there has been a history of distrust between the key stakeholders for various reasons. However we must move forward to achieve everyone's objective of a high level of consumer safety. It is evident that the aims of IDEA, which **all stakeholders** should be able to accept as highly desirable, will only be achieved through the development of trust in the process and the continuing commitment by all stakeholders i.e. industrial scientists, dermatologists, academic scientists, regulators and consumer representatives.

The focus of this first year has been to characterise the scope of the task, to identify priorities for action and by whom and how the actions should be taken forward.

The **Supervisory Group**, 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

Proceedings of the event

December 13th, 2013

1. Agenda
2. Summary adopted during the Annual Review by the participants
3. Questions & Answers exchanged during the Annual Review 2013

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: Friday 13 December 2013, starting at 10.00 AM

Draft Agenda

IDEA project: scientific work plan on allergens – Annual Review: progress monitoring

10.00-10.15 WELCOME AND OPENING BY THE COMMISSION

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.

10.15-10.45 INTRODUCTION – OVERVIEW OF THE IDEA PROJECT *(M. Vey / H. Bender/J. Bridges)*

→ Commitment of the industry to protect the consumer and genesis of the IDEA project
→ Factual description of the IDEA project
→ The process of moderating the sessions
→ The supervisory Group

10.45-11.30 CHARACTERIZATION OF FRAGRANCE ALLERGENS WORKSHOP – AUGUST 28-29, 2013 *(H. Greim)*
Progress report on the discussions, main recommendations made by the leading scientists who attended the workshop and report of the actions taken.

11.30-12.15 QRA WORKSHOP – MARCH 19-20, 2013 *(J. Bridges)*
Progress report on the discussions, main recommendations made by the leading scientists who attended the workshop and report of the actions taken.

12.15-12.45 LUNCH

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

12.45-13.30 PRE- & PRO-HAPTENS WORKSHOP – MAY 28-29, 2013 *(J. Bridges)*
Progress report on the discussions, main recommendations made by the leading scientists who attended the workshop and report of the actions taken.

13.30-13.45 THE COMMISSION'S EXPECTATIONS OF THE IDEA PROJECT *(DG SANCO B2)*

13.45-14.00 THE ANNUAL REVIEW IN SUMMARY *(H. Bender)*

14.00-14.15 NEXT STEPS OF THE IDEA PROJECT AND PLAN FOR 2014 *(M. Bongi)*

14.15 CLOSING BY THE COMMISSION

IDEA Annual Review 2013 – Summary

adopted during the Annual Review by the participants

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

December 13th, 2013

- The IDEA Project is showing promise of delivering against its objectives of:
  i. multi-stakeholder dialogue,
  ii. common understanding of science and,
  iii. an aligned set of actions

  all this to minimize fragrance-induced contact allergy.

- The approach of multi-day workshops for a given topic is seen as effective to address key questions related to fragrance allergy as judged from the reports and the quality of recommendations and resulting action plans.

- All three topics covered in this year's workshops will require follow-up in next year's workshops, including questions raised at the IDEA Annual Review.

- The success of IDEA will largely depend on the ability to timely deliver against agreed recommendations and action plans.

- The IDEA Annual Review proved useful and is recommended also in future as the tool to monitor progress.

Dr. Hans Bender
IDEA Workshops Moderator

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IDEA Annual Review 2013

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December 13th, 2013

During the Annual Review several issues were highlighted by the attendees. In particular:

General remarks

- The IDEA project is an excellent initiative but the process, at least for some aspects and to ensure delivery of quality results, will take several years – this should not hinder important interim measures to be taken.
- Measures taken by the industry on the specific material HICC maybe not always have been adequate or timely in the past. This experience is maybe not a good example to judge on effectiveness of risk management measures but can serve as an excellent case study for the IDEA project.
- The QRA is a promising tool but still to be regarded as under development and further refinement is needed. -Based on the recommendations made in March 2013, the Industry has invested a lot of resources in revamping the QRA. Most of the work is now completed and a comprehensive report of the improvements incorporated into the methodology will be presented at the second QRA workshop to be held in March 2014. The basic elements of the QRA approach were shortly summarized, for more information on the QRA methodology see: http://www.ideaproject.info/QRA-methodology
- As a not directly related topic, challenges to performing risk assessments on fragrance compounds (trade secret protection limited resources and expertise of SME's etc.) were mentioned.
- The new regulation on fragrance allergens for some elements will rely on the QRA methodology, which requires the availability of a revised QRA methodology by June 2014.

Involvement of SCCS, JRC and the Supervisory group

- The respective roles of JRC and SCCS will have to be clarified for what concerns the scientific assessment of the QRA and its subsequent application.

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- SCCS members pointed out that in the IDEA Annual Review their role would be that of observers. In parallel the Chair of the IDEA Supervisory Group reminded all the IDEA workshop participants that their contribution as experts was expected.
- Jim Bridges, Chair of the IDEA supervisory Group offered to be in dialogue on any concerns regarding transparency of the process or other concerns related to how IDEA is executed, as we are still on a learning curve.
- Role of the Supervisory Group might further evolve.

Human data

- Good human data are of highest relevance - Patch testing (properly conducted diagnostic patch tests) is the gold Standard for clinical data requiring expertise and should only be done by experienced dermatologists.
- Contact allergy is the relevant endpoint, when there is a rise following exposure to a particular fragrance this is a demonstration that consumers have been exposed to a too high level.
- Establishment of contact points to scrutinize clinical reports for plausibility is most welcomed; industry needs to critically follow the published literature and dermatologists should be encouraged to participate in projects to feedback to the industry the results of patch testing before publication.
- Retrospective analysis on important datasets from trusted data centers such as ESSCA (European Surveillance System of Contact Allergies) are essential to understand the skin sensitization potential of individual fragrance allergens, inform the risk assessment process and, possibly develop structure-activity models.

HRIPT

- The HRIPT is not used as a predictive tool by the industry but only as a confirmative tool, this should address ethical concerns.
- An HRIPT on 100 people needs to be critically looked at with regard to its predictive value for the general population.
- Common practice is to test the finished product in HRIPT to ensure that it does not cause induction of skin sensitization. However, while an HRIPT conducted on 100 volunteers (and resulting in no reaction) can be regarded as a good background, it does not offer the guarantee that the finished product will never cause skin sensitization issues. Therefore, cosmetovigilance is a very important post-marketing tool to ensure that the safety assessment of products adequately protect consumers.

Inter-individual differences

- Inter-individual variability, which came up at all three workshops, is important to look into more deeply It is recognized that in the clinics there is a focus on the high end of sensitization due to the selected population.

- The observation that some people are sensitized to a chemical and do not develop the pathology and why others do is an important topic still to be better understood.

Exposure

- Clinical data should be linked as much as possible with information about exposure of a material to the general population as this leads to additional important information in ranking priorities.
- Assessing consumer exposure adequately and with a set of harmonized tools remains a big challenge across all types of industry sectors and regulations – A broad EU survey to generate a standard set of habits and practices of consumers would be very useful.
- The Industry has developed a promising model aiming to evaluate the aggregate exposure of consumers to fragrance allergens – this model was presented at the first IDEA workshop and a proposal made for its incorporation into the QRA will be presented at the March 2014 workshop.

Pre- and pro-haptens

- For the pre- and pro-hapten discussion it was recommended to also look into the role of transporters. The question will be posed to the workshop participants and addressed at the next IDEA workshop on pre- and pro-haptens if needed.
- The pre- and pro-hapten problematic is not specific to fragrance ingredients and most of the conclusions developed during this workshop are also valid for other types of substances.
- Many uncertainties remain on the complicated topic of pre- and pro-haptens. Further scientific investigations and deeper insight will be necessary before usable risk assessment methods become available.
- Some materials can be both pre- and pro-haptens, which can be activated inside and outside the skin – while pre-hapten formation can be prevented, that of pro-haptens most likely cannot.
- Oxidation might not only contribute to increased haptens but consideration should also be given to other effects potentially caused by the radical mechanism linked to it.
- The work on a joint development of a broadly applicable analytical method for the determination of hydroperoxides has not yet started. There will be an open call to the IFRA workshop participants for participation. Many hurdles need to be addressed, starting with the availability and even transportation of adequate standards.

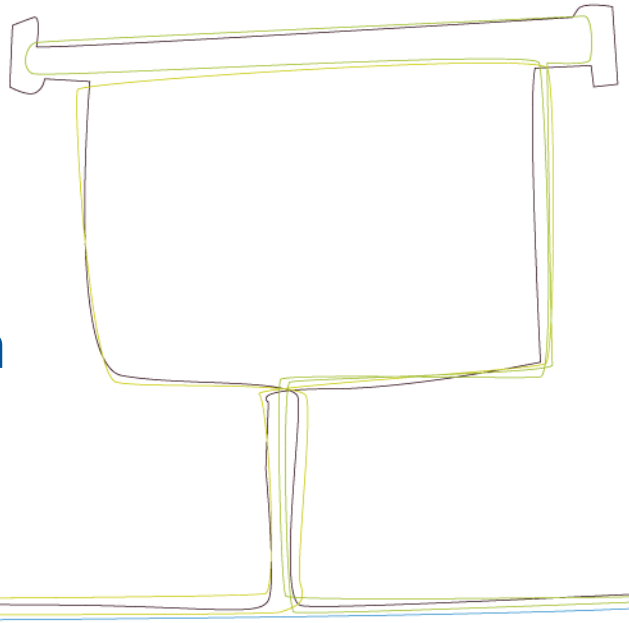
OVERVIEW OF THE IDEA Project

1. Slides presented by Dr. Matthias Vey, Dr. Hans Bender and Prof. Jim Bridges
2. Industry proposal for a joint work plan
3. Modus Operandi

IDEA

International Dialogue for the Evaluation of Allergens

A Multi-stakeholder Dialogue with Experts on Fragrance Allergy in partnership with the EU Commission



IDEA Annual Review – December 13th, 2013

Background

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- Fragrance induced allergy identified as an important issue in late ‘90s with increased number of allergic patients in clinics up to the year 2000.

- Fragrance industry recognized that its tools and procedures did not adequately address this human health issue.

- Approaches like the QRA aiming to ‘eliminate’ allergy were not sufficiently developed with and adopted by all relevant stakeholders.

Background

- The fragrance industry was not the master of its own destiny by relying too much on other organizations for dealing with the issue of fragrance allergens.
- SCCS Pre-consultation opinion on fragrance allergens in cosmetics (December 2011) served as a ‘wake-up’ call.
- In early 2012 IFRA decided to ‘step out of the shadows’, adopt a more prominent role and become fully engaged.
- Developing the tools to ensure a high level of consumer safety required a multi-stakeholder approach (incl. Academia, relevant services of the EU Commission, Dermatologists and Downstream User Industries)

Work Plan

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- Work plan was designed from the outset to be conducted in partnership with the EU Commission.
- Officially announced at public hearing on the SCCS opinion on March 5th, 2012.
- Draft program presented to the EU Commission in April 2012.
- Iterative process to refine the Work Plan throughout 2012.
- Official endorsement by Commissioner Tonio Borg March 14th, 2013.

The Work Plan – basis for IDEA

Key items of the Work Plan related to Risk Assessment are:

- Definition of fragrance allergens
- Definition of fragrance allergens of specific concern
- Pre-haptens
- Pro-haptens
- QRA

IDEA is the project executing the Work Plan

IDEA – Strategic Objectives

IDEA
International Dialogue for the Evaluation of Allergens

- **Allow for an open and transparent dialogue** leading to a comprehensive understanding of fragrance allergens and the assessment of the risk for the population.
- Using this as a basis to **develop effective, risk based strategies to protect the consumer**, **which are agreed by the partners in the dialogue**.
- **Ensuring that these strategies are understood and adopted** by the the fragrance and downstream user industries.

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Multi-stakeholder approach to allow on open exchange on different points of view on the same topic

MC Escher
1898 - 1972

IDEA – Steps in the process

- Develop a **transparent framework based on current scientific understanding** for assessing fragrance ingredients, in cooperation with all key stakeholders in a timely, prospective and sustainable way.
- Identify particular areas of concern and how they should be addressed.
- **Build a predictive model** dealing with the management of allergens.
- Ensure the relevance of the findings from the methodology to the real life situation trough regular review.

The Annual Review

Under the auspices of the EU Commission the aim is to:

- **Critically review** the progress made.
- Provide a platform to allow an **open minded exchange** and pose questions regarding the general program and its further development.
- **Update the program and priorities** when needed based on this exchange.
- **Further broaden the stakeholder involvement** in the IDEA project to other industry sectors and globally.

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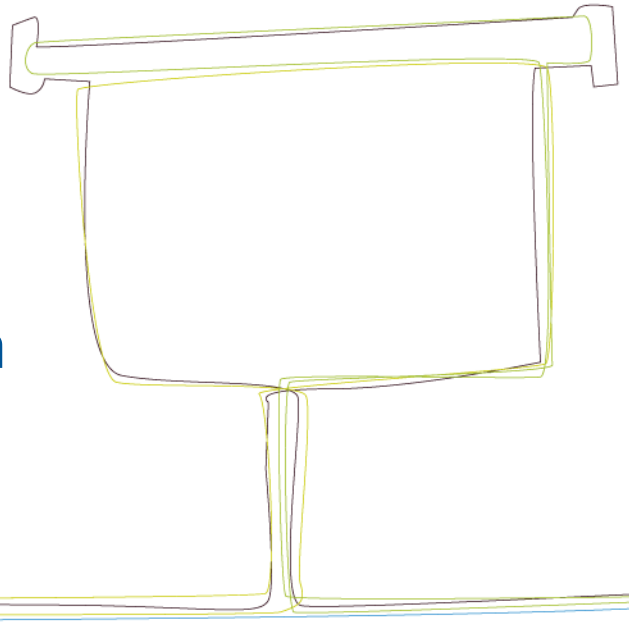
A Multi-stakeholder Dialogue with Experts on Fragrance Allergy in partnership with the EU Commission



IDEA Annual Review – December 13th, 2013

The IDEA Project Program and Timetable

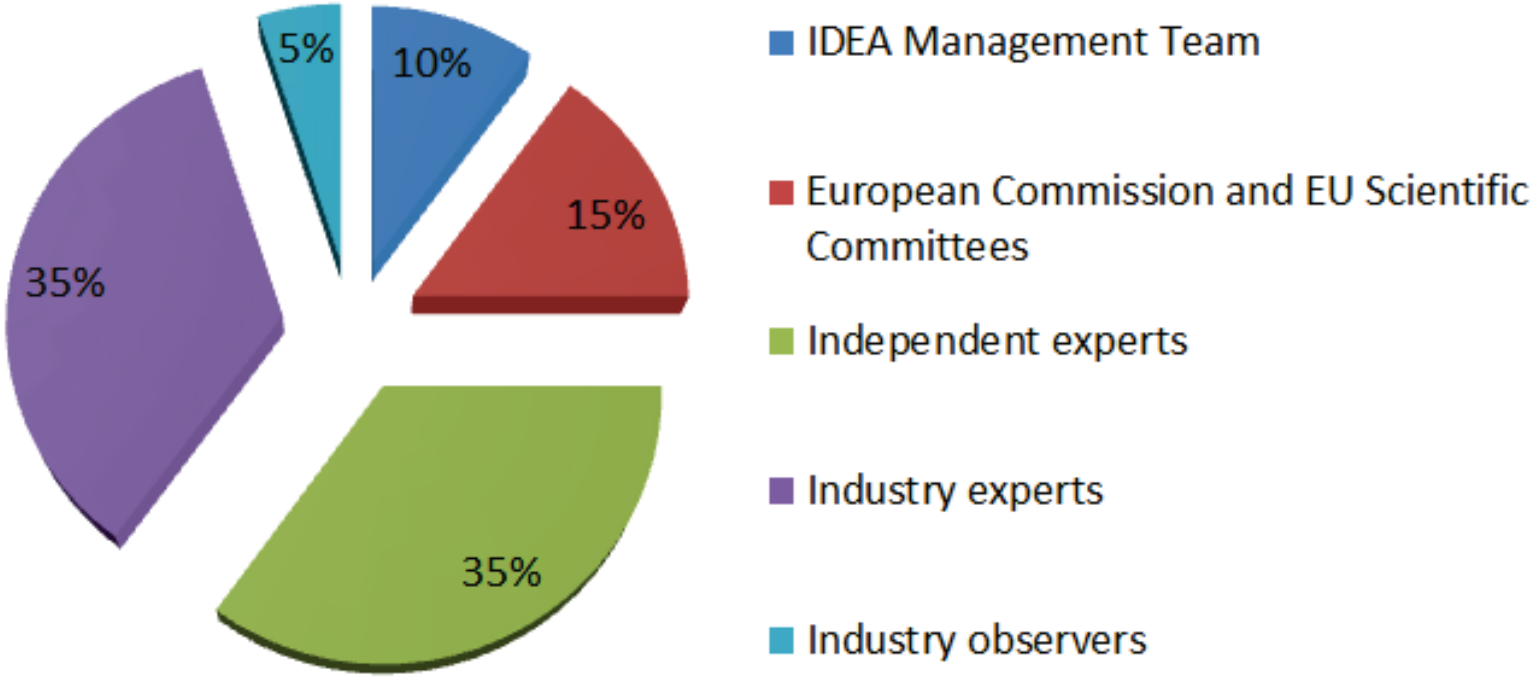
WS I (QRA)

WS II (Pre- & Pro-haptens)

WS III (Characterization of Allergens)

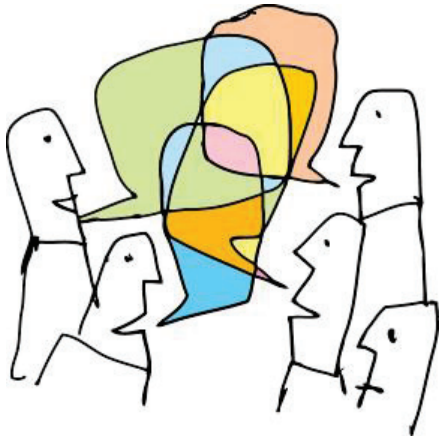
Annual Review

Participants in the workshops



- Participants are invited based on expertise and knowledge regarding the topic of the WS.
- The list of participants is overseen by the Supervisory Group and DG Sanco.

Outcome of the workshops

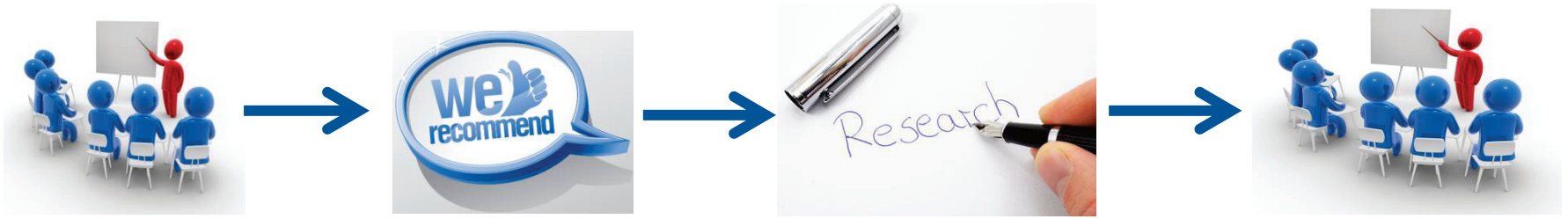


Conclusions at the meeting (Moderator and participants)

Progress report (Rapporteur of the WS)

Stakeholder consultation leads to refinement and final version of both the conclusions and the progress report

Recommendations made at the workshops



- The WSs result in jointly agreed recommendations how to improve the RA methodologies discussed.
- Based on the recommendations IFRA (together with RIFM) develops an action plan, which is presented to the WS participants.
- Industry takes on the action items with involvement of other stakeholders as required.
- Results are presented and critically evaluated at the next WS.

Principles that underpin IDEA

Modus Operandi

IDEA Supervisory Group

- Tripartite, continuing collaboration and transparency is vital for the success.
- A general Modus Operandi is essential and is shared with all participants.
- The Supervisory Group is accountable for the governance of IDEA and to ensure the scientific integrity of the WS debates.
- http://www.ideaproject.info

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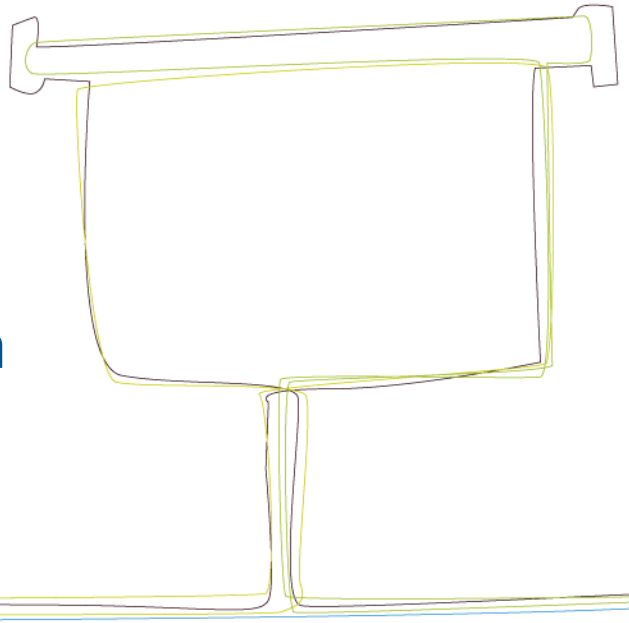
International Dialogue for the Evaluation of Allergens

A Multi-stakeholder Dialogue with Experts on Fragrance Allergy in partnership with the EU Commission

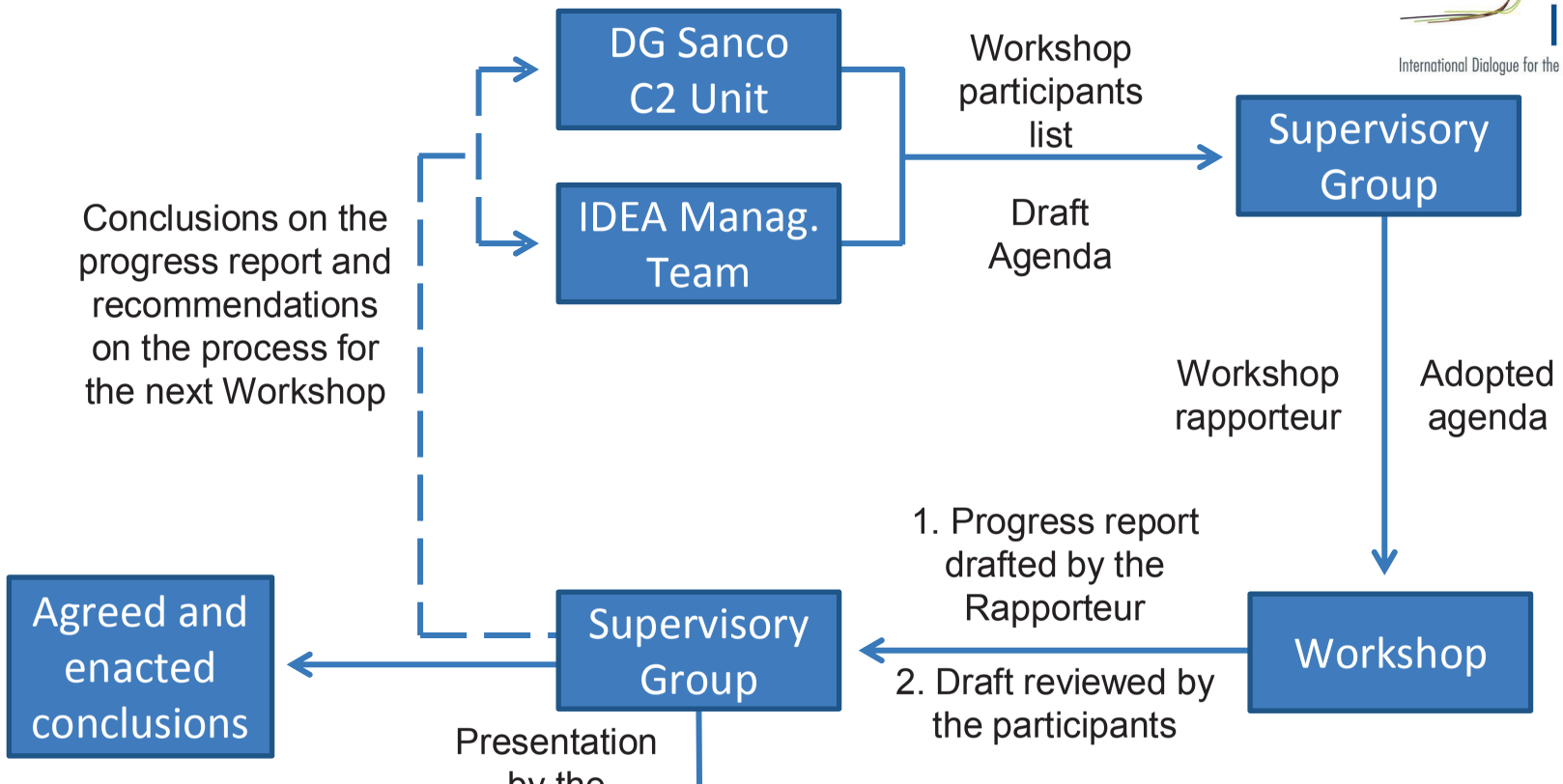


IDEA Annual Review – December 13th, 2013

The IDEA Supervisory Group

- Currently consisting of four members with no vested interests in industry activities.
- Role: to supervise the process and to ensure the scientific integrity and full transparency of the overall project.
- Tasks include:
  - Validate the **participants list** of all IDEA WSs.
  - Agree the **program** of all IDEA WSs.
  - Nominate a Supervisory Group Member before each WS to serve as the **Rapporteur**, who has to ensure the scientific integrity of the discussions.
  - Adopt the **report** of the Rapporteur and the proposed action program.
  - Be available to discuss any concerns of the stakeholders on the scientific aspects

The Supervisory Process



Supervisory Group:
Prof. Jim Bridges (Chair)
Prof. Helmut Greim
Dr. Alain Khaiat
Dr. Christin Mowad

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International Dialogue for the Evaluation of Allergens

Thank you for your attention

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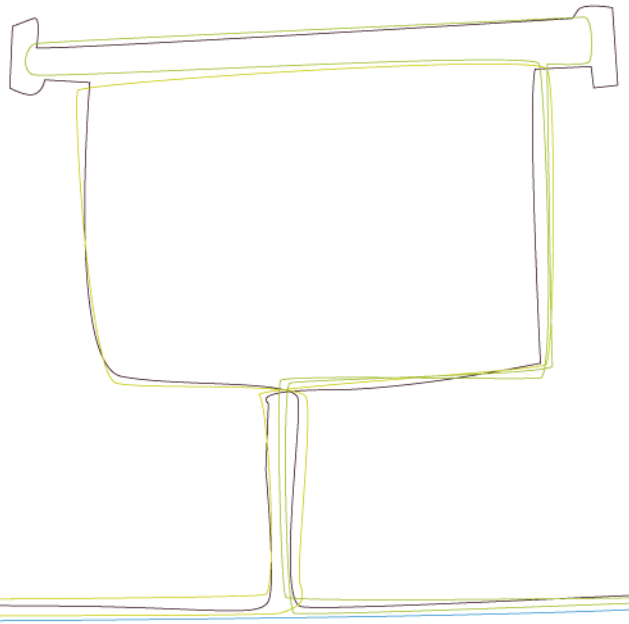

Industry proposal for a joint work plan

Develop a shared common understanding of risk assessment methodologies, processes and criteria to identify fragrance allergens of concern

Background

Based on regular contacts with EU Commission (DG Sanco) and the conclusions of the Public Hearing on Fragrance Allergens which took place on March 5th, 2012, the Industry understood the need for further scientific work enabling the definition of explicit criteria and the clarification of identified areas of concern in order to provide an agreed and transparent framework for assessing fragrance ingredients in a prospective way. This work does not only concern the Fragrance Industry but embraces multi stakeholders, including Academia, the relevant services of the EU Commission, Dermatologists and the Downstream User Industry.

This need for clarity was already highlighted in the first part of the draft Industry proposal presented to the EU Commission on April 13th, 2012. The items of this final Industry proposal for a joint work plan related to risk assessment are:

- Definition of fragrance allergens
- Definition of fragrance allergens of specific concern
- Pre-haptens
- Pro-haptens
- QRA

The Strategic Intent

The strategic intent of this proposal is to ***prevent further uncertainty*** for the fragrance and downstream industries in an area which is critical to consumer safety. It is also intended to provide the industry with a better visibility for business continuity. Indeed, it is vital for business to rely on a robust prospective risk assessment approach securing the most predictive extrapolation in the area of fragrance allergy. This scientific approach should also take into account the relevance of its findings in real life, through regular review. This is critical to enhance consumer confidence in the safe use of products. In addition, without such a prospective approach, the current situation could jeopardize investments in innovation and leading to a significant loss of added value and competitiveness for business.

The work plan

This document represents the proposal for a scientific work plan, which is intended to lead to a shared common understanding of methodologies, processes and criteria, and could become the basis of a robust approach for a multi-stakeholder risk assessment program.

The work plan proposes **four specific tasks** which should be addressed in order to develop a common understanding of the risk assessment process:

- **Task I**: Define the concept of 'fragrance allergens'
- **Task II**: Define the concept of 'allergens of specific concern'
- **Task III**: Address the specific problem of pre- and pro-haptens
- **Task IV**: Address the validity of the QRA methodology and the possibilities of further refinement

In combination, these tasks should set an open and transparent dialogue which should lead to a comprehensive understanding of fragrance allergens and the assessment of their risk to the population.

The aim of the workshops and the whole program is to lead to procedures and guidance documents for all parties involved. Those guidance documents, if meaningful and efficiently applied, should help create the required certainty in the evaluation process and master the management of fragrance allergens in the future.

The overall timeline of accomplishing all 4 tasks is assumed to be about 3 to 7 years. For the completion of the technical aspects a minimum time period of 3 years is foreseen and additional time will be needed to discuss and translate agreed actions into a framework that will provide all stakeholders involved with a secure business environment in which to operate in the future.

Some tasks should be able to be addressed in a much shorter timeframe, especially as those will be the basis for other tasks. This is especially true for task 1, which should be able to be completed within about a year. A more detailed outline of timelines, organizational aspects and deliverables will be presented in a separate document.

All tasks may require a series of workshops, but only if necessary. If the goal of the task can be achieved in one workshop this will be the end of the task.

The Supervisory Process

In order to secure the optimal governance of the project, it is foreseen to nominate a Supervisory Group. Its mission would be to supervise the process and to ensure the scientific integrity and the full transparency of the overall project.

The Supervisory Group (SG) would be composed of 5 to 7 members with no vested interests in Industry activities. The members would be jointly nominated by the EU Commission and IFRA.

The remits of this group would be to scrutinize all aspects of the work plan implementation in order to guarantee the neutrality of scientific debates and experts' selection procedures. The Supervisory Group would review the draft agenda and related activities.

Furthermore, for each workshop, the Supervisory Group would nominate a rapporteur amongst its members. This rapporteur would attend the workshop and, assisted by IFRA project management, write the report based on its outcome. This progress report would be reviewed by the Supervisory Group to draw conclusions and set recommendations in view of improving the overall process.

The monitoring Process

We recommend, in partnership with DG SANCO, to host an annual review on fragrance allergens. The review is aimed to ***monitor and validate the progress made*** by the experts and to ***update the program and priorities*** when needed. Rapporteurs of the workshops held during the year will present their reports at this occasion. This event will be the appropriate platform to ensure that ***all stakeholders can express their views and ask questions***.

As stated before, the Industry must engage with a broader group of stakeholders. This group will inevitably bring with it a variety of perspectives and positions. This collaborative effort will not only result in a stronger method of managing allergens, but will also build a lasting relationship which may serve as a model for other fragrance associated topics relating to the on-going enhancement of consumer safety.

The yearly review organized under the auspices of the EU Commission will involve broad stakeholder participation with the aim to build a common understanding of fragrance allergens and implement a new integrated forward looking management process, based on a number of components that can easily be enacted.

The first review will serve as a kick off for the series of workshops end of 2012 or early 2013.

The participation in the Review should be globally oriented as the topic of fragrance allergens is not limited to Europe and such a fundamental discussion should be carried out with a global perspective. Therefore we would suggest inviting also members of the International Cooperation on Cosmetic Regulation (ICCR).

Task I: Define the concept of fragrance allergens

I.1 Why do we need a definition of fragrance allergens?

Some fragrance ingredients have the potential to cause dermal sensitization. However, such fragrance allergens may be described in various ways, so there is a need to define them via a collaborative approach between stakeholders to ensure that effective consumer safety can be delivered.

A clear understanding of what is a skin sensitizer and what are the tools to identify it remains a prerequisite to define a fragrance allergen. Allergy includes two phases:

- Induction of specialized immunological T cell memory in an individual by repeated exposure to an allergen (i.e. the immune system learns to react).
- Elicitation, i.e. production of an immune system (T cell) mediated allergic response subsequent to exposure of a sensitized individual to the allergen (visible skin reaction). Usually, lower doses are necessary for elicitation than are required for induction.

Skin sensitization is not an 'all or none' phenomenon: there is a sequence of immunobiological events that need to be activated to produce first an induction of sensitization and secondly to elicit a clinical reaction. In consequence, induction and elicitation of contact allergy are threshold phenomena and allergic contact dermatitis therefore is to a considerable extent a preventable disease.

I.2 What are the different options?

The simplest level of definition is by hazard classification. There exists already a formal definition of substances, including fragrances, which present an allergenic hazard, under the UN GHS and EU CLP regulations. This definition is primarily developed to protect workers handling raw materials. This may result in the classification of a substance used in fragrances as a skin sensitizer, which is important to ensure correct classification & labeling and subsequent handling during manufacturing. This approach also has implications for the labeling of some consumer products, for example detergents in the EU.

The UN GHS criteria are certainly a useful element to take into consideration but insufficient for addressing the full scope of the topic as it is only a hazard assessment tool.

Several in vivo test methods have been used to identify skin sensitizers. Traditional guinea pig methods identify allergenic hazard based on the % of animals exhibiting a response after repeated applications of the substance at a fixed concentration. However, guinea pig tests are not designed for the determination of potency, although in the recent ATP to the CLP Regulation a scheme is proposed to distinguish between two potency categories based on guinea pig data. In contrast, the murine LLNA is more widely used not only to determine the potential of a material to induce contact sensitization, but also for the measurement of the relative potency. Much work has been done to correlate the dose-response data obtained in the mouse LLNA with what is known about potency in humans.

Of great relevance in the near future is the development and validation of in vitro methods, since this area is progressing rapidly, being one of the most important research topics nowadays linked to skin sensitization. How these methods will deliver potency as well as hazard information is a key question of relevance to risk assessment.

Another important element in understanding skin allergies is clinical (patch test) data. As recently pointed out by Basketter and White in the Editorial to Contact Dermatitis (**2012**, *Contact Dermatitis*, **67**, 1-2), for the dermatologist facing a patient with a suspected allergic contact dermatitis, the application of a baseline patch test series, often supplemented by additional selected substances based on the patient's history, represents a key component of their diagnostic 'toolbox'.

Initial patch test data provide the information that these materials are contact allergens. A comprehensive risk assessment system therefore has to include them as an important alert instrument since diagnostic patch test data offer:

• an indication that exposure to a substance may cause allergy in the population

• a means to compare the relative importance of contact allergens in terms of the frequency of reactions

• a means of following contact allergy trends over time

The recently published SCCS Opinion contains a classification of (fragrance) allergens using the number of positive patch test results from clinics as the qualifying element.

Research has been initiated to further refine the patch testing protocol (execution, standardization of patch test material, verification of reactions as allergic rather than irritating). This is important work that will help provide additional value to this important instrument.

It is well recognized that positive patch tests identify whether a patient has contact allergy to a substance, (with the exclusion of false positive patch tests are correctly identified), but do not directly determine whether it has relevance for the eczema that led to the consultation. It does not identify what exposures caused the induction of contact allergy (e.g. natural versus consumer product exposure, or which product type) nor does it give any dose-response information or inform on what types of exposure may be tolerated This must be derived from the clinical history (anamnesis), evidence of relevant exposure, the experience of the dermatologist and more importantly through use tests such as (repeated) open application tests.

A comprehensive risk assessment approach should therefore also include the thorough consideration of the aspect of clinical relevance.

Finally, other information, not adequately incorporated so far, and that could be of relevance, e.g. cosmetovigilance data from consumer product companies and/or poison centers, are also important when identifying the existence or emergence of allergy in consumers.

I.3 Recommended actions

Industry, the dermatological community, and regulators need to work together to find a common ground and understanding of how to best integrate clinical (and cosmetovigilance) data into the risk assessment process.

The industry is proposing a new approach to bring the stakeholder input together in a collaborative program, with a structured framework that will enable more effective dialogue but also clearer approaches to defining allergens as well as processes to assess their risk. It is envisaged that this would be managed with a combination of industry/non-industry toxicologists, clinical and experimental dermatologists as well as risk assessors, to enable a comprehensive, robust and pragmatic weight of evidence based approach to address the risks deriving from fragrance allergens.

Task II: Define the concept of 'allergens of specific concern'

II.1 What do we mean by allergens of specific concern?

The need is to agree on criteria for the identification of a (fragrance) allergen, which would define how to identify a 'significant risk to the general population'.

Industry, the dermatological community, and regulators will work together to find a common ground and understanding on how to integrate clinical, cosmetovigilance and exposure data into the risk assessment in order to produce an accurate definition of "allergens of specific concern". For instance, different levels of concern may be defined:

- Magnitude of the issue (low, medium or high percentage of population effected)
- Categories of allergens (all sensitizers, rare allergens, common allergens, allergens of (very) high concern, etc.)
- Sources and levels of exposure

In this respect there is a need to address questions related to the above definitions such as what defines a substance for which a risk assessment technique such as the QRA (based on avoidance of induction) is considered sufficient versus what defines an allergen for which other more restrictive measures need to be considered necessary.

II.2 What should be discussed and researched within the risk assessment process?

Several areas of the risk assessment process require further refinement and understanding to allow their integration into a common methodology. This need is particularly true for the exploitation of data that underline the definitions of fragrance allergens and allergens of specific concerns:

- Use of toxicological data:

  This generally addresses primary prevention by attempting to identify safe exposure levels, which avoid the induction of skin sensitization. The QRA approach is clearly defined and published and is the basis of the existing IFRA Ingredient Standards on sensitization. However, there are still areas for further research and potential improvement (e.g. consideration of aggregate exposure). This is part of the fourth task.

- Use of clinical data:

  Data from dermatology clinics is at the forefront of the identification of substances that cause allergy in the general population. However, dermatologists are not routinely included in the discussion on risk assessment. In addition to the interpretation of data, including dermatologists in active consideration of approaches to risk assessment will provide for a collaborative approach to establishing safe use conditions. The following aspects need to be considered in incorporating correctly use clinical data in the risk assessment process:

  - Determination of contact allergy via the use of the patch test and whether there is a need for refinement to this tool (e.g. Nosbaum et al, 2009).
  - Differentiation of cases with likely induction of sensitisation by the ingredient from cases with likely cross-reaction in elicitation (with allergy induced by a different chemical).
  - The relationship between patch test exposure conditions and real life exposure (e.g. Maibach et al.) and clinical relevance of a positive patch test response (e.g. Ale and Maibach, 2010; DeGroot 1999, EDEN study data)
  - Consideration of a scientific study to investigate the clinical relevance of positive patch tests.

- Definition of levels of concern: A clear definition is required to identify levels of concern of allergens. For instance, this definition may be based on an absolute number or percentage of patients within dermatological clinics reacting to a substance, number of clinically relevant cases per year, percentage of general population with (clinically relevant) reactions, etc. It might further be worthwhile to discuss cases of sensitization in relation to the marketed amount of an ingredient and use levels or more sophisticated stochastic analyses like allergy incidence in predicted exposed subpopulations.
- Potential role of alternative techniques to patch testing (like immunologic systems).
- Potential role of sample provision to dermatologists to facilitate diagnosis (is the system sufficiently effective?).

- Use of Cosmetovigilance data:

  Cosmetovigilance data is an important source of information that is mostly held within consumer product companies, but can be used to identify emerging issues or substances of concern. The availability and quality of this data needs to be further explored to understand the potential usefulness of such data within this process.

  Consumer product companies could consider sharing data perhaps through a third party (to protect confidentiality), to enable a broad on-going use of sensitization incidence information to drive prioritization and decision making.

II.3 Consideration on the use of elicitation thresholds for risk assessment.

Discussion is needed on reliable protocols/measures to determine those thresholds and how far elicitation thresholds could be a relevant and reliable model for use in risk assessment. One focus should be comparing thresholds from ingredients with different potency, particularly weak sensitizers, the category that contains the majority of fragrance sensitizers.

The Research Institute for Fragrance Materials (RIFM)[1] is actively engaged in an elicitation threshold study for Eugenol, which could further inform these discussions. Insights from the already initiated Repeated Open Application Test (ROAT) with Oakmoss (containing atranol and chloroatranol) could also prove helpful.

We recommend that the appropriate use of elicitation thresholds for risk assessment be discussed and protocols/measures be agreed to determine them. The organization of a workshop of experts seems to be the best option to address the questions outlined above.

[1] The Research Institute for Fragrance Materials (RIFM) is a non-profit scientific institute founded by the Fragrance Industry in 1966 for the purpose of generating and evaluating safety data on fragrance ingredients. The scientific foundation of RIFM is built around its independent Expert Panel (REXPAN). It is comprised of internationally known academic dermatologists, pathologists, toxicologists and environmental scientists, none of whom has any other connection to the fragrance industry, and whose work involves the safety evaluation of fragrance ingredients under conditions of intended use. Additional expertise is provided by adjunct groups with knowledge in genetic toxicity, respiratory science, reproductive effects, environmental fate and epidemiology. The results of their evaluations are published in peer-reviewed scientific journals, and their decisions regarding restrictions of use are promulgated through the IFRA Standards.

Task III: Address the specific problem of pre- and pro-haptens

III.1 Why do we address pre- and pro-haptens under the same task?

The issues around pre- and pro-haptens have been highlighted and it is important to find a common agreement on how to assess the risk related to these materials.

By definition both pre- and pro-haptens are not allergenic themselves but can give rise to allergenic species. According to the general understanding:

- a pre-hapten is a chemical substance that can be transformed into an allergenic species via abiotic processes;
- a pro-hapten is a chemical substance that can be transformed into an allergenic species by the action of skin enzymes.

It is important to understand that the discrimination between pre- and pro-haptens cannot always be made and it is quite common that a chemical substance be converted into a hapten both via biotic and abiotic pathways (e.g. hydrolysis and oxidation can happen both biotically or abiotically). Given that the resulting hapten is often the same regardless of the conversion pathway, we recommend to use the term “abiotic/biotic transformations” rather than pre- and pro-haptens.

III.2 What should be discussed with regard to abiotic transformation?

Air oxidation can transform benign fragrance ingredients into allergenic species. A substantial body of research (mainly publications by A.T. Karlberg), partly funded by the fragrance industry, to identify the allergenic species resulting from oxidation has been carried out. Industry has collected information on the presence of oxidized materials in fragrance raw materials, compounds and finished products, both unopened and after being opened and used for up to five years. Such analytical information of ‘real life exposure’ in combination with clinical data helps to understand the importance of this mechanism. However, many knowledge gaps remain. Therefore, we recommend that a dialogue be established to discuss the need for additional research on the abiotic transformation. The questions to be addressed can be divided into two categories:

➔ *Technical questions related to the manufacturing process:*

- A research program, e.g. a stability study and analysing for intermediates and by-products of the short-life hydroperoxides could be considered.
- Should such a study have specific focus (targeted peroxides and by-products) or a broad focus (determine general peroxides values)? Is it sufficient to have the key focus on hydroalcoholic products or does it needs to be enlarged to cover other product forms? Are there product categories of specific concern (Skin creams, Hair dyes, Deodorants)?
- Should aromatherapy products get included in the investigations as consumers can be exposed to higher doses of putative pre-haptens in these products?
- Is there sufficient protection of typical consumer products against the risk of abiotic transformation? What value do the measures have that already have been put in place by Industry (product format, antioxidants, etc.)?
- How does ‘maturation’ happen, under which conditions does it usually take place, and does it potentially lead to peroxide formation?

➔ *Toxicological questions:*

- Scope – is it justified based on experience to consider terpene peroxides to be a relevant cause of allergic contact dermatitis through the use of cosmetic products?
- What information does patch testing with oxidized materials provide?

- Clinical relevance – can observed patch test reactions be linked to consumer products containing oxidized materials? Could high exposures to oxidized materials stimulate various T-cells to react to give rise to non-specific elicitation reactions?
- Commission independent laboratories to determine the presence of oxidized linalool or limonene. What other exposures should be considered?
- Standardization of oxidized patch test material – how to ensure that all dermatologists test with the same material. Should we envisage testing only with defined hydroperoxides instead of an oxidation mixture?

Given the complexity of this debate, we suggest that a workshop be organized with experts to clearly define what the issues are and how to progress and manage them.

III.3 What should be discussed in relation to the hydrolysis issue?

Some fragrance ingredient categories (esters, acetals, Schiff bases) can undergo a biotic or abiotic transformation of hydrolysis to produce a skin sensitizer. Depending on the degradation pathway (biotic or abiotic), the suggested actions differ:

III.3.1 Abiotic transformation

In the case of hydrolysis we know what would be the potential allergen formed and its potency. Formation of this allergen during production and shelf life can be monitored, and it would therefore be possible, based on historical or analytical data, to determine the risk of hapten formation by hydrolysis, taking into consideration the complexity resulting from various product categories. It is important to notice that each ester (or acetal or Schiff base) has its own chemical reactivity, and kinetic studies may lead to an enhanced understanding of the hydrolysis issue. The outcome of such studies would be the estimated probability to observe hydrolysis products for a given material in a given matrix.

As mentioned under item III.2, an in-depth dialogue between experts, starting with a workshop and followed by research options, may be necessary to define these issues and how to manage them.

III.3.2 Biotic transformation

Less information is available on whether hydrolysis in the skin is an important mechanism, especially on the kinetics of this process. Limited studies with isolated rat skin cytosol and rat skin microsomes on Isoeugenyl- and Eugenyl-acetate indicate that these esters do not fully hydrolyse in a time-dependent manner. This preliminary study did not give clear-cut answers and confirmatory results are needed.

Kinetic and skin penetration studies should be a key to understand what happens on the skin. Isoeugenyl esters may be a possible starting point as they are the sole materials for which significant rates of positive patch tests have been reported. The data resulting from these studies should be of help to answer the following questions:

- Scope – is it justified based on experience to predict biotic transformation to be a relevant cause of allergic contact dermatitis through the use of cosmetic products?
- What is the ratio of biotic versus abiotic hydrolysis? What are the percentages of observed reactions due to biotically-generated haptens versus abiotically-generated haptens?

Task IV: Address the validity of the QRA methodology and the possibilities of further refinement

IV.1 Where is the Fragrance Industry with the QRA today?

The QRA approach is considered by the industry as an important step forward in dermal sensitization risk assessment, and the method, first published in 2001 (Gerberick et al., Contact Dermatitis, 45:333-340) has been implemented by the fragrance industry since 2006. An update has been published in 2008 (Api et al., Regulatory Toxicology and Pharmacology, 52:3-23) and the QRA Expert Group[2] encourages further refinement to the QRA for fragrance ingredients. Some areas of improvement are considered below.

- *Consumer Exposure:*

  Improved exposure data (Hall, 2011) is being incorporated into the QRA methodology. In addition, RIFM has sponsored work to investigate the effects of aggregate dermal exposure. The outcome of this work is being accounted for in the methodology and we suggest that an open discussion be held on the validity of the QRA and on this initiative in particular.

- *Safety Assessment Factor (SAF):*

  A paper which specifically addresses the use of uncertainty factors in QRA for skin sensitization has been published (Felter, et al., Contact Dermatitis, 2003, 47:257-266). However it is acknowledged that further dialogue on SAFs would be appropriate. This would include better clarification of what the SAFs are applied to (e.g. not to clinically diseased skin).

- *Acceptable Exposure Levels (AEL) and Exposure Data:*

  A more detailed explanation of AELs and how they are applied should be provided. There also is a need for more details on the pragmatic approach and a review of aspects of having high calculated values in (mainly) rinse-off products.

- *Current boundaries of the QRA*

  While occupational exposures to consumer products can be an important source of exposure they are not considered in the current QRA. This mainly stems from a lack of adequate exposure data.

  Furthermore the QRA methodology does not cover aromatherapy (neither workers nor customers). These currently not reflected exposures remain a potential area of research.

- *Use of Diagnostic Patch Test Data and Retrospective Analysis*

  Diagnostic patch test data from dermatology clinics are not used in the primary determination of safe use levels based on induction. This is because these data are a measure of elicitation of allergic contact dermatitis, not induction. Nevertheless, the diagnostic patch test data provide feedback on whether thresholds of used based on the QRA has been correctly established (see Task II.2).

  A review of retrospective data for three fragrance ingredients has been published (Api et al., 2010). Retrospective review of other fragrance ingredients and other non-fragrance ingredients should also be considered.

  Thus, clinical results from the dermatology community (including targeted studies) and company post-market surveillance data should be used to evaluate the effectiveness of QRA-based interventions.

[2] The QRA Expert Group is a RIFM Task Force of ten toxicologists from the fragrance and the downstream users industry. This group worked on the adaptation of the QRA methodology to the Fragrance Industry and continues to watch the outcome of the QRA implementation in view to improve the model.

IV.2. Recommended action

The best way to address the validity of the QRA methodology and the possibilities of further refinement would be to organize an in-depth dialogue between experts. We recommend that a specific workshop be held on the QRA methodology.

IDEA
International Dialogue for the Evaluation of Allergens

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. The remits of this group is to scrutinize all aspects of the work plan implementation in order to guarantee the

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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 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.

IDEA WORKSHOP

Characterization of Fragrance Allergens

August 27-29th, 2013

1. Programme and list of participants
2. Obligations on the need to continue the discussion in a follow-up workshop
3. Rapporteur's progress report
4. Recommendations
5. Slides presented by Prof. Helmut Greim

IDEA
International Dialogue for the Evaluation of Allergens

IDEA Workshop

Characterization of Fragrance Allergens

August 27-29th, 2013

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

Tuesday, August 27th

3:00 - 6:30 p.m.	Welcome and registration
5:00 - 5:15	Workshop opening – *Hans Bender and Matthias Vey*
5:15 - 6:00	Definition and common understanding of 'skin sensitizer' – mechanistic and clinical insights *Speaker: An Goossens*
6:30 - 9:30	Walking dinner (Juniper or terrace depending on weather conditions, Dolce La Hulpe)

Wednesday, August 28th (9:00 a.m. to 6:00 p.m.) – Day 1 (Formal presentations)

Each lecture consists of a presentation followed by at least 15 minutes of discussion

<u>First session – Tools for the identification of skin sensitizer</u>

9:00 - 9:40 a.m.	Available data from animal and *in vitro* testing used to identify skin sensitizers *Speaker: David Basketter*
9:40 – 10:20	New immunological tests to identify skin sensitizers *Speaker: Marc Vocanson*

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10:20 - 10:40 Coffee break

10:40 - 11:30 Available data from diagnostic patch test and clinical studies (HRIPT, ROAT, etc.)
Speaker: Klaus Andersen

11:30 - 12:20 Approach followed by the SCCS to characterize fragrance allergens
Speaker: Wolfgand Uter

12:20 - 1:00 Lunch

Second session – Critical review of the tools used for identification of skin sensitizers

1:00 - 1:40 p.m. Diagnosis of allergic contact dermatitis in 2013
Speaker: Margarida Gonçalo

1:40 - 2:20 Use of monitoring tools (cosmetovigilance, epidemiology data, etc.) and data centers / expert networks (ESSCA, IVDK, etc.) to characterize fragrance allergens
Speaker: Wolfgang Uter

2:20 - 3:00 What do we know about dose dependency of sensitization and elicitation of allergic diseases?
Speaker: Peter Friedmann

3:00 - 3:20 Coffee break

3:20 - 4:00 Clinical relevance of diagnostic patch tests: pros & cons
Speaker: Jean-François Nicolas

Third session – Enhance the industry's reactivity

4:00 - 4:40 How can the diagnostic process be improved to enhance the industry's reactivity?

Speaker: Graham Ellis

Fourth session – Summary of the Rapporteur and Moderated debate

4:40 - 5:00 Summary of the situation and suggestions of the Rapporteur (*H. Greim*)

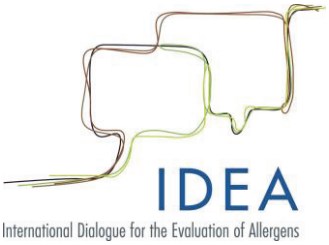
5:00 - 6:00 Moderated debate and key conclusions of Day 1

5:30 - 6:00 End of Day 1

6:30 - 9:30 Reception followed by a dinner (Brasserie 135, Dolce La Hulpe)

Thursday, August 29th (9:00 a.m. to 4:30 p.m.) – Day 2 (Open discussion)

9:00 - 9:30 a.m.	Adoption of the agenda and wrap-up of Day 1
9:30 - 10:10	What could be an ideal clinical tool for the diagnostic of skin sensitizers? *Speaker: Jean-François Nicolas*
10:10 - 10:30	Coffee break
10:30 - 12:30	The participants will be subdivided into three working groups:
Meeting room 1	How to improve the approach followed by the SCCS to characterize fragrance allergens? *Moderator: Wolfgang Uter*
Meeting room 2	How to improve the diagnostic process for determining the culprit in Allergic Contact Dermatitis so as to enhance industry's responsiveness? *Moderator: Graham Ellis*
Meeting room 3	How to improve diagnostic patch-testing, looking at both established procedures and emerging methodologies (biomarker)? *Moderator: Jean-François Nicolas*
12:30 - 1:10	Lunch
1:10 - 3:00 p.m.	Presentation of the conclusions and recommendations of the three working groups and establishment of priorities.
3:00 - 3:20	Coffee break
3:20 - 4:30	Conclusions of the workshop and next steps
4:30 p.m.	End of Day 2 and workshop closing



List of participants (33):

Prof.	Klaus	Andersen	Odense University Hospital, Denmark
Dr.	Anne Marie	Api	RIFM, USA
Dr.	David	Basketter	Consultant in toxicology, UK
Prof.	Donald	Belsito	Columbia University Medical Center and RIFM Expert Panel Member, USA
Dr.	Hans	Bender	Consultant *(Moderator of the Workshop)*, Germany
Dr.	Halyna	Breslawec	PCPC, USA
Prof.	Magnus	Bruze	Lunds Universiteit and RIFM Expert Panel Member, USA
Dr.	Peter	Cadby	Chanel, France
Prof.	Thomas	Diepgen	Ruprecht-Karls University, Germany
Mr.	Graham	Ellis	Givaudan, Switzerland
Prof.	Peter	Friedmann	University of Southampton, UK
Prof.	Tony	Gaspari	University of Maryland, USA
Dr.	Nicola	Gilmour	Unilever, UK
Dr.	Margarida	Gonçalo	University of Coimbra, Portugal
Prof.	An	Goossens	KULeuven, Belgium
Prof.	Helmut	Greim	Technical University of Munich *(Rapporteur of the Workshop)*, Germany
Dr.	Peter	Griem	Symrise, Germany
Ms.	Susanne	Hoeke	EU Commission – DG Sanco – Risk Management Unit, Belgium
Dr.	Etje	Hulzebos	I.F.F., The Netherlands
Prof.	Daniel	Kaplan	University of Minnesota, USA
Dr.	Maya	Krasteva	L'Oréal, France
Dr.	Naveed	Honarvar	BASF, Germany
Dr.	Fred	Lebreux	International Fragrance Association, Belgium
Dr.	Sylvie	Lemoine	A.I.S.E., Belgium
Dr.	David	Lovell	University of Surrey, UK
Prof.	Hans	Merk	Universitätsklinikum Aachen, Germany
Prof.	Jean-François	Nicolas	University of Lyon, France
Dr.	Florian	Schellauf	Cosmetics Europe
Dr.	Scott	Schneider	Firmenich, USA
Dr.	Theodor	Schumacher	Smartpractice, Germany
Prof.	Wolfgang	Uter	University Erlangen, Germany
Dr.	Matthias	Vey	International Fragrance Association, Belgium
Dr.	Marc	Vocanson	Institut national de la santé et de la recherche médicale, France

IDEA
International Dialogue for the Evaluation of Allergens

IDEA Workshop on

Characterization of Fragrance Allergens

August 27-29th, 2013

Obligations on the need to continue the discussion in a follow-up workshop

December 4th, 2013

Characterizing fragrance allergens and dealing with allergens of concerns are topics which have been addressed in the third workshop of the IDEA project that took place August 28 - 29, 2013. Unlike the initial two workshops, highly technical in nature, this third workshop touched upon a topic with foundations from both scientifically derived data and equally important clinical observations build over decades of patient / dermatologist relationship.

Based on this and on the breadth of the subject, the workshop participants have continued the discussions beyond the 2 ½ day workshop, demonstrating that reaching a common understanding is not achieved yet.
This issue was reported to the IDEA Supervisory Group which agreed that the conclusions drawn at the workshop merit further reflection and discussion and should not be regarded the final word on the topic.
Because there is a strong will from all participants to reach such an alignment for the benefit of the long term deliveries, a second workshop will take place and resume the discussion where it left off last August.

Having established working definitions of contact allergy (CA) and allergic contact dermatitis (ACD) at the first event, this subsequent workshop will consider the relationship between CA and the diagnosis of ACD and will focus on:

1. Understanding the link between CA and ACD, including the definition of clinical relevance,
2. How the uncertainties associated with patch testing, including false positives and negatives, can be minimized,
3. The clarification of dermatological and immunological principles that would be required for the establishment of a complementary diagnostic tool and,
4. The development of a framework to enhance the communication between the dermatologists and the industry.

Thereafter, a comprehensive set of conclusions shall be derived after careful review by all the participants at the 2nd workshop. Nevertheless, it should be mentioned that, albeit the strenuous nature of the topic, the workshop participants have already provided a major and decisive breakthrough on the definition of 'contact allergen'. This definition and other important advances are reported in the Rapporteur's progress report.

This second event dedicated to the characterization of fragrance allergens is scheduled in May 2014 and the exact dates will be confirmed beginning of the next year.

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IDEA
International Dialogue for the Evaluation of Allergens

Rapporteur's Progress Report on the IDEA Workshop on

Characterization of Fragrance Allergens

August 27-29th 2013

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.

Some fragrance ingredients have the potential to cause skin sensitization. However, such fragrance allergens may be described in various ways and the need to define them via a collaborative approach between stakeholders was clearly identified. A clear understanding of what is a skin sensitizer, what are the tools to identify it and how to combine these tools adequately remains a prerequisite to characterize a fragrance allergen. The aim of this workshop was to characterize fragrance allergens, which specifically are contact allergens, to define their relevance and to discuss possible ways to improve their identification and the diagnostic of related contact allergies.

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2. Rapporteur's progress report

a. Introduction

Allergic Contact Dermatitis (ACD) to fragrance results from a complex combination of factors including (but not limited to) the exposure pattern, the allergen potency, the genetic predisposition and the age. ACD is a disease involving the immune system and producing delayed-type reactions. ACD arises as the result of two essential stages: an induction phase, which primes and sensitizes the immune system for an allergic response, and an elicitation phase, in which this response is triggered. It is now generally accepted by the Dermatology community that both the sensitization and the elicitation phases are triggered by a threshold mechanism, the dose triggering the induction generally being higher than the threshold triggering an elicitation reaction. For this reason, safe use levels preventing induction and/or elicitation can be derived for each allergen via an appropriate risk assessment methodology.

ACD should not be confused with Contact Allergy (CA), an asymptomatic state, which simply means that the immune system has been exposed to an allergen and can recognize it, with subsequent ACD after sufficient exposure. Furthermore ACD has to be distinguished from irritant contact dermatitis (ICD), which is a non-specific reaction of the immune system in response to a chemical or a physical irritant. There is no specific immune memory in ICD, which is transient after an acute contact, although it may become chronic on iterative exposure. In contrast to ICD, ACD represents a serious safety concern for consumers. Therefore the workshop only focused on this second, and less frequent, type of contact dermatitis.

Metals, fragrances and preservatives are the most important contact allergens but other ingredient types (e.g. hair dyes, antioxidants) are also frequently reported as skin sensitizers. In the context of this workshop, only the skin sensitization endpoint was taken into consideration for the characterization of fragrance allergens.

The prevalence of CA and ACD to fragrance allergens in the general population is around, respectively, 6% and 2% and about 15% in all tested patients having an ACD. Apart from a possible genetic predisposition of populations the body region where products are applied also has its importance since the use pattern of products and the genetic predisposition of populations seem to have a clear impact on the prevalence (e.g. Italy versus Sweden).

Physical examination and patient history undertaken by an experienced dermatologist are the initial diagnostic steps to suspect (fragrance) allergens are responsible for a skin reaction. Patch-testing is the only available tool for the identification of contact allergens. The skin sensitization potential is usually examined by hazard assessment tools (animal studies like LLNA, *in vitro* and *in silico* studies). Patch-testing cannot usually provide quantitative information on the allergen potency unless the levels of exposure to sensitizing agents are individually known. However, the degree of individual sensitization can be estimated from the patch test reaction's morphology (shape, size, edge effect, etc.). Beyond the negative, IR (irritant), or ? (doubtful), +, +, ++ or +++ reactions reflect the intensity of sensitization corresponding to the inter-individually varying elicitation thresholds in serial dilution patch testing.

Patch testing for the diagnosis of fragrance allergy usually starts with the application of fragrance mixes (FMI and FMII), which are standardized mixtures of the most common fragrance allergens. In case of a positive reaction to these fragrance mixes their ingredients are tested whenever possible to allow precise identification of the individual

allergen(s). In cases of suspected fragrance/cosmetic allergy, if the patient does not react to the fragrance mixes neither to its ingredients or additional commercial fragrance allergens, the practitioner has to investigate the consumer product that triggered the skin condition. The dermatologist has several options including the patch-testing of ingredients as far as labeled on-pack (by virtue of the EU cosmetic / detergent regulations), with the notable exception of fragrances beyond those 26 presently required to be labeled) and the request to the product manufacturer for information and provision of test materials regarding those fragrances not available as commercial allergens.

Patch-testing can be used for other purposes than the diagnosis of ACD and notably to define the prevalence of CA to specific fragrance allergens (epidemiologic studies) and to ensure that a fragrance allergen does not sensitize humans when used at a specific concentration in the HRIPT (Human Repeated Insult Patch Test). Repeated Open Application Test or Use Test, are another form of human testing that helps to determine a person's elicitation threshold for a fragrance ingredient in real-life conditions and then to evaluate consumer tolerance.

Several parameters need to be carefully tuned in order to get meaningful patch-testing results. For instance, the allergen concentration should not be too low (risk of a doubtful or false-negative reaction) or too high (risk of a false-positive reaction and/or sensitizing the patient). Doubtful reactions should be avoided.

The aim of this workshop was to characterize fragrance allergens, which specifically are contact allergens and to discuss possible ways to improve the tools used for the diagnosis of CA and the clinical relevance of reactions established with these tools. Furthermore, this workshop was intended to discuss the existing diagnostic process in view to enhance industry's responsiveness each time a consumer product is responsible for adverse skin reactions. Finally, this workshop was designed to optimize knowledge sharing on general concepts linked to fragrance allergens between dermatology practitioners and to pave the way forward for a better and easier identification and characterization of fragrance allergens.

b. Definition

All concepts related to the identification of fragrance allergens are tightly linked to the definition of 'contact allergen'. For this reason, the development of a commonly-agreed definition of 'contact allergen' was regarded as a prerequisite for further discussions. Definitions of contact allergen were given by several presentations including the below operational definition used by the SCCS in its recent Opinion on fragrance allergens in cosmetic products:

> *A fragrance substance, or a natural mixture of substances (extract), which (in some cases after chemical modification or bio-activation),*
> - *based on several published reports of sufficient quality, has caused contact sensitization in patients, or*
> - *according to a historical human max. test / HRIPT is a sensitizer, or*
> - *has been identified as contact allergen in guideline animal methods or*
> - *can be categorized as likely allergen if limited human or experimental data is combined with structure activity considerations*

The SCCS used this definition to propose a two-part approach for the identification and characterization of fragrance allergens: a first 'fishnet' aimed at identifying all contact allergens about which consumers/dermatologists should be informed. Based on this list of allergens, a second 'fishnet' was used to identify contact allergens of concern within the subset of 'established allergens in humans' following the SCCS criteria.

This methodology was regarded as valid but, regarding 'fishnet 1', some workshop participants highlighted four potential points of refinement:

- Extensive guidance under the CLP Regulation has been developed meanwhile regarding the interpretation of human data. This guidance, which includes some differences with the SCCS approach, was not available at the time the SCCS did its work and could serve as a reference.
- Have a critical evaluation of the quality of the studies, comparable to the Klimisch criteria for toxicological studies. Relate the clinical data to exposure.
- Complement animal data with human data as much as possible.

Regarding 'fishnet 2', it was suggested that subcategories (such as 'alert', 'concern' and 'high concern') based on defined levels of concern be used to refine the existing classification of contact allergens. Potential criteria for the categorization into these levels of concern might be the relative frequencies from consecutive clinical testing (rather than absolute cases), the clinical data on the proven cases of ACD and the consumer exposure. Finally, blinded ROAT studies with scented products mimicking actual use could be an option to confirm the assignment of contact allergens to above subcategories.
The criteria outlined above could be integrated into an appropriate risk assessment/management system. Additionally, the workshop participants agreed that current evidences on the prevalence of ACD to fragrance ingredients in the general population should be reviewed. In light of conclusions established during this workshop, it was suggested that product category-related exposure information be combined with similarly stratified clinical data. In this regard, it was recommended that definition of product categories be developed, taking into consideration Annex I of the Cosmetics Regulation, CLP, and the IFRA categories.

The workshop participants agreed to set a more general definition of 'contact allergen' and the following proposal was developed during the workshop:

> *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.*

c. Tools to identify contact allergens

Specific emphasis has been laid on the different methodologies to identify a sensitizing fragrance ingredient with the general agreement that, in principle, valid human data should override animal data.
Several tools already exist for the identification and the characterization of contact allergens:

c.1. Predictive Tests (Animal studies)

The Buehler Guinea Pig Test and the Local Lymph Node Assay (EU B42, OECD 429) are regarded as reliable test methods for the identification of contact allergens. Except the Buehler test the other Guinea Pig tests are not considered to provide reliable indication for potency. These predictive animal studies are mainly used for the hazard assessment of fragrance allergens but animal welfare considerations imply the replacement of these tools by *in vitro* / *in silico* testing.

c.2. Tests in Humans

As of today, patch-testing is the gold standard to diagnose ACD and with other skin tests (e.g. ROAT) to carry out tolerance studies in the general population. ACD is a disease with many faces that need to be recognized by dermatologists. It can be difficult to distinguish from other skin problems. As a human in vivo test, special attention should be paid to the analysis of patch-test results to reduce the risk of false negatives and false positives. The great majority of human data is derived from diagnostic tests in patients. Other human studies can present some ethical issues.

The HRIPT (Human Repeated Insult Patch Test) is nowadays used as a confirmatory test in the safety evaluation of skin sensitizers, employing exposure doses/area considered non-inducing, usually consisting of two phases. In the Induction phase (Phase I) the allergen under investigation is applied to the skin a few times (typically 9 x 24-hour or 48-hour exposures) during the course of a 3-week period and to each of 100 to 200 volunteers. This is followed by a 2-week rest period after which the skin is exposed to the allergen again on both the induction site and a naïve site using a 24-hour to 48-hour patch-test (Phase II or Elicitation Phase). A response in Phase II is usually allergic in nature and skin reactions are scored over the subsequent few days.

The repeated open application test (ROAT) or use test is, as its name states, an open exposure test that intends to mimic real-life exposure situations. This dose-response test intends to evaluate the tolerance of the sensitized individual or sub-population to a given allergen and gives qualitative or even quantitative information on the elicitation threshold. A finished product (or a well-defined vehicle containing the allergen under investigation) is applied once or twice per day for a 1-3 week period in sensitized individuals. Several test sites may be challenged at the same time using different test concentrations. Application of the test agent or allergen containing solution is either performed by rubbing the sample at the test site or by using a micropipette followed by spread. The marked challenge site is inspected according to a pre-determined reading schedule (e.g. at day 2, 3, 4, 7, 14 and 21). A positive response usually develops after 2-4 days of application, but for weaker allergens or to lower allergen dose/area it can develop later. Dose-elicitation data can be derived from a group of thus tested sensitized persons in terms of a (fitted) dose-response curve of the cumulative response to doses/area cumulated over time, until first appearance of a positive result.

Large inter-individual variations in the concentration triggering the elicitation reaction is observed. These variations generally reflect the strength of the sensitization determined by varying induction doses/area but might be caused by recent exposures to the investigated allergen. However, there are many other reasons for false positives and

negatives. These include methodological problems as well as insufficient scoring of the test results. The methodological problems include insufficient concentration for elicitation, difficulties to obtain the relevant test samples at appropriate concentrations (a too low concentration of the sensitizing agent may result in a negative patch-test) and inappropriate performance of the test.

Although the human patch test has been formalized by commonly agreed protocols, the individual dermatologist's experience still determines the reliability of the diagnosis to an important extent. For this reason, patch-tests should only be performed by sufficiently trained dermatologists. This expertise in running patch-tests was regarded as particularly crucial in case of slight effects due, for instance, to the weak potency of allergens in relation to their patch test concentration and patients' specific sensitivity. In these situations, expertise plays an important role in the ability to correctly diagnosing patch test reactions and contributes to avoid false positive and negative diagnostic results.

Furthermore, the workshop participants identified other potential targets for improvement and further research, respectively:

- Use of appropriate concentrations and vehicles where these have not yet been firmly established
- Test with patients' own products whenever possible
- Better availability of appropriate test samples for breakdown patch testing.
- More structured and efficient communication between the dermatologists and the products manufacturers (in particular when the culprit cannot be spontaneously identified)
- More dose-response tests (ROAT's) in volunteers with documented contact allergy to a fragrance substance
- Consideration of impact of the vehicle, impurities, additives, etc.
- Standardized documentation and timely reporting of test results including clinical history

Considering that the regulatory agencies and the industry need to collect all available information for respectively regulatory and safety evaluation purposes, there was agreement that any relevant information should be made publicly available, especially in the peer reviewed scientific literature. This is exemplified by part of the sources that were evaluated by the SCCS for the development of its scientific Opinion on fragrance allergens:

- Manual search of the journal "Contact Dermatitis"
- Medline search of CAS numbers identified in reviews and clinical studies already retrieved
- Manual search of all RIFM reviews published in "Food Chem. Tox." (last 20 years)
- "Top 100" substances in terms of volume used and "Top 101-200" substances if R43 (as supplied by IFRA)
- Animal test data (GPMT, LLNA, Buehler test) requested from IFRA, eventually LLNA reports' summaries.

c.3. In vitro / in silico studies

Accelerated by the legal ban of animal testing, the development of *in vitro* and *in silico* alternatives aims at the identification of fragrance allergens but also for the determination of their potency (non-sensitizing, very weak, weak, moderate or strong sensitizers). The existing assays (DPRA, KeratinoSens, h-CLAT, MUSST, TBD, etc.) are

complementary and need to be jointly used according to a sound integrated testing strategy to deliver meaningful conclusions.

However, in spite of the numerous technological progresses made this last decade on in-vitro testing, the determination of allergens potency still remains to be developed (including above-mentioned integrated strategy) and validated. More efforts should be done to improve the existing tools or to create new tools able to deliver quantitative estimates.

d. Tools to monitor contact allergens

Since premarketing methods to characterize contact allergens are not always perfect, the post-marketing surveillance of CA and relevant sensitizers and refine the risk assessment methodologies / risk management measures where necessary. These monitoring tools include:

- Appropriate diagnosis in patients by dermatologists, which is seen as the basis for objective evaluation, and collection, analysis and publication of this clinical data
- Epidemiological studies
- Consumer reports collected by companies, which can be helpful but need to be verified with regard to ACD and the actual sensitizer
- Cosmetovigilance results collected by networks of dermatologists (e.g. REVIDAL in France)

The optimal approach to be followed by dermatologists to identify the contact allergen that has caused a particular case of ACD is adequate documentation of history and skin effects, patch testing with commercial test series and possibly culprit consumer product. Additional breakdown testing of product ingredients is sometimes required, especially if patch testing with commercial allergens does not yield an unequivocal explanation of ACD to a cosmetic product. If the suspected culprit allergen is not part of the commercial test series, further liaising with the product manufacturer is required. The results of this research should be reported to the product's manufacturer (for voluntary risk management measures) and to a "suitable public body" collecting the data in view of further analysis and publication.

The European legislation (e.g. Cosmetic Regulation) foresees that undesirable effects resulting from the use of consumer products should be reported to the competent authorities and Member States shall ensure that the information is made accessible to the relevant specialists.
For instance, the French surveillance network REVIDAL/GERDA promotes intense cooperation between experts and publishes their case collections. In Germany the IDOC (Information and Documentation Centre) for contact allergies provides a broad collection of physicians' reports and publications. One of IDOC's main missions is to liaise with the industry and to provide assistance to dermatologists for the access to chemically-defined allergens. Once the diagnosis completed, test results are communicated to IDOC which, after evaluation, can forward them to the industry. This flexible system allows early detection of hitherto non-considered cosmetic allergens.
However, and similarly to the French network, the sharing of available information maintained by IDOC can be hampered by confidentiality issues. Inconsistent medical quality of the IDOC data can also be a problem.

These surveillance networks are useful but their efficiency depends partly on industry's responsiveness. The workshop participants identified several ways to improve the current diagnostic process in view to enhance the responsiveness of the industry. First, it was remarked that trade associations like IFRA could play a key role on a worldwide basis in the identification of consumer product companies for the dermatologists to contact. Secondly, there is a need for a standardized method on how to supply appropriate samples to dermatologists. This method would formalize samples dilution and vehicles.
Furthermore, a formal mechanism should be developed to ensure an exchange of information between the dermatologists and the industry once the patch-test on provided samples is conducted beyond the case-by-case approach as in IDOC. Additionally, a formal mecchanism would be needed to review the clinical data collected on fragrance allergens with the aim of revising risk assessment and risk management of these ingredients and of activating the pro-active surveillance wherever it is regarded as necessary.

e. Potential improvements of diagnostic patch-testing

As of today, the only established methodology to diagnose CA is patch-testing. Its optimal use requires education and training. Efforts should be made to improve the education of dermatologists beyond academia and to certify their competence in the procedure.

The development of supplementing and/or alternative diagnostic tools is an interesting area of research. At the present time, basic science methodologies (e.g. immunological assays) to study the pathophysiology of ACD already exist but still require evaluation of diagnostic usefulness and eventual translation into clinical practice.
It was agreed that the development of a "blue/red indicator test" allowing a microanalysis of the doubtful or weak positive patch tests could be useful to the dermatology community. This tool should be able to quickly determine whether or not the observed reaction is a true contact sensitization. However, the usefulness and value of such a technique that is not yet on the horizon for regular use would have to be confirmed by scientific clinical trials conducted in selected expert patch-testing centers.

The concept of clinical relevance was intensely debated during the workshop. It was agreed that the assessment of clinical relevance of a positive patch-test is based on clinical evaluation of patient's history, the exposure to that allergen and its temporal relation with ACD and on the characteristics of the allergen and the ACD. The predictive value of a positive patch-test depends on sensitivity and specificity as well as the prevalence of ACD in the tested population. Often, identification of the culprit allergen is complicated by patients reacting to more than one allergen in subsequent patch tests.
ROAT in individual cases will help to assess the clinical relevance in those patients in whom it cannot be determined otherwise. An eczematous ROAT response will distinguish the irritant or allergic nature of the reaction if appropriate controls are included.

f. Recommendations

Based on the discussions and conclusions of the three breakout groups, the workshop participants proposed to further explore the following points:

- While the patch-test is a proven diagnostic instrument, further research should aim at reducing uncertainties (false positives and negatives).
- Improve categorization of contact allergens (high and low concern) for C&L, risk assessment and risk management.
- Improve data collection (e.g. by specific centers) in view to collect, scrutinize and publish all useful clinical data.
- Improve the communication between dermatologists and industry, the main recommendation being to establish a standardized procedure for providing samples to the dermatologists and to communicate results of the clinical investigations to industry.
- Better understand the difference of prevalence of skin sensitization, which may be caused by specific genetic predispositions and consumer habits (e.g. north vs. south of Europe or Europe vs. USA).
- Provide further justification for the notion that many low dose exposures are more potent than a single high dose.
- Better understanding of how best to establish the link between CA and ACD in terms of dose elicitation data.
- Provide *in vitro* methodologies for risk assessment purposes and, notably, for the quantitative determination of allergens potency.
- Consider the development of a new diagnostic tool that might help further improve diagnosis of CA for the benefit of the patient
- Define the concept of 'levels of concerns'.
- Develop definition of product categories (taking into consideration Annex I of the Cosmetics Regulation, CLP, and the IFRA categories).
- Understanding geographical differences in prevalence – for instance, US dermatologists at the workshop noted that positive patch tests to HICC/HMPCC were quite rarely observed in the US. A proposal that this is due to differences in exposure was subsequently confirmed to be an unlikely explanation.

Prof. Helmut Greim
Rapporteur of the workshop

APPENDIX 1: Additional reading

- "A proposed relevance scoring system for positive allergic patch test reactions: practical implications and limitations", J.-M. Lachapelle, *Contact Dermatitis*, **1997**, 36, 39-43.

- "Operational definition of a causative contact allergen – A study with six fragrance allergens", J.J. Hostynek and H.I. Maibach, *Exogenous Dermatology*, **2003**, 2, 279-285.

- "The relationship between exposure dose and response in induction and elicitation of contact hypersensitivity in humans", P.S. Friedmann, *British Journal of Dermatology*, **2007**, 157, 1093-1102.

- "*Risk factors associated with sensitization to hydroxyisohexyl 3-cyclohexene carboxaldehyde*", W. Uter, J. Geier, A. Schnuch and O. Gefeller, *Contact Dermatitis*, **2013**, *69*, 72-77.

- "*Categorization of fragrance contact allergens for prioritization of preventive measures: clinical and experimental data and consideration of structure–activity relationships*", W. Uter, J.-D. Johansen, A. Börje, A.-T. Karlberg, C. Lidén, S. Rastogi, D. Roberts and I. R. White, *Contact Dermatitis*, **2013**.

- "*The critical review of methodologies and approaches to assess the inherent skin sensitization potential (skin allergies) of chemicals*" (Part I, II & III), J. P. Thyssen, E. Giménez-Arnau, J.-P. Lepoittevin, T. Menné, A. Boman and A. Schnuch, *Contact Dermatitis*, **2012**, *66*, 11-70.

IDEA
International Dialogue for the Evaluation of Allergens

Recommendations of the IDEA Workshop on

Characterization of Fragrance Allergens

August 28-29, 2013

Usually, the recommendations made by workshop participants imply the development of scientific studies and programs that can be resource intensive. These recommendations are usually addressed by the industry.

This workshop was different in the sense that its action items require less technical work but more strategic reflections for future directions. Therefore, most of the recommendations need to be addressed by the workshop participants and appropriate task forces will be convened by IFRA and RIFM to this end. IFRA and RIFM identified the need for five task forces and assigned remaining action items.

Beyond their technical expertise, IFRA and RIFM will also provide logistical assistance necessary to the organization of required meetings, webinars and conference calls.

1) Expanding existing methodology TF:

- Proposed participants: Prof. Klaus Andersen, Prof. Magnus Bruze, Prof. Margarida Gonçalo + IDEA Management Team.

- Mission: expand on the existing methodologies with regard to:
  - High dose / low dose effects.
  - The link between Contact Allergy and Allergic Contact Dermatitis.

- Deliverable:
  - A presentation at the next workshop highlighting the key conclusions of this task force.
  - Plan for further scientific studies.
  - Adapt methodologies and communication as appropriate.

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2) Fragrance Allergens Categorization TF:

- Proposed participants: Klaus Andersen (Odense University Hospital), David Basketter (DABMEB Consultancy), Don Belsito (Columbia University Medical Center), Peter Cadby (Chanel), Graham Ellis (Givaudan), Helmut Greim (IDEA Supervisory Group), Maya Krasteva (L'Oréal), Scott Schneider (Firmenich), Benjamin Smith (Firmenich), Theodor Schumacher (Smart Practice), Ian White (St. John's Institute of Dermatology) + IDEA Management Team.

- Mission: improve the categorization of contact allergens for further use in risk assessment and risk management.

- The resulting categorization system should clearly define the 'levels of concerns' (based on appropriate indicators).

- Consumer exposure / product category is important and non-ambiguous product categories should be defined.

- Deliverable:
  - A draft framework of criteria for a better categorization of fragrance allergens to be presented at the next workshop.

3) Data Collection TF:

- Proposed participants: Prof. An Goossens (KULeuven), Prof. Axel Schnuch (IVDK) + IDEA Management Team.

- Mission: improve data collection by specific centers in view to collect, scrutinize and publish all useful clinical data.

- Deliverable:
  - A report recommending actions to improve collection of clinical data (to be presented at the next workshop).

4) Communication TF:

- Proposed participants: Mr. Graham Ellis, Dr. Nicolas Gilmour, Prof. An Goossens + IDEA Management Team.

- Mission: improve the communication between dermatologists and industry.

- Deliverable:
  - A draft standard procedure for improved communication exchange of samples and results of clinical investigations between dermatologists and industry (to be presented at the next workshop).

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5) Other action items:

- Better understand the differences of prevalence of skin sensitization between various geographies (e.g. Europe vs. USA) Activities may include:
  - Better understanding of specific consumer habits (involving customer associations like PCPC or CosEU but also RIFM).
  - Prof. Peter Friedmann: investigation of possible genetic variations.
  - Prof. Thomas Diepgen: provide more information on geographical variations on prevalence.

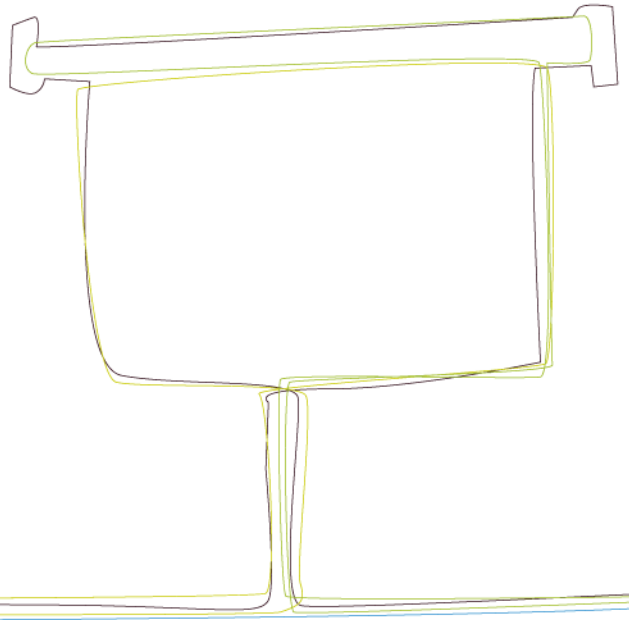
- Explore hypothesis that many low dose exposures are more potent than single high doses. The proposed participants and tasks would be:
  - Dr. Peter Cadby and Prof. Peter Friedmann: investigation and report at the next workshop.

- Monitor the developments of new diagnostic tools that might help further improve diagnostic of Contact Allergy. Alternatives are likely to be based on immunological concepts. The proposed participants and tasks would be:
  - Prof. Ian Kimber and Prof. Tony Gaspari.

IDEA
International Dialogue for the Evaluation of Allergens

Rapporteur's Progress Report on the IDEA Workshop on

Characterization of Fragrance Allergens



August 28-29, 2013

Prof. Helmut Greim
Member of the IDEA Supervisory Group

Contact Allergy (CA) and Allergic Contact Dermatitis (ACD)

IDEA
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- Priming and sensitization (induction) of the immune system leads to CA, which is **symptomless**.
- Sufficiently high re-exposure (elicitation) may lead to **immune response** (ACD) – with clinical symptoms. Not all CA results in ACD.
- Both phases follow a **threshold mechanism**.
- **Preventing induction** via use of adequate RA and RM measures **prevents elicitation**.

Definition of ‘contact allergen’

- A jointly agreed definition of ‘contact allergen’ was regarded as a pre-requisite for further discussions.
- The following general definition was agreed:

> *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, however, there is significant inter-individual variability.*

Tools to identify skin sensitizers

- There are three types of tools to identify contact allergens:
  - Animal studies: provide reliable hazard assessment information; but raise animal welfare considerations.
  - *In vitro* / *in silico* studies: are increasingly effective at determining hazard potential; however, current methods are unable to identify potency.
  - Human studies: predictive human tests (e.g. HRIPT) should only be used to confirm no effect levels.
- Good quality human data should override animal data.

Diagnostic tools for CA

- Patch-testing is the **only available diagnostic tool** to identify contact allergens.

- The **ROAT** is used to determine the elicitation threshold of an allergen in real-life conditions.

Criteria for the categorization of allergens

- The categorization criteria used in the SCCS Opinion on fragrance allergens (SCCS/1459/11) were presented at the workshop.
- Points of refinement to the SCCS Opinion categorization criteria were identified:
  - Put the clinical data into perspective with **exposure** (clinical relevance).
  - Complement animal data with **human data** as much as possible.

Criteria for the categorization of allergens: Proposed refinements

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- Use guidelines developed under EU CLP Regulation for the **interpretation of human data**.
- Have a critical evaluation of the **quality of studies** (e.g. Klimisch scoring system).
- Use relative frequencies from consecutive clinical testing (rather than absolute cases).
- Give more weight to the clinical data on proven cases of ACD.
- Blinded ROAT studies mimic real-life conditions and can provide complementary information on the issue.

Criteria for the categorization of allergens: Proposed refinements

- Taking these points of refinement into account, the categorization criteria used in the SCCS Opinion could become the basis of an effective framework for the risk assessment / management of fragrance allergens.

- **'Levels of concern'** (based on consumer exposure per product category and relative frequencies of positive patch-testing) need to be defined.

Expand existing diagnostic methodology

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- Ensure better **availability of appropriate test samples**.
- Use of **appropriate test concentrations** (to avoid false positives and false negatives).
- Test with **patients' own products** whenever possible and ensure good communication with product manufacturers to facilitate the identification of the culprit ingredient.
- Incorporate additional information on **secondary parameters** (e.g. vehicles, impurities, additives, etc.).
- Offer educational support for professional patch-test reading

Other diagnosis tools

- As of today, the only established methodology to diagnose contact allergy is patch-testing. This is the gold standard.
- However, the participants agreed that there is room for the development of less invasive, time consuming and demanding supplementary diagnostic tools.
- The development of an immunological-based test (e.g. blue/red indicator test), allowing a detailed analysis of doubtful reactions would be of great value.

Additional information to monitor and to help identify potential contact allergens

- Post-marketing surveillance (i.e. cosmetovigilance)
- Epidemiological studies
- Collection and analysis of large sets of clinical data

The optimal diagnostic approach

- Documentation of patient's history and skin effects.
- Patch-testing with commercial test series and possibly culprit (consumer) product.
- Additional breakdown testing of (consumer) products is usually necessary. The information can be accessed via:
  - Ingredient labeling on the packaging.
  - The product manufacturer. In this case, excellent communication has to be ensured between industry and the dermatology community.
- Results should be communicated to relevant networks / data centers (e.g. Revidal / Gerda).

Good communication / interface between dermatologists and Industry (upstream and downstream)

- Sources of information, including:
  - Manufacturers of finished product
  - Compounders of fragrance
  - Trade associations (e.g. IFRA, Cosmetics Europe, …)

- Ensure standardized method to supply appropriate samples to dermatologists (standardization of vehicles, dilution of samples, normalization of labeling, etc.)

- Ensure a mechanism to communicate results between dermatologists and industry.

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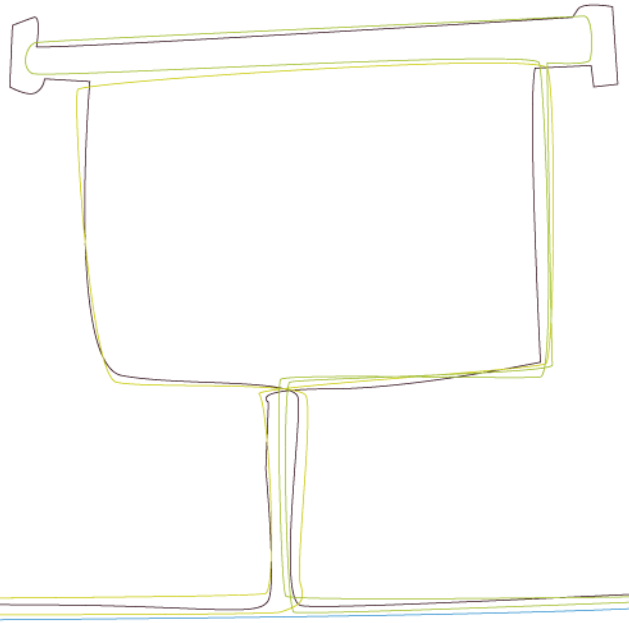
Progress report on actions taken

Characterization of Fragrance Allergens



Process and timeframe

- This workshop focused more on primarily strategic directions. As such a broad involvement of the workshop participants is needed to address these recommendations.

- The next workshop on characterization of fragrance allergens is scheduled for May 2014.

Proposed Actions

- Fragrance allergens characterization TF
- Expanding existing methodology TF
- Data collection TF
- Communication TF
- Other recommendations

Fragrance Allergens Categorization TF

- Call for participation sent to all workshop participants (dermatologists and toxicologists are preferred).
- Mission: improve the categorization of contact allergens for further use in risk assessment and risk management.
- The resulting categorization system should clearly define the 'levels of concerns' (based on appropriate indicators).
- Consumer exposure / product category is important and non-ambiguous product categories should be defined.
- Deliverable:
  - A draft framework of criteria for a better categorization of fragrance allergens to be presented at the next workshop.

Expanding existing methodology TF

- Call for participation sent to all workshop participants (clinicians are preferred).
- Mission: expand on the existing methodologies with regard to:
  - High dose / low dose effects.
  - The link between CA and ACD.
- Deliverable:
  - A presentation at the next workshop highlighting the key conclusions of this TF.
  - Plan for further scientific studies.
  - Adapt methodologies and communication as appropriate.

Data Collection TF

- Call for participation sent to all workshop participants (dermatologists are preferred).
- Mission: improve data collection by specific centers to collect, scrutinize and publish all useful clinical data.
- Deliverable:
  - A report recommending actions to improve collection of clinical data. To be presented at the next workshop.

Communication TF

- Call for participation sent to all workshop participants (dermatologists and industry experts are preferred).
- Mission: improve the communication between dermatologists and industry.
- Deliverable:
  - A draft standard procedure for improved communication exchange of samples and results of clinical investigations between dermatologists and industry (to be presented at the next workshop).

Other recommendations

- Better understand the differences of prevalence of skin sensitization between various geographies (e.g. Europe vs. USA). Activities would include:
  - Better understanding of specific consumer habits (involving customer associations like PCPC or CosEU).
  - A geneticist or a specialist of genetic variations
  - An epidemiologist
- Explore hypothesis that many low dose exposures are more potent than single high doses.
  - A toxicologist and a dermatologist
  - Report at the next workshop.

Other recommendations

- Monitor the development of a new diagnostic tools that might help further improve diagnosis of CA. Alternatives are likely to be based on immunological concepts.
  - A toxicologist and a dermatologist

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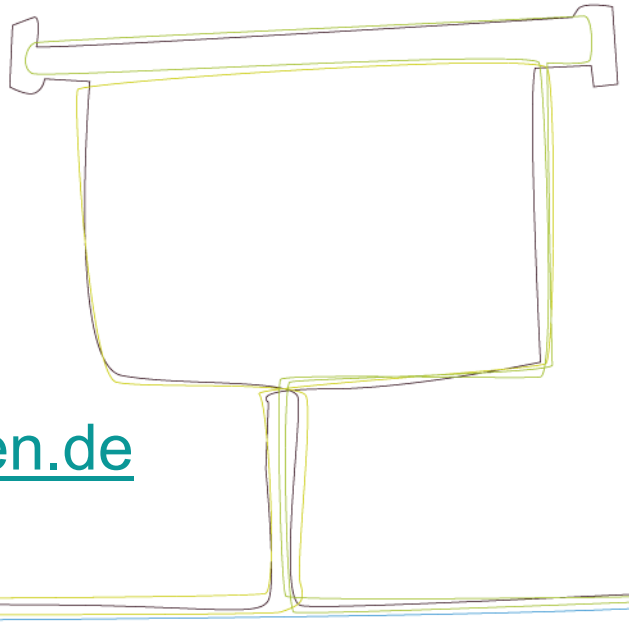
International Dialogue for the Evaluation of Allergens

Thank you for your attention

Prof. Helmut Greim
IDEA Supervisory Group

Email: helmut.greim@lrz.tu-muenchen.de



IDEA WORKSHOP

Risk Assessment of Pre- & Pro-Haptens

May 28-29th, 2013

1. Programme and list of participants
2. Key conclusions
3. Rapporteur's progress report
4. Recommendations
5. Slides presented by Prof. Jim Bridges

IDEA
International Dialogue for the Evaluation of Allergens

IDEA Workshop

Risk Assessment of Pre- & Pro-Haptens

May 28-29th, 2013

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

Final Programme

Monday, May 27th

4:00 - 6:30 p.m.	Welcome and registration at the IDEA Workshop
6:30 - 9:30	Walking dinner (Juniper or terrace depending on weather conditions, Dolce La Hulpe)

Tuesday, May 28th (9:00 a.m. to 5:30 p.m.) – Day 1 (Formal presentations) – Meeting room Teck

Each presentation consists of a 30 minutes lecture followed by 20 minutes of discussion.

9:00 – 9:10 a.m.	Opening of the meeting – *Dr. Hans Bender and Dr. Matthias Vey*

First session: Abiotic and biotic transformations

9:10 – 10:00	Toxicokinetic insights into the formation and the inactivation of haptens. *Speaker: Prof. David Roberts*
10:00 – 10:50	State of knowledge on abiotic hapten formation (autoxidation, hydrolysis, …) using examples of fragrance ingredients and state of the art on the technical management of those transformations. *Speakers: Dr. Andreas Natsch and Dr. Chris Powell*

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10:50 – 11:10	Coffee break
11:10 – 12:00	State of knowledge on biotic transformations linked to fragrance ingredients. *Speaker: Prof. Glenn Sipes*
12:00 – 12:50	First conclusions on the topic of abiotic and biotic transformations.
12:50 – 1:30	Lunch

Second session – Clinical considerations

1:30 – 2:20	Clinical studies, dermatologic observations and toxicological considerations on haptens occurring from abiotic transformation of fragrance ingredients. *Speaker: Prof. Ann Therese Karlberg*
2:20 – 2:40	Recent clinical studies on oxidized fragrance terpenes. *Speaker: Dr. Johanna Bråred Christensson (discussion at 3:50 p.m.)*
2:40 - 3:30	Clinical studies, dermatologic observations and toxicological considerations on haptens occurring from the biotic transformation of fragrance allergens. *Speaker: Prof. Jean-Pierre Lepoittevin*
3:30 - 3:50	Coffee break
3:50 - 5.30	Discussion and prioritisation of areas requiring additional research for a better comprehension of biotic and abiotic transformation as basis for adequate risk assessment.
5:30 p.m.	End of Day 1
6:30 - 9:30	Reception followed by a dinner (Brasserie 135, Dolce La Hulpe)

Wednesday, May 29th (9:00 a.m. to 4:30 p.m.) – Day 2 (Open discussion)

9:00 - 9:30 a.m.	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 Mangrove I	Working group on abiotic transformations – Discussion on current tools and need of identification, prediction, control and areas for additional research.
Meeting room Mangrove 2	Working group on biotic transformation – Discussion on current tools and need of identification, prediction, control and areas for additional research.
Meeting room Teck	Working group on clinical studies – Discussion on current tools of identification of biotic and abiotic transformations (autoxidation, hydrolysis, etc.) of fragrance ingredients, clinical relevance of findings and areas for additional research.
12:30 - 1:10	Lunch
1:10 - 3:00	Presentation of the conclusions and recommendations of the three working groups and establishment of priorities.
3:00 - 3:20	Coffee break
3:20 - 4:30	Conclusions of the workshop and next steps
4:30 p.m.	End of Day 2 and workshop closing

List of participants (30):

Prof.	Donald	Belsito	Columbia University Medical Center, USA and RIFM Expert Panel Member
Dr.	Hans-J.	Bender	Consultant *(Moderator of the Workshop)*
Prof.	Brunhilde	Blömeke	University of Trier, Germany
Dr.	Johanna	Brared-Christenson	University of Gothenburg, Sweden
Dr.	Halyna	Breslawec	PCPC, USA
Prof.	James	Bridges	University of Surrey, UK *(Rapporteur of the Workshop)*
Prof.	Magnus	Bruze	Lunds Universiteit, Sweden and RIFM Expert Panel Member
Dr.	Peter	Cadby	Chanel, France
Dr.	Michael	Calandra	Firmenich, USA
Dr.	Alain	Chaintreau	Firmenich, Switzerland
Dr.	Dominique	Favier	IFF, France
Prof.	Ellen	Fritsche	University of Düsseldorf, Germany (Day 1 only)
Dr.	Federica	de Gaetano	EU Commission - DG SANCO – Unit B2
Prof.	David	Gawkrodger	Royal Hallamshire Hospital, UK and Vice-chairman of the SCCS
Dr.	Carsten	Goebel	Procter & Gamble, Germany
Prof.	An	Goossens	Katholieke Universiteit Leuven (Day 1 only)
Prof.	Ann-Therese	Karlberg	University of Gothenburg, Sweden
Dr.	Jon	Lalko	RIFM, USA
Dr.	Fred	Lebreux	International Fragrance Association, Belgium
Prof.	Jean-Pierre	Lepoittevin	University of Strasbourg, France
Dr.	Andreas	Natsch	Givaudan, Switzerland
Dr.	Camilla	Pease	Environ (Day 1 only)
Dr.	Chris	Powell	Unilever, UK
Prof.	David	Roberts	Liverpool John Moores University
Dr.	Florian	Schellauf	Cosmetics Europe, Belgium
Prof.	Axel	Schnuch	IVDK / University of Göttingen, Germany
Dr.	Theodor	Schumacher	Smartpractice, Germany
Prof.	Glenn	Sipes	University of Arizona, USA
Dr.	Matthias	Vey	International Fragrance Association, Belgium
Dr.	Jonathan	Warr	Takasago, USA

IDEA
International Dialogue for the Evaluation of Allergens

Key conclusions of the IDEA Workshop on

Risk Assessment of Pre-& Pro-Haptens

May 28-29th 2013

Dolce La Hulpe Brussels
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The workshop produced a number of key conclusions on the work to date and identified a range of specific action steps:

- 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 is common. There is presently insufficient data on exposure to these **oxidation** products to make a correlation to disease (allergic contact dermatitis).
- On biotic and abiotic **oxidation**, the data 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.
    - There is a need for more rigorous protocols (including ROAT) for clinical studies.
    - Different concepts of relevance (individual, group-related and epidemiologic data) need to be refined.
- The development of new analytical methodologies such as HR MAS-NMR is a key requirement to elucidate in situ phenomena.
- The workshop produced a range of recommendations to identify and characterize pre- & pro-haptens, ranging from chemical characterization to confirmation through clinical studies.
- Future work should be conducted in transparency and with participation from stakeholders with relevant expertise.

The participants

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Rapporteur's Progress Report on the IDEA Workshop on

Risk Assessment of Pre-& Pro-Haptens

May 28-29th 2013

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 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 review the current understanding of biological and chemical mechanisms involved in pre- and pro-haptens activity, and consider the potential implications for risk assessment. The main focus was on the processes of oxidation and hydrolysis. The workshop was aimed to enable the experts to bring all available inputs together to jointly identify, if needed, priorities for further research and agree on their design.

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2. Rapporteur's progress report

The workshop covered the whole area of pre- and pro-haptens from theoretical chemistry considerations to clinical practice observations. There was very active participation of workshop participants. This summary does not address all the technical details presented but rather focusses on the main conclusions and areas for further work.

A. Current scientific understanding of Pre- & Pro-Haptens

Pre- and pro-haptens are hapten precursors. To be an effective hapten a chemical needs to be:

- Able to gain access in sufficient concentrations to the target protein(s) in the skin that are responsible for the initiation of sensitization. A balance between hydrophilicity and lipophilicity has been identified as an important property for a hapten or pre- or pro-hapten to penetrate skin epidermal cells,
- Sufficiently reactive with the critical target sites of the protein(s),

However, to be an effective hapten, a chemical does not need to be markedly cytotoxic (or cause other substantial cell damage). If cytotoxic, then this chemical must only be so at higher doses than needed for sensitization to occur.

In order to act as a hapten some chemicals need to undergo conversion to more chemically reactive forms.
A pre-hapten is a chemical that needs to be chemically (abiotically) activated. Such activation can in principle arise:

i) During processing or storage of a raw material/formulation
ii) On the surface of the skin as a result of application
iii) Following skin penetration

Only in situation i) is there generally certainty about the mode of activation.

A pro-hapten is a chemical that is a substrate for the so called drug metabolising enzymes (biotic activation). To access these enzymes a chemical must penetrate the surface of the skin. In practice it may be difficult to identify whether a chemical is a pro-hapten.
On current evidence the most common pathways for hapten formation from precursors are oxidation and hydrolysis. It would appear that if a chemical is a pro-hapten it has the potential to be a pre-hapten too. However the converse does not necessarily apply. Thus pre-haptens are likely to be more common than pro-haptens. The number of fragrance ingredients in general use that can act as pre- or pro-haptens is unknown, there might be many hundreds. The LLNA data bases indicate that of those allergens that have been identified approximately two thirds direct acting haptens. It needs to be recognised that the formation of the hapten and its availability to the receptor protein will need to exceed a critical concentration (threshold amount) for sensitization to be initiated. It was pointed out that fragrance manufacturers are likely to avoid using fragrance materials that are unstable in the final cosmetic product.

A.1. Oxidation reactions that may lead to hapten formation

Activation of a pre- or pro-hapten can arise due to oxidation of:

- a double bond to form an epoxide
- a catechol or hydroquinone to form a quinone
- an allylic or benzylic C-H group to form a hydroperoxide
- an alcohol group to a carbonyl group.

In addition, reactions such as oxidative dehalogenation and photo-oxidation can occur.

A.2. Hydrolysis reactions that may lead to hapten formation

Some pre- and pro-haptens require conversion to form an alcohol or aldehyde in order to be activated. This can occur due to hydrolysis of:

- Schiff bases
- Esters (of particular importance are likely to be formates and acetates)
- Acetals

For some chemicals a two-step process involving both hydrolysis and oxidation may need to occur for the formation of an effective hapten (e.g. hydrolysis to an alcohol followed by oxidation to an aldehyde).

Data presented at the workshop provided good qualitative evidence that sensitizers can be formed in some formulations of fragrances (fragrance compounds or finished products) under realistic conditions..

Pre-haptens. It was evident that for a variety of reasons in investigations of fragrances the focus has been on pre-haptens. Studies on specific model and real fragrance products show that hydroperoxides are indeed formed although at concentrations that are lower than those generated under experimental conditions. Clinical studies on hydroperoxide-sensitive subjects using repeated open application tests showed that their elicitation thresholds may be quite low but may still be higher than levels of hydroperoxides measured in model and aged fragrance cosmetics.

Pro-haptens With regard to metabolic activation, it was pointed out that in the wider area of modes of toxicity of chemicals (metabolism of chemicals to reactive species that initiate toxicity), there is a very rich literature. This literature is concerned primarily with toxicity arising in organs other than the skin, in particular the liver, kidneys and lungs and with genotoxicity and cytotoxicity endpoints. Nonetheless many of the enzymes responsible for the formation of reactive species are also present in the skin. It may also be relevant that metabolic activation of a number of chemicals involves reactions other than oxidation and hydrolysis e.g. reduction and conjugation.

A.3. Factors affecting hapten formation

i) Oxidation reactions

The following factors were identified as having a potentially important influence on hapten formation from pre-haptens:

- Oxygen availability: This may be reduced if there are other components in the medium/formulation that compete for the oxygen.
- Temperature: As in all chemical reactions, the temperature plays an important role in hapten formation according to the Arrhenius equation.
- Alternative pathways for the chemical that do not result in hapten formation. It was noted that individual pre- and pro-haptens may be converted to a number of metabolites/products. This may result in the formation of haptens with differing potencies and/or the inactivation of the haptens formed and/or products that are not haptens.

Rate limiting factors for pro-hapten oxidation to haptens are the same as for pre-haptens but in addition include:

- Availability of an appropriate enzyme in the skin (e.g. a suitable isoform of Cytochrome P450).
- Ability of the pro-hapten to reach the enzyme. Availability of any relevant cofactors e.g. NADPH.

ii) Hydrolysis / solvolysis reactions

For hydrolysis of pre- and pro-haptens the requirements are basically the same as for oxidative reactions with the exception that:

- Hydrolysis can occur under both aerobic and anaerobic conditions.
- Abiotic hydrolysis and solvolysis are more dependent on the pH of the medium.

For the above reasons the sensitizing effects of pre- and pro- haptens that form haptens in the skin are likely to be less reproducible than the effects of substances that are direct sensitizing agents.

A.4. Understanding of the causes of human variability in the effects of pre- and pro- haptens

The principal reasons for inter-individual differences in the initiation of sensitization are not well characterised. In regard to pro-haptens it is probably relevant from studies in organs other than the skin, that major inter-individual differences due to genetic factors occur and that these may result in individual differences in toxicity. It is likely that genetic differences in skin drug metabolising enzymes also occur. For pre-haptens it is not clear whether greater inter-individual variation occurs than for haptens and if so what the critical factors are.

A.5. Known fragrance pre and/or pro-haptens

Particular attention was given at the workshop to the terpenes alpha-terpene, limonene, linalool and Geraniol. Other examples of initiation that were considered in some depth were cinnamic alcohol, cinnamic aldehyde, isoeugenol and eugenol.

A.6. Prediction of pre-and pro-haptens properties

The development of a structure activity (SAR) model for predicting pre- and pro- haptens would be valuable. The prediction of which fragrance ingredients will act as pre- and/or pro-haptens is limited at present for a number of reasons. Particularly:

- The restricted range of chemical classes that have been investigated in depth.
- The complexity of factors that influence the rate of formation and lifetime of the resulting haptens (see above and figure 1).
- Lack of knowledge of the critical sites on the proteins whose modification results in initiation of sensitization.

Key considerations in developing reliable prediction models that were discussed include:

- Determination of bond energy at vulnerable sites in a chemical.
- Determination of parameters influencing the kinetic rate of reactions (pH, oxygen availability, temperature).
- Improvement in the understanding of the ability of human skin to generate soft electrophiles/nucleophiles/free radicals.
- Assessment of lipophilicity and hydrophilicity of the pre- and pro-haptens and the resultant haptens.

- Understanding of the stability of the resultant haptens in the skin (the skin is a potential reservoir for both the absorbed pre- and pro- haptens and for the resultant haptens).

A.7. Prevention of the impacts of pre-and pro-haptens

The use of antioxidants to limit oxidative pre-hapten conversion to haptens was discussed. The conclusion that emerged was that prediction was not straightforward. In some circumstances the addition of antioxidants appeared to be beneficial but in others not.

Key factors in the generation of haptens are summarised in the following figure.

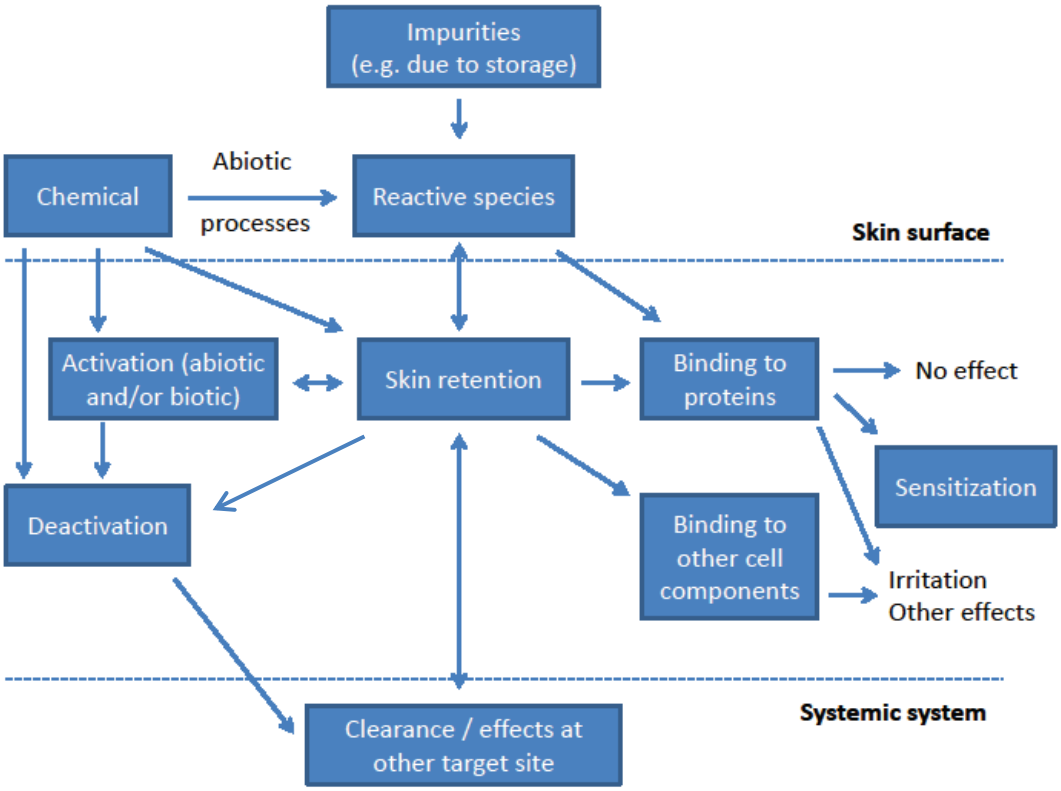

Figure 1: Distribution, transformation and effects of pre- and pro-haptens

The above approach should be integrated with the development of the Dermal Sensitization QRA (topic of the first IDEA workshop).

B. Methodological considerations

Progress in the identification, characterization and understanding of the modes of action of pre- and pro-haptens depends on the general availability of suitable methodologies.

Several stages can be identified in the process of establishing whether a fragrance is a pre- or pro-hapten (see also figure 2):

- Characterisation of physicochemical properties (informed by SAR / bond energy considerations)
- Obtaining evidence that it can form reactive products (under relevant abiotic / biotic conditions)

- Found to be a skin sensitizer in animal test(s)
- Found to cause a positive skin reaction in patch test(s) of allergic patients
- Estimates / measurements indicate that sufficient concentrations of the hapten can be generated to exceed the threshold for initiation under real world exposure conditions.

Suitable methodologies are required at each stage. A general requirement is also a reliable supply of well characterized high purity reference compounds (e.g. for analytical purposes).

B.1 Laboratory methods

Methods to measure / estimate hapten formation:

The chemically reactive nature of the products generated and consequently their instability makes this a crucial area. Several methods were mentioned (but not discussed in any detail) such as:

- Oxidation studies using a PetroOxy apparatus.
- Chemical methods for separating and characterizing the haptens generated e.g. use of chromatography, colorimetry, specific trapping agents, mass spectrometry.
- Magic angle spinning NMR: this technique appears to be of particular value in detecting the interactions of the generated hapten with cellular proteins.
- Chemical and biological models for studying hapten formation and their interactions.

Models for biotic transformation.

For studies on biotic and abiotic transformation by the skin, animal or human skin biopsy samples have been used by a number of researchers. Often homogenates or cell fractions have been used. These can provide useful information on conversion pathways and relative rates of formation of reactive products for different pre- and pro- haptens.

Lack of availability and relative poor reproducibility of such preparations in the past has resulted in the development of some skin culture models (e.g. the reconstructed human skin epidermis model). This preparation has good reproducibility but its relationship to normal human skin requires further examination. It is noted that the stratum corneum is not well developed and the source of keratinocytes is uncertain. More comparisons are also needed with skin biopsy samples on the drug metabolising capability.

Models for sensitization:

The favoured method is the local lymph node assay (LLNA) although non-animal testing alternatives are currently being investigated. The correlation between LLNA and patch test results is good (around 85% consistencies) but further studies are needed to determine its reliability in identifying different pro- and pre-haptens.

B.2 Clinical methods

B.2.1 Exposure assessment methods

- Information access:

  A major barrier to progress is the problem of estimating total real life exposure of consumers to individual fragrances and to other closely structurally related chemicals. A further issue is that there is often inadequate knowledge of the cosmetic matrix formulation(s) of consumer products. This is relevant because components in a formulation can have a substantive influence on the ability of pre- and pro- haptens to be converted to a hapten and/or on the half-life of the hapten.

- Measurements and modelling:

  Methods are available to determine the abiotic or biotic transformation of fragrances on the skin albeit it is particularly challenging to detect and quantify the generation of reactive products. As yet there is no viable methodology to determine hapten formation in the skin of patients.

B.2.2 Methods to identify and characterize pre- and pro-hapten sensitizers

Two types of study were identified for patch testing:

- Studies in individual patients
- Studies in randomized groups of volunteers

Some studies were described in outline that involved solvent extraction to remove a fragrance and its transformation products from the skin and measure them.

There was also some important discussion on the interpretation of patch testing results (a particular concern being consistency in categorization of fragrances as mild irritants and doubtful sensitizers).

Furthermore, the hypothesis was mentioned that low levels of weak sensitizers while not producing strong reactions may nonetheless lead to a subclinical state that can only be triggered via very high exposure doses. It was therefore recommended to reconcile clinical and exposure data under this hypothesis (this will be an important topic of the workshop on identification of sensitizers).

A framework was developed at the workshop for the identification of important pre- and prohaptens. It is a staged approach to facilitate prioritisation of fragrances for in depth study. To enable simplicity the various feed-back loops that might be important for individual investigations have been omitted.

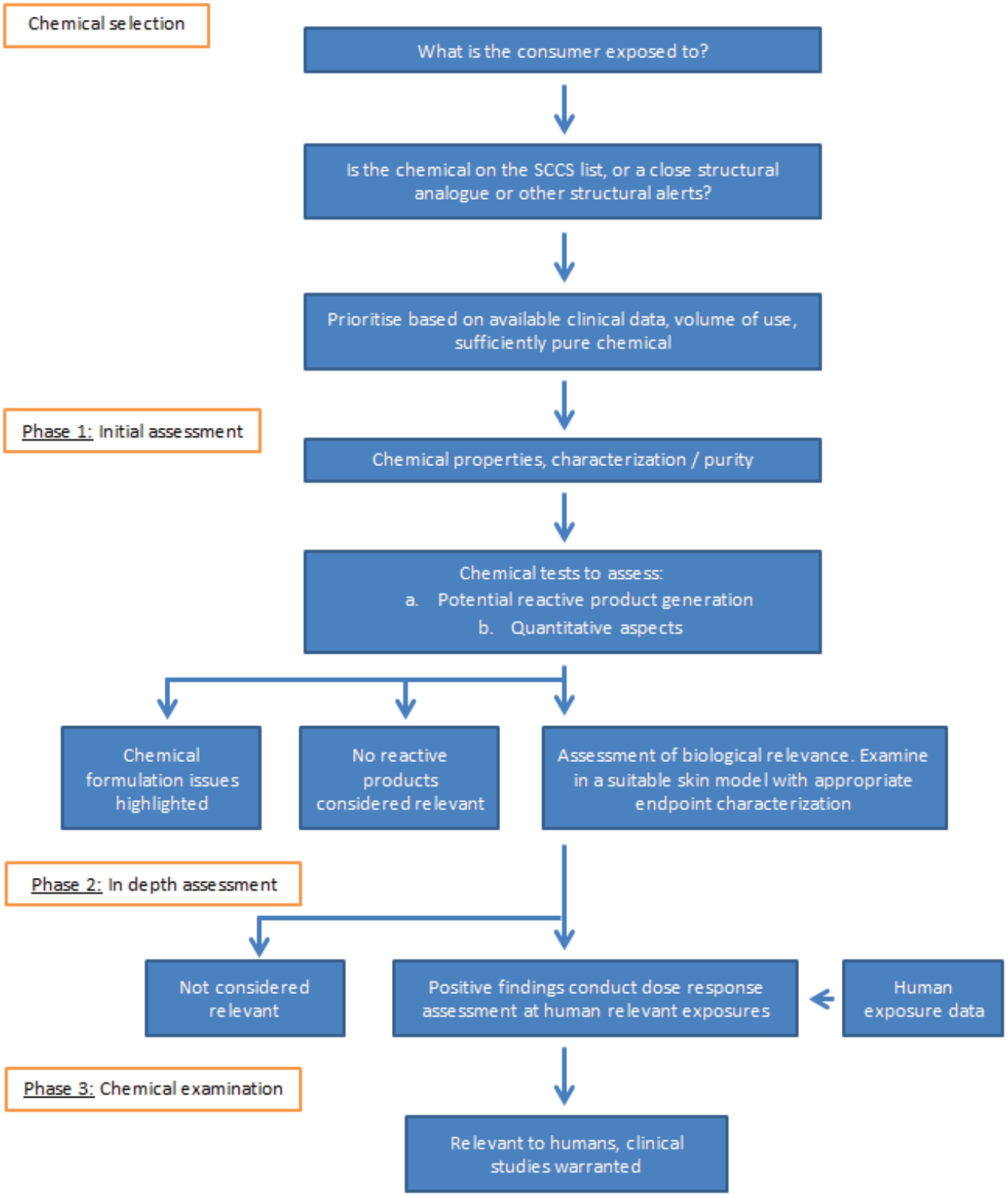

Figure 2: A staged approach for pre- and pro- hapten identification and characterization

C. General conclusions

- There are many fragrances with the potential to act as pre- and/or pro- haptens. Very few have been studied; the majority of these are terpenoids.
- There is a serious lack of reliable information on real life exposures to fragrances and closely related chemicals.
- Many of the tools required to investigate the significance of individual pre and pro haptens in the initiation of allergic contact dermatitis are already available. In addition there are some promising new developments.
- Even for the well-studied pre- and pro- haptens, the linkage between initial exposure, initiation and subsequent elicitation of allergic contact dermatitis is not fully established.

D. Priorities for further work

1. Identify and characterize the actual consumer exposure from all sources to fragrances and closely related structures.
2. Select and ensure the general availability of a suitable range of pure reference fragrance ingredients.
3. Develop new analytical techniques for the detection and quantification of haptens (e.g. hydroperoxides) in fragranced products and biological media (e.g. skin).
4. Develop a suitable SAR tool(s) to identify likely pre- and pro-haptens.
5. Characterize and develop skin models, particularly human skin models for studying hapten formation, protein interactions and subsequent fate.
6. Include pre- and pro-haptens in the development of Dermal Sensitization QRA (to be linked to the action items of the first IDEA workshop).
7. Examine how pre-hapten conversion to haptens can be minimized by improved formulation and storage.
8. From a clinical perspective, focus on pre- and pro-haptens that have been well characterized in laboratory studies.
9. Develop strategies for bridging the knowledge gap between induction and elicitation.

The participants agreed that in order to accomplish these important objectives, improved transparency and close collaboration between all active stakeholders in this field is a key to successfully addressing the issue. The subsequent follow-up from this workshop will provide the framework for achieving the expected outcomes. Further discussions are needed to identify and implement an effective and sustainable forum

APPENDIX 1: Additional reading

- Cinnamyl alcohol oxidizes rapidly upon air exposure / I. B. Niklasson, T. Delaine, M. N. Islam, R. Karlsson, K. Luthman and A.-T. Karlberg / Contact Dermatitis 2013.
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- Stability of Essential Oils: A Review / C. Turek and F. C. Stintzing / Comprehensive Review in Food Science and Food Safety 2013.
- Haptens, pro-haptens and pre-haptens, or electrophiles and proelectrophiles / A. O. Aptula, D. W. Roberts and C. K. Pease / Contact Dermatitis 2007.
- Ann-Therese Karlberg, Moa Andresen Bergström, Anna Börje, Kristina Luthman and J. Lars G. Nilsson. Allergic Contact Dermatitis–Formation, Structural Requirements, and Reactivity of Skin Sensitizers. Chem. Res. Toxicol. 2008, 21, 53–69
- Determinants of skin sensitization potential / D. Roberts, A. Aptula / Journal of applied toxicology 2008.
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International Dialogue for the Evaluation of Allergens

Recommendations of the IDEA Workshop on

Risk Assessment of Pre- & Pro-Haptens

May 28-29th, 2013

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

1) Analytical development:

IFRA AWG[1]: First, the group will 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 IFRA AWG will also assess the half-life of these chemicals as well as any other parameters related to their conservation.

IFRA AWG: These references will be used to develop new analytical methods for the detection and the quantification of chemically-defined haptens, resulting from abiotic transformations, in fragranced products. These methods will have to be sensitive, specific and target limits of quantification below the estimated induction levels and limits of detection below the estimated elicitation levels.

IFRA AWG and RIFM: With the assistance of the workshop participants, the IFRA AWG and RIFM will try to 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.

2) Risk assessment

RIFM: A suitable SAR tool(s) will be developed to identify likely pre- and pro-haptens. RIFM will contract experts of the chemical reactivity to set and refine structural rules for the identification of materials likely to undergo abiotic transformations. These rules would be incorporated into existing models such as ToxTree.

[1] The IFRA Analytical Working Group (AWG) will supervise all action points related to chemical synthesis and analytical developments. The practical execution of the action items will be ensured by a contract laboratory, or placed under the collective responsibility of the group depending on the type of work involved.

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RIFM: A task force of experts will be convened to characterize and develop human skin models for studying hapten formation, protein interactions and subsequent fate. These models, possibly based on the HR MAS-NMR technique and Skin-Like Cytochrome P450 Cocktail, will be used to assess the risk that pro-haptens represent for the consumer.

RIFM: Based on chemical, cellular, and molecular understanding of dermal sensitization, an exposure-based quantitative risk assessment (QRA) can be conducted to determine safe use levels of fragrance ingredients in different consumer product types. RIFM will review the available pre- and pro- haptens potency and exposure data in view to include concerned fragrance ingredients in the development of the QRA. The recommendations made on pre- and pro-haptens will be taken into consideration when refining the QRA methodology.

IDEA Management Team: The workshop participants recommended that the industry develops strategies for bridging the knowledge gap between induction and elicitation. This recommendation was taken into consideration for the organization of the third IDEA workshop dedicated to the characterization of fragrance allergens (August 28-29, 2013). From now on, the link between induction and elicitation will be studied by this group and all progresses made reported to all idea workshop groups.

3) Risk management

IFRA: Once fully developed and validated, the methods developed by the IFRA AWG will be transferred to a contract laboratory in view to analyze marketed products for haptens presence. This cyclic survey will contribute to determine the actual consumer exposure to haptens. The consumer exposure estimated for each selected hapten will be compared to the clinical prevalence of skin sensitization to this hapten and potentially used to feed the risk assessment process. Furthermore, the results of this survey will play an important role for the post-marketing risk management: companies responsible for products containing problematic concentrations of haptens will be informed and encouraged to correct the situation.

IFRA and other trade associations: A task force will be formed with the help of other trade associations (such as Cosmetics Europe and PCPC) to examine how pre-hapten conversion to haptens can be minimized by improved formulation and storage. This group will consider all aspects of the supply chain (formulation, packaging, storage, etc.) and act quickly to implement optimal practices throughout the industry.

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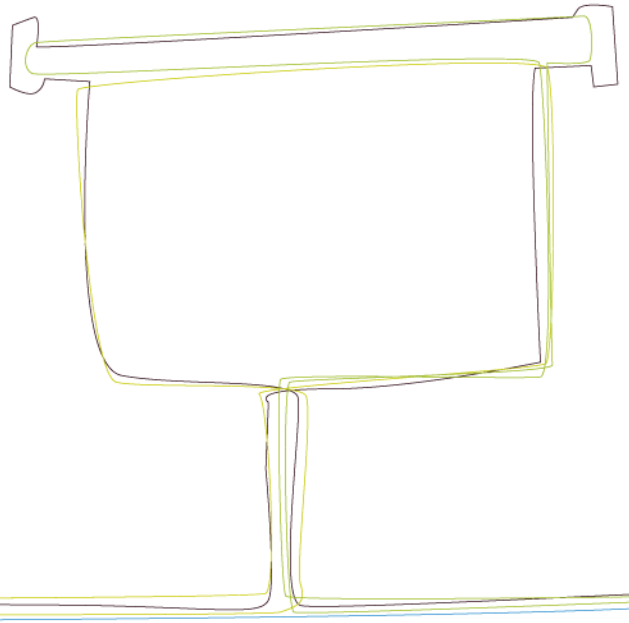
Rapporteur's Progress Report on the IDEA Workshop on

Risk Assessment of Pre- & Pro-Haptens



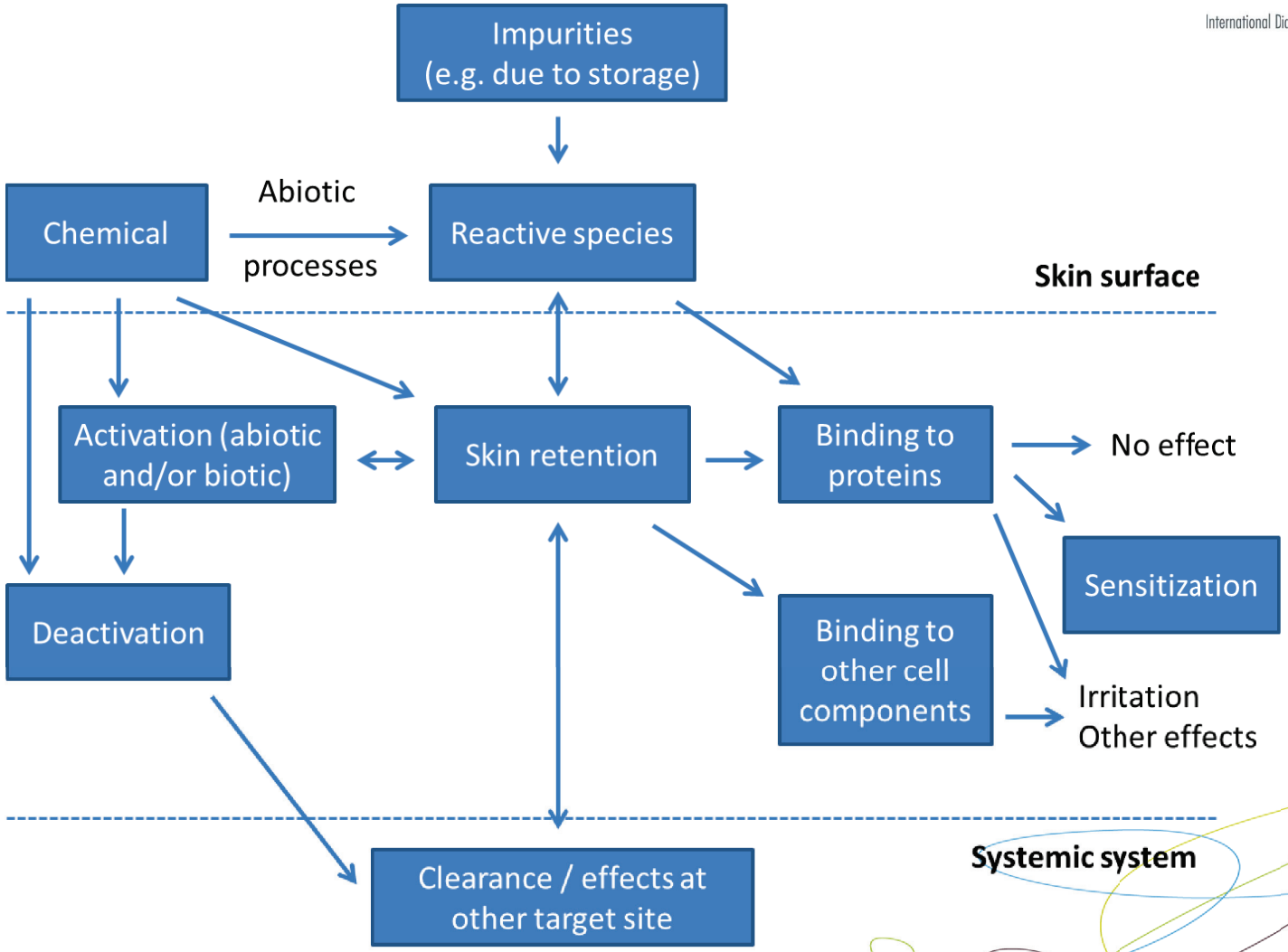
May 28-29, 2013

Prof. Jim Bridges
Chairman of the IDEA Supervisory Group

Current understanding of pre- & pro-haptens

- A **hapten** is a small low molecular weight molecule that can induce and elicit an immune response.
- **Pre- & pro- haptens** are hapten precursors and are often non-sensitizing themselves.
- **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.

Distribution, transformation and effects



The difference between pre- & pro-haptens

- 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).
- Pre-haptens appear to be more common than pro-haptens.

The transformation of pre- & pro-haptens

- Most common pathways for hapten formation from precursors are **oxidation** and **hydrolysis.**

- Rate of abiotic / biotic activations and of **risk of sensitisation initiation** depends on:

  a. Chemical factors (reactivity, storage conditions, etc.)

  b. Inter-individual variability

Oxidation to form a hapten

- Functional groups that may oxidize and lead to the formation of haptens are: double bonds, allylic or benzylic C-H bonds, alcohols, aldehydes, …
- Factors affecting **abiotic** formation of haptens are:
  - Oxygen availability
  - Temperature
  - Competing alternative pathways that do not result in hapten formation.
- Other parameters for **biotic** transformation:
  - Availability of appropriate enzyme in the skin.
  - Ability of pro-hapten to reach the enzyme.

Hydrolysis to form a hapten

- Some functional groups are prone to hydrolysis: Schiff bases, esters (eg formates), acetals, …
- Parameters influencing hydrolysis are basically the same as for oxidative reactions except that:
  - Hydrolysis can also occur under anaerobic conditions.
  - Abiotic hydrolysis (and solvolysis) very much depends on the pH of the medium.

Current understanding of these transformations

- Pre-haptens:
  - Good qualitative evidence that sensitizers can be formed in some formulations under realistic conditions.
  - Studies on fragranced consumer products show concentrations of formed haptens are generally much lower than those generated under experimental conditions.
- Pro-haptens:
  - Literature on metabolic activation is very rich but primarily in organs other than skin and focused on endpoints other than sensitisation.
  - However, relevant enzymes also present in the skin.

Understand Inter-individual human variability

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- Further investigation is necessary to better characterize the potential inter-individual differences in the initiation of sensitization.
- For pro-haptens, it is likely that genetic or other differences in skin metabolising enzymes play a role in skin sensitization.
- For pre-haptens, it is not clear if inter-individual variation occurs or if it is important.

Needs: Prediction of pre- and pro-haptens properties

- Development of a **structure-activity model** would be valuable.
- Model should include:
  - Determination of bond energy at “vulnerable” site(s).
  - Determination of parameters influencing the kinetic rate of reactions (pH, oxygen, availability, temperature, etc.)
  - Ability of human skin to generate electrophiles, nucleophiles, radicals
  - Physical properties of precursors and resultant haptens.
- Targets the understanding of skin sensitisation potential of resultant haptens

Needs: Laboratory methods

- The development and use of:
  - Methods to measure / estimate hapten formation: magic angle spinning NMR, chromatography with use of trapping agents, oxidation stability studies, …
  - Models for biotic transformation: animal / human skin biopsy samples, skin culture models (further developments needed).
  - Tools to identify skin sensitization potency (LLNA, HRIPTs and in-vitro methods).
- Current methods and tools will need refinements and adaptations to provide adequate information on pre- and pro-haptens.

Needs: Clinical methods

- **Identify / characterize** pre- and pro-haptens via experimental methods.
- Assess **total real-life exposure of consumers** to haptens resulting from biotic / abiotic transformation of fragrance ingredients:
  - Attention should be paid to the development of viable methodology to determine hapten formation in the skin.

Conclusions on risk assessment/management

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- No reliable way to identify, characterize and quantify haptens from fragrance ingredients. **Staged approach** to identify / characterize these chemicals was proposed and could be adopted (see progress report).
- Most tools (analytical, biological or clinical) for investigation in skin or in products exist but need to be adapted / refined for pre- and pro-haptens.
- Resulting knowledge to be incorporated into QRA ensuring high level of consumer protection.

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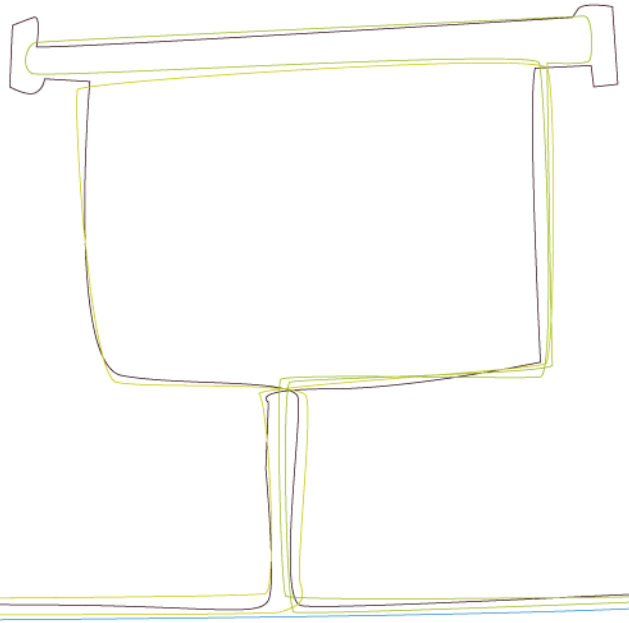
Progress report on actions taken

Risk Assessment of Pre- & Pro-Haptens



Process and timeframe

- The recommendations made during the workshop:
  - pertaining to risk assessment are addressed by RIFM
  - Recommendations pertaining to chemical analysis and risk management are addressed by IFRA.

- Preliminary results are available and consolidated results will be presented at the next workshop on pre- and pro-haptens (September 2014).

Risk assessment (ONGOING)

- Data on pre- and pro-haptens are currently being collected to develop a suitable Structure-activity model.
- A research project is underway developing human skin models for studying hapten formation and protein interactions. The role that skin metabolism has in this characterization is also being explored.
- Research is ongoing to incorporate pre- and pro-haptens in QRA methodology.
- A framework has been developed for the identification of important pre & pro haptens requiring further study.

Analytical development (ONGOING)

- IFRA Analytical Working Group (chaired by Dr. Alain Chaintreau, workshop participant) supervises the development of procedures to prepare, purify and assess the stability of haptens currently not commercially available (e.g. hydroperoxides).
- Objective is to get a suitable range of pure references, necessary to allow the development of an analytical method for the quantification of haptens.
- This analytical method is critical for the subsequent execution of *in vitro* / biological assays and clinical investigations.

Risk management (PENDING)

- Once fully developed, the quantification method 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.
- 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

Prof. Jim Bridges
IDEA Supervisory Group

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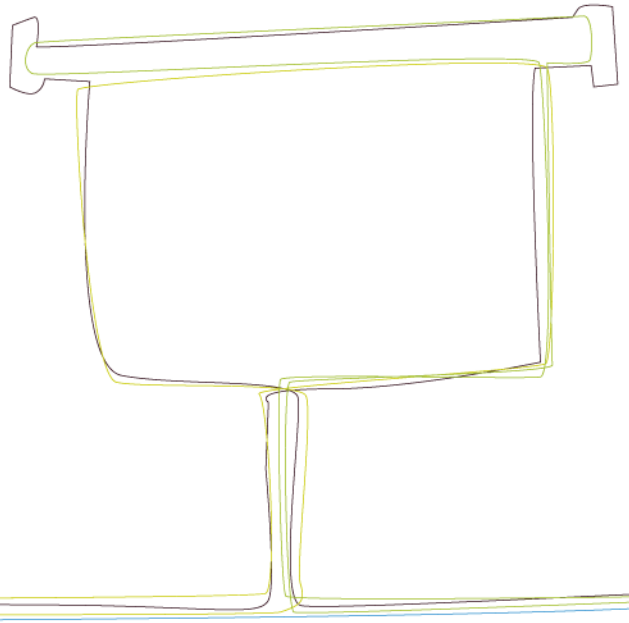

IDEA WORKSHOP

Validity of the QRA Methodology & Possibilities of Further Refinement

March 19-20th, 2013

1. Programme and list of participants
2. Key conclusions
3. Rapporteur's progress report
4. Recommendations
5. Slides presented by Prof. Jim Bridges

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IDEA Workshop

Validity of the QRA Methodology & Possibilities of Further Refinement

March 19-20th, 2013

Dolce La Hulpe Brussels
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Final Programme

Monday, March 18th

4:00 - 6:30 p.m.	Welcome and registration at the IDEA Workshop
6:30 - 9:30	Reception (walking dinner)

Tuesday, March 19th (9:00 a.m. to 5:00 p.m.) – Session 1 (Formal presentations)

Each presentation consists of a 40 minutes lecture followed by 20 minutes of questions

9:00 - 9:30 a.m.	Opening of the meeting – H. Bender and M. Vey
9:30 - 10:30	*Scientific basis, details and evolution of the QRA methodology* – A.-M. Api
10:30 - 11:00	Coffee break
11:00 - 12:00	*The QRA methodology such as used today by IFRA to set Standards based on induction levels* – G. Ellis
12:00 - 1:00	Lunch

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1:00 - 2:00	*Potential areas of improvement of the current QRA methodology* – SCCS Member (J. Duus Johansen)
2:00 - 3:00	*Assessment of the effectiveness of the QRA methodology* – A.-M. Api
3:00 - 3:30	Coffee break
3:30 - 4:30	*Recent progresses in the calculation of the aggregate exposure to fragrance ingredients* – B. Safford
4:30 - 5:30	Moderated Discussion with the Lecturers and conclusions of Day 1
5:30 p.m.	End of the Session
6:30 - 7:30	Champagne tasting
7:30 - 9:30	Dinner

Wednesday, March 20th (9:00 a.m. to 4:30 p.m.) – Session 2 (Open discussion)

9:00 - 9:30 a.m.	Adoption of the agenda and wrap-up of Day 1
9:30 - 10:30	Consumer exposure

Improved exposure data (Hall, 2011) is being incorporated into the QRA methodology. In addition, RIFM has sponsored work to investigate the effects of aggregate dermal exposure.

The outcome of this work is being accounted for in the methodology and we suggest that an open discussion be held on the validity of the QRA and on this initiative in particular.

10:30 - 10:45	Coffee break
10:45 - 11:45	Acceptable Exposure Levels (AEL) and Exposure Data

A more detailed explanation of AELs and how they are applied should be provided. There also is a need for more details on the pragmatic approach and a review of aspects of having high calculated values in (mainly) rinse-off products.

11:45 - 12:30	Dose Response Assessment - Safety Assessment Factor (SAF)

A paper which specifically addresses the use of uncertainty factors in QRA for skin

sensitization has been published (Felter, et al., Contact Dermatitis, 2003, 47:257-266). However it is acknowledged that further dialogue on SAFs would be appropriate. This would include better clarification of what the SAFs are applied to (e.g. not to clinically diseased skin).

12:30 - 1:15 Lunch

1:15 - 2:15 Assessment Tools of the QRA Methodology (LLNA, HRIPT, etc.) and Retrospective Analysis (Diagnostic patch test)

The aim of this session is to address the necessary tools for the QRA methodology and controlling its effectiveness.

LLNA and HRIPT studies have been and are still used as the basis to identify the "No Expected Sensitization Induction Level" of fragrance allergens.

Diagnostic patch test data from dermatology clinics provide a means to investigate whether thresholds of use based on the QRA have been successful. Also company post-market surveillance data can be used for this purpose.

2:15 - 2:30 Coffee break

2:30 - 3:30 Current Boundaries of the QRA Methodology

While occupational exposures to consumer products can be an important source of exposure they are not considered in the current QRA. This mainly stems from a lack of adequate exposure data.

Furthermore the QRA methodology does not cover aromatherapy (neither workers nor consumers). These currently not reflected exposures remain a potential area of research.

3:30 - 4:30 Conclusions of the Workshop and Next Steps

4:30 p.m. End of the Session and Workshop Closing

List of participants (28):

Dr.	Anne Marie	Api	RIFM
Dr.	David	Basketter	Consultant
Dr.	Hans-J.	Bender	Consultant *(Moderator of the QRA Workshop)*
Prof.	Donald	Belsito	Columbia University Medical Center and RIFM Expert Panel Member
Dr.	Christophe	Brault	LVMH
Prof.	James	Bridges	University of Surrey and SCENIHR Chair *(Rapporteur of the QRA Workshop)*
Prof.	Magnus	Bruze	Lunds Universiteit and RIFM Expert Panel Member
Prof.	Pieter-Jan	Coenraads	University Medical Centre Groningen
Prof.	Wolfgang	Dekant	University of Würzburg, SCHER Member and RIFM Expert Panel Member
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
Dr.	Federica	De Gaetano	EU Commission – DG Sanco – Risk Management Unit
Dr.	Nicola	Gilmour	Unilever
Dr.	Peter	Griem	Symrise
Dr.	Petra	Kern	Procter & Gamble
Dr.	Christine	Lafforgue	Université Paris sud 11
Dr.	Fred	Lebreux	International Fragrance Association
Dr.	Cronan	McNamara	Crème Global
Prof.	Hans	Merk	Universitätsklinikum Aachen
Prof.	David	Roberts	Liverpool John Moores University and Member of the SCCS WG on Fragrance Allergens
Prof.	Vera	Rogiers	Vrije Universiteit Brussel and SCCS Vice-chair
Dr.	Bob	Safford	Consultant
Dr.	Florian	Schellauf	Cosmetics Europe
Prof.	Axel	Schnuch	IVDK / University of Göttingen
Prof.	Wolfgang	Uter	University Erlangen and Member of the SCCS WG on Fragrance Allergens
Dr.	Matthias	Vey	International Fragrance Association
Dr.	Ian	White	Guy's & St Thomas' NHS Hospitals and SCCS Chair

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Key conclusions of the IDEA Workshop on

Validity of the QRA Methodology & Possibilities of Further Refinement

March 19-20th, 2013

Dolce La Hulpe Brussels
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The workshop produced a number of key conclusions on the work to date and identified a range of specific action steps:

- On risk assessment:

QRA is seen as a promising tool to prevent induction of contact sensitization for people with normal skin. However, it requires further refinements for the general population as follows:

- Prospective and retrospective evaluation of its effectiveness by clinical and epidemiology data using sensitization as the relevant endpoint
- Review of underlying methodologies and assumptions:
  - SAFs (Safety Assessment Factors)
  - NESILs (No Expected Sensitization Induction Levels)
  - Exposure (accumulation, aggregate exposure, chemical analysis, usage, retention and professional exposure)
- Adaptation for people with compromised skin

- On risk management:
  - Commitment to act promptly on new insights
  - Labeling and Provision of information on ingredients as an important complement to QRA and in-market validation

- On prospective and retrospective evaluation
  - For retrospective work, the group strongly encouraged to consider all available historical data. Data on preservatives might also contribute to validation of QRA for fragrances.

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- For prospective work, focus should be on compliance with IFRA Standards, sensitization trends in the general population confirmed by clinical epidemiology data.
- For prospective work, clinical monitoring of new chemicals could provide important confirmation.

- On refinement of QRA for the general population
  - SAFs are seen as being set appropriately with current state of knowledge. Re-evaluation of the inter-individual variability factor with scientific rationale is considered essential.
  - An estimate of expected new induction when following QRA is encouraged.
  - There could be value in developing 'QRA 2.0', based on latest data and including aggregate / occupational exposure.

The participants

IDEA
International Dialogue for the Evaluation of Allergens

Rapporteur's Progress Report on the IDEA Workshop on

Validity of the QRA Methodology & Possibilities of Further Refinement

March 19-20th, 2013

Dolce La Hulpe Brussels
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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 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.

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2. Report of the Rapporteur :

Issues discussed at the workshop:

The following issues were discussed in detail:

A. Primary and secondary prevention:

Both the induction and the elicitation steps are likely to involve a threshold exposure level below which adverse effects will not occur. Thus safe use levels should be able to be derived using an appropriate risk assessment methodology. Induction and elicitation are different effects; the thresholds for which need to be determined by different methodologies. QRA in its present form is only applicable to prevent induction (primary prevention).

It is evident that a parallel procedure is needed to estimate the risks of elicitation. According to some epidemiologic studies, up to 25% of the population could be sensitized (not necessarily to fragrances). However, this estimate does not indicate the clinical relevance: i.e. skin sensitization is not necessarily accompanied by clinical effects. Nonetheless, an effective primary prevention would ultimately minimize the secondary issue(s).

B. The QRA procedure for allergens:

The intention of QRA is to replace the former risk assessment methodologies. Practical considerations have led to the setting of a default maximum pragmatic level (MPL) of the fragrance ingredients identified as dermal sensitizers for some product types. This MPL is defined as that "not exceeding the usual concentration of the fragrance compound in the finished product". The concept of MPL is deemed doubtful and not desirable. In addition to the methodological concerns, the MPL complicates the assessment of the effectiveness of the QRA.

The QRA follows traditional toxicological methodology lines. Dermal QRA has been used extensively on fragrances but there have also been attempts to work on other materials than fragrances (e.g. preservatives).

The QRA uses the classical risk assessment framework comprising:

- Exposure assessments based on dose per unit area of exposed skin, site of exposure and duration of exposure and frequency of exposure. Exposure assessment is done by assessing an individual chemical in an individual product. Other sources of exposure to the same chemical, such as an occupational exposure, from other domestic products are not generally considered.
- Risk assessment uses default (safety assessment factors) to arrive at an '*acceptable exposure level* (AEL)'.
- Hazard identification (NOAEL/NESIL) and hazard characterization (main tools are a combination of HRIPT, PT in humans. In animals the GP maximization test was widely used, more recently , the local lymph node assay (LLNA) has come to prominence

Safety factors are used to allow for uncertainties in various parts of the risk assessment, in particular:

- Identification of the threshold (NESIL) for induction.
- Inter-individual variability.

- Vehicle and/ or product matrix effects.
- Variation in exposures due to differences in use.

i) Identification of the No- Expected Sensitization Induction Level (NESIL):

Different views were expressed regarding the methodologies and assumptions leading to the NESIL calculation. Some felt that they were generally well acceptable some details needed refinement that only. For instance, the use of a dose per unit area was regarded as adequate but the reference to DNCB[1] maybe not appropriate to depict a methodology for fragrance ingredients. Others expressed the view that extensive improvements were needed. Concerns were expressed about guideline #6 (LLNA data only) due to the uncertainty of extrapolating animal testing results to humans. It was clarified that the NESIL, even based on LLNA data only, never equals the EC3. An additional safety factor is used to convert the test result into the NESIL. It was argued that more transparency could be provided on this additional safety factor.

The participants agreed that the capacity of the QRA to mitigate the risk of sensitization depends very much on the quality of testing data. Participants recommended that the Weight of Evidence (WoE) NESIL guidelines should be applied where robust data is available. The question was raised for the HRIPTs, as no clear guidance seems to exist for the dose selection. Another concern about HRIPT was the ethical aspect of this testing.

QRA 2. The question of the future absence of animal testing data was raised. Some new tools are already showing promise as a replacement for the skin sensitization data in animals. These should be introduced when properly validated as part of the development of the QRA.

ii) Consideration of Inter-individual variability:

The current QRA is intended to protect the general population. Currently, no particular attention is paid to people with compromised skin (e.g. atopic skin).

The current QRA considers a single safety factor of 10 to cover all sources of variability between individuals such as the age, the gender, the ethnicity, the inherent dermal barrier and the genetic effects. Main criticism was the arbitrary aspect of this value, as there is no scientific basis to set this safety factor at 10. This number should be substantiated, based on scientific data and potentially reconsidered at the light of sensitive population's specific problems. Indeed, it was argued that up to 10 % of the population (and even more if children are included) have a compromised skin. This safety factor should have to take this subgroup into account.

Regarding the safety aspect, pros and cons were raised for the single factor of 10. On the hand, the NESIL is confirmed by an HRIPT which adds an additional layer of precaution to this safety factor and the overall approach was viewed as conservative. On the other hand, there are experimental data linking the state of the skin and the risk of skin sensitization and showing that people with compromised skin might develop skin sensitization much more easily than the normal population (up to 100 or even 1000 times more easily). For this reason, the extrapolation of clinical observations to the general population should be treated with caution as this sensitive subgroup differs

significantly from the general population. This greater sensitivity could be partly explained by the enhanced skin penetration of compromised skins although this parameter is not sufficient to explain all cases.

QRA 2. It was agreed that further studies on the inter-individual variability should concentrate on three points:

- The ability of skin to allow permeation to occur.
- The enzymatic / metabolic specificities.
- The genetic differences.

One case of induction per million exposed people was seen as a reasonable target for consumer protection.

iii) Vehicle or product matrix effects:

The participants agreed that product matrix effects come just after the inter-individual variability in terms of importance and should also be the object of a special attention. The scale of 1, 3 and 10 was regarded as somehow arbitrary and additional scientific data should be collected to substantiate these safety factors. Furthermore, the same matrix effect of 3 was assigned to product types with very variable matrices (e.g. deodorants, hand washing detergents, baby creams). The rationale behind this categorization is not easy to follow and the participants recommended the implementation of a transparent and properly justified categorization procedure.

All participants agreed that the product matrix can indeed influence the immune reaction by virtue of an enhanced skin permeation. However, more important than the skin permeation is the bioavailability which is the true indicator of the Langerhans cells' capacity to capture a hapten and trigger the immune reaction.

Furthermore, it was agreed that the vehicle affects the outcome of LLNAs and HRIPTs although no clear consensus was reached concerning the magnitude of this impact. It was reported that DMSO and ethanol tend to increase the actual response, while DEP tends to lower it. For this reason, the safety factor should not focus solely on the intrinsic properties of the product matrix but also consider the differences existing between the experimental and the real-life conditions. This logic could lead to a safety factor under 1, as some matrices are likely to limit the allergens potency observed in laboratory.

The presence of irritants was also regarded as important for careful consideration. This variable is relatively difficult to evaluate, as it implies a sound examination of all ingredients of each consumer product. A recommendation was to develop a statistical model taking all the matrix parameters into account.

These various elements contribute to rationalization of a product matrix effect. Several studies going in this direction were reported, such a ROAT conducted on HICC-containing cosmetics and for which the observed elicitation rates in ethanol-based products were 5 to 7 times higher than in cream-based products.

QRA 2. Further work on matrix effects is needed to provide a better basis for incorporation of matrix effects in the QRA.

iv) Use considerations:

Likewise, the scale of this safety factor (1, 3 and 10) was regarded as rather arbitrary and additional scientific data should be collected to substantiate it. The small difference between the safety factor of a shampoo and the one of a deodorant was questioned and further studies requested to bring clarity to this aspect.

Occlusion was regarded as an important parameter as it has an important impact on the risk of induction. It was mentioned that both HRIPTs and LLNAs are conducted with fully-occlusive chambers while the fragrance allergens present in consumer products partly evaporate in normal conditions.

The review of the three safety assessment factors led to the conclusion that a scientific rationale should be identified for all safety factors

QRA 2. Data needs to be collected (retrospective evaluation) and produced (prospective evaluation) in view to re-evaluate the SAF in a transparent and systematic way using a more biological approach. Thus, use and matrix factors address basically the same thing, namely the skin penetration and the presentation of the hapten to the immune system. These two factors could be replaced with a safety factor on the body areas and another linked to the consumer product.

C. <u>Exposure assessment:</u>

Professional (occupational), pharmaceutical and alternative medicine (e.g. aromatherapy) use of fragrances does not fall under the scope of the QRA currently applied by the fragrance industry.

i) Aggregate exposure assessment:

The state of development of the RIFM aggregate exposure model was presented.
Particular issues discussed were:

- Household care products and detergents have been excluded because they do not represent a significant exposure for the consumer. On the other hand, it becomes evident that specific product types can drive the aggregate exposure. The model gives accurate predictions of this exposure.
- The need to identify the uncertainties in the assessment. Several elements of variability are already captured in the sensitivity analysis (e.g. natural variability across people's habits, bodyweights, etc. / level of the fragrance ingredient in the fragrance compound / level of the fragrance compound in the finished product) and the model provides exposure data with a standard deviation. However, the presentation of the uncertainty needs to be more transparent.
- Assumptions on retention. A retention factor of 1 % for a rinse-off product is used based on empirical observations but should be investigated further.
- The problems of how to aggregate exposure at different body areas. It was agreed that these cannot be summed as different lymph nodes are implied. Thus, the aggregate exposure model can only be used to sum the contributions of product types applied to the same site. (NB In the SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation, aggregate exposure to cosmetics products is calculated to be

17.4g/day based on addition of deterministic values for a range of products. The products used in this model account for 96.7% of this figure but it was mentioned that the remaining 3.3 % might deliver at very small locations the most significant dose per unit area).

- The current form of the model assumes that the fragrance allergens accumulate over 24 hours (then the clock is reset and the aggregate exposure restarts from zero). This parameter was not regarded as substantiated.

QRA 2 It was recommended that precise data be collected on the product types driving the exposure. The exposure evaluation needs to be global rather than limited to the product categories of interest to the fragrance industry. Emphasis should be given to understand the consumer exposure to unregulated product types like aromatherapy and OTC products. Occupational exposure also needs to be considered. Attention should be paid to cocktail effects and cross-reacting sensitizers for the calculation of the exposure. For instance, cinnamyl alcohol could quickly get metabolized in the skin into cinnamal therefore cinnamyl alcohol should also be considered when evaluating the consumer exposure to cinnamal.

In respect of occupational exposure for example, the following topics were regarded as important:

- Definition of the scope of professional products to consider (e.g. occupations to include in the model). The participants agreed that non-cosmetic uses of fragrance should be excluded from the model. Furthermore, there as a consensus that this is not possible to examine all professional uses and the work should focus on one or two occupations.
- Definition of the data requirement (e.g. product types, fragrance use levels, exposure scenarios).
- Identification and collection of the relevant data sources (in the literature and in the industry).
- Production of the missing data (via surveys in the industry or at the workplace).

Studies conducted on nurses or hairdressers could be of interest to initiate an occupational exposure assessment.

D. <u>Data sources for developing the QRA:</u>

The participants strongly encouraged the industry to carefully monitor the effectiveness of the QRA via the collection of literature / clinical data and the establishment of a broad dialogue between the industry and the dermatologists.

Relevant clinical data is readily available in the literature and needs to be compiled. The value of clinical data was discussed as it usually gives an indication of the elicitation rate. The participants agreed that this information is, nonetheless, an excellent way of determining whether induction took place. In that sense, data on sensitized people is useful and the evolution of these figures over time can be a marker of the QRA effectiveness. An effective means of data validation is an essential prerequisite for its use.

Several data centres such as ESSCA (European Surveillance System of Contact Allergies) hold important datasets that might be used as basis for a retrospective analysis. The data sources utilized should include information on non-fragrance ingredients. Beyond its application to fragrance materials, it was mentioned that the QRA was used for the risk assessment of transition metals (nickel, chromium) and 5 preservatives, but it remained unclear how the outcome impacted on the market.

E. Further validation of the QRA:

i) Retrospective analysis:

This depends on the availability of comprehensive high quality data (see data sources above). Retrospective analysis of 5 preservatives was regarded as very promising. This is because preservatives are used at relatively constant levels for a given product category, which tends to facilitate the analysis and eliminate some biases.
The retrospective analysis of fragrance ingredients was regarded as more complex (due to the wide range of use levels) but nevertheless very important and the participants strongly encouraged the preparation of a retrospective analysis on individual fragrance ingredients.

ii) Prospective analysis:

This initiative should involve as many stakeholders as possible in the industry and the medical community. The QRA model is based on assumptions and its results inevitably involve some uncertainty. Clinical feedback via an enhanced dialogue with the dermatologists should be used to assess whether the QRA threshold values are adequate. This could be facilitated by developing a system in partnership with ESSCA, IVDK and/or KUL where patients experiencing allergic reactions would be followed up to first understand which consumer product may have caused the problem and secondly determine whether or not fragrance allergens are implied in this problem. Information would be gathered on the alleged product (use level, batch number, etc.) to fill a database linking the exposure and the clinical prevalence. Products reported by the patients (according to the above procedure) should be analysed for IFRA compliance in order to understand whether or not the induction (or the elicitation) reaction is due to the presence of an allergen above its QRA level. Market trends should be monitored to evaluate the risks of induction as early as possible. The industry should also inform the dermatologists as early as possible about new fragrance ingredients placed on the market.
New studies should focus on specific ingredients as it is probably the most robust approach to measure the effectiveness of the QRA. Indeed, the monitoring of fragrance mixes might lead to overlooking the effects of individual fragrance allergens.

Both for retrospective and prospective analyses, the prevalence data of a given allergen should be considered with regard to respective exposure data this should be before and after the application of the QRA. Relative potency in the form of a Sensitization Exposure Quotient (SEQ) was presented. This SEQ seems to provide a fair estimate of the allergens' potency and might be of help for the confirmation of hazard assessments and the adjustment of consumer exposure.

F. Development of IFRA Standards:

It was noted that the companies at the IFRA Board level are very attentive to participate in the development and the implementation of all scientific progresses leading to a better protection of the consumer. The IFRA compliance is important and more efforts should be done by the fragrance industry to ensure that the market effectively complies with the IFRA Standards.

The development of IFRA Standards is regarded as a lengthy and complicated process, as a consequence it may be unable to respond rapidly to new skin sensitization threats. It was mentioned that consumer products with corrected levels of a given fragrance allergen take years to appear on the marketplace. This delayed risk management can translate into the sensitization of a part of the population. As a consequence, secondary prevention measures have to be taken on top of the primary prevention (eg. HICC).

G. General recommendations:

i) Risk assessment:

- Characterize the mode of action of chemically induced allergens and how (and why) it varies between humans and between humans and animals. This includes the processes by which matrix factors influence uptake.
- Identify the potential hazard test replacements/ improvements and the implications for uncertainty of extrapolation.
- What is the suitability of the current data base to inform the process? Is it sufficient yet to enable SAR/QSAR?
- Improve the scientific basis for support of each of the adjustment/ default factors. This needs a better understanding of human variability in response and the elucidation of the reasons for this.
- Develop further the aggregate exposure model. Include co-exposure and cross reactivity of related chemicals.
- Characterize the influence of other factors in a product (eg. irritants) on the allergenicity of individual fragrances.
- Use clinical data to identify the success or not of the safe levels set based on the QRA.
- To facilitate progress on the work on safety factors in particular it was proposed that an ad hoc working group should be established.

ii) Communication:

Participants made several recommendations to the Industry in order to speed up the process and ensure a proactive management of the skin sensitization risks:

- Improve the dialogue with the dermatologists: the dermatologists are the frontline agents to diagnose new skin sensitization issues in the general population. Their feedback is precious and needs to be collected via appropriate channels in order to react immediately when new problems occur. The outcome of this surveillance should be integrated to the IFRA Standards development process.
- In line with this first recommendation, the dermatologists should be made aware as soon as possible about new fragrance ingredients coming on the market. For the time being, there is no way to understand how, when and where the patients have been exposed to a new fragrance allergen. An early understanding of the issue would significantly decrease the number of people sensitized to a new fragrance allergen. The participants agreed that the labelling of fragrance ingredients is likely the most appropriate solution.
- Organize web-based events with the dermatologists (e.g. webinars, forums) to involve them directly and effectively in IFRA Standards development process.

iii) Risk management:

Appropriate risk management measures need to be taken to better inform the consumer on the fragrance allergens content of cosmetic products. The labelling of fragrance allergens contained in all cosmetic products is therefore needed. It was noted that this concept might result in a requirement for the full disclosure of the fragrance formulae composition.

iv) Discussions with regulators:

It has to be recognized by the regulators that several markets (e.g. aromatherapy) are independent of the fragrance industry and it was recommended that the regulator ensures adequate consumer information on these product types.
Furthermore, and regarding products scented by the fragrance industry, the responsibility of the fragrance industry ends at the delivery of an IFRA compliant formula and this is up to the downstream users to ensure the safety of marketed consumer products.

Professor Jim Bridges
Workshop Rapporteur

Appendix 1 – Additional reading on QRA:

- Api, A.-M. *et al.* (2008). Special Issue: Dermal Sensitization Quantitative Risk Assessment for Fragrance Ingredients. Regulatory Toxicology and Pharmacology, **52**(1), 1-73.
- SCCP Opinion on Dermal Sensitisation QRA (SCCP-1153-08).
- Felter, S.P., Robinson, M.K., Basketter. D.A. and Gerberick, G.F. (2002). A review of the scientific basis for uncertainty factors for use in quantitative risk assessment for the induction of allergic contact dermatitis. Contact Dermatitis, **47**(5), 257-266.
- The IFRA-RIFM QRA Informational Booklet (att.10).
- 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.

Appendix 2 – Glossary of abbreviations:

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AEL:	Acceptable Exposure Level
DEP:	Di**e**thyl Phthalate
DG-SANCO:	Directorate General for Health and Consumers
DMSO:	Dimethyl Sulfoxide
DNCB:	2,4-Dinitrochlorobenzene
EC3:	Effective Concentration for a SI of 3 in proliferation of lymph node cells
ESSCA:	European Surveillance System of Contact Allergies
GP:	Guinea Pig
HICC:	4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde
HRIPT:	Human Repeat Insult Patch Testing
IFRA:	International Fragrance Research Association
IVDK:	Information Network of Department of Dermatology
KUL:	Katholieke Universiteit Leuven
LLNA:	Local Lymph Node Assay
MPL:	Maximum Pragmatic Level
NB:	Note Well
NESIL:	No Expected Sensitization Induction Level
NOAEL:	No Oserved Adeverse Effect Level
PT:	Patch Test

QRA:	Quantitative Risk Assessment
QSAR:	Quantitative Structure Activity Relationship
ROAT:	Repeated Open Application Test
SAF:	Safety Assessment Factor
SAR:	Structure Activity Relationship
SEQ:	Sensitization Exposure Quotient
SCCS:	Scientific Committee on Consumer Safety
SG:	Supervisory Group
RFIM:	Research Institute for Fragrance Materials
WoE:	Weight of Evidence

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Recommendations of the IDEA Workshop on

Validity of the QRA Methodology & Possibilities of Further Refinement

March 19-20th, 2013

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

i) Risk assessment (RIFM):

- RIFM QRA Expert Group – reconvened to facilitate progress on the work on safety factors in particular to address the following:
    - Sensitization Assessment Factors - review the scientific basis for support of each of the adjustment/ default factors.
        - Inter-Individual Variability - This needs a better understanding of human variability in response and the elucidation of the reasons for this. Characterize the mode of action of chemically induced allergens and how (and why) it varies between humans and between humans and animals. Identify the potential hazard test replacements/ improvements and the implications for uncertainty of extrapolation.
        - Matrix Effects - processes by which matrix factors influence uptake. Characterize the influence of other factors in a product (e.g. irritants) on the allergenic potential of individual fragrance ingredients.
    - Use clinical data to identify the success or not of the safe levels set based on the QRA.
        - Design a prospective study in collaboration with the relevant stakeholders (e.g. ESSCA, IVDK)
        - How can retrospective data be used - What is the suitability of the current database to inform the process? Is it sufficient yet to enable SAR/QSAR?
    - Consider professional exposure from consumer products (e.g. professional use of hair care products or hand cleansers, etc.)
    - This Expert Group will come into operation as early as possible in order to deliver its first results at the next IDEA QRA Workshop taking place in March 2014. A status update is foreseen (most likely by conference call) before the end of the year.

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- RIFM Aggregate Exposure Task Force – Continue to develop further the aggregate exposure model. Include co-exposure and cross reactivity of related chemicals.

ii) Communication – improve the dialogue with the dermatologists (RIFM and IFRA):

- Expand the dialogue with the dermatologists (RIFM): RIFM has one formal avenue for a regular dialogue with European dermatologists (ESCD Fragrance Working Group). RIFM would like volunteers from the dermatology community to assist in establishing other dermatology working groups. This action is important to quickly and effectively obtain feedback from dermatologists and act as needed.

- Better involve the dermatological community in the Standards development process and ensure the possibility to comment on proposed risk management measures (during the consultation of IFRA Standards). The dermatologist community should be involved as best as possible during the Consultation period taking place before each new IFRA Amendment, by e.g. regularly sharing the proposed new Standards with ESCD, ASCD, EADV and other relevant groups (especially in Asia and South America). It may be envisioned that webinar could be scheduled to all interested parties on the rationale behind the IFRA Standards proposed in the Amendment.

iii) Risk management (IFRA):

- Address with the IFRA Scientific Committee the specific problem of the Maximum Pragmatic Level. This approach should be revoked and only the true QRA levels should be reported in all IFRA Standards.

- Ensure with the help of the IFRA Scientific Committee that all progresses made on the Dermal Sensitization QRA are implemented in the existing IFRA Standards without undue delay. The revision of SAFs and the development of the new RIFM aggregate exposure model should be carefully monitored.

- Set a working group to develop creative solutions in view to better inform the consumer on the presence of potential fragrance allergens in consumer products. The existing communication procedure between the dermatologists and the industry will be extended to more countries and strengthened in view to improve the flow of information between practitioners and the fragrance houses when a fragrance compound is the suspected cause of a skin reaction. The strategic intent behind this communication plan being to ensure that products on the market are safe and comply with scientifically well-founded risk reduction measures, keeping the risk of fragrance allergy to a minimum.

iv) Discussions with the regulators and trade associations (IFRA):

- Continue the dialogue with the regulators and explain that several markets (e.g. aromatherapy, OTC products) are independent of the fragrance industry.

- Continue the dialogue with the trade associations responsible of these markets (e.g. Association of the European Self-Medication Industry). Explain to these associations that the Dermal Sensitization QRA should be applied

wherever it is applicable and appropriate risk management measures should be implemented elsewhere to prevent induction as much as possible.

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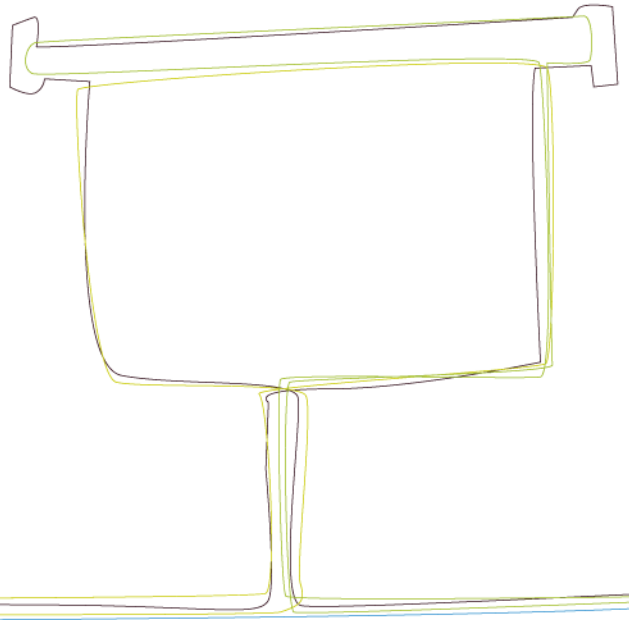
Rapporteur's Progress Report on the IDEA Workshop on

Validity of the QRA Methodology & Possibilities of Further Refinement

March 19-20, 2013

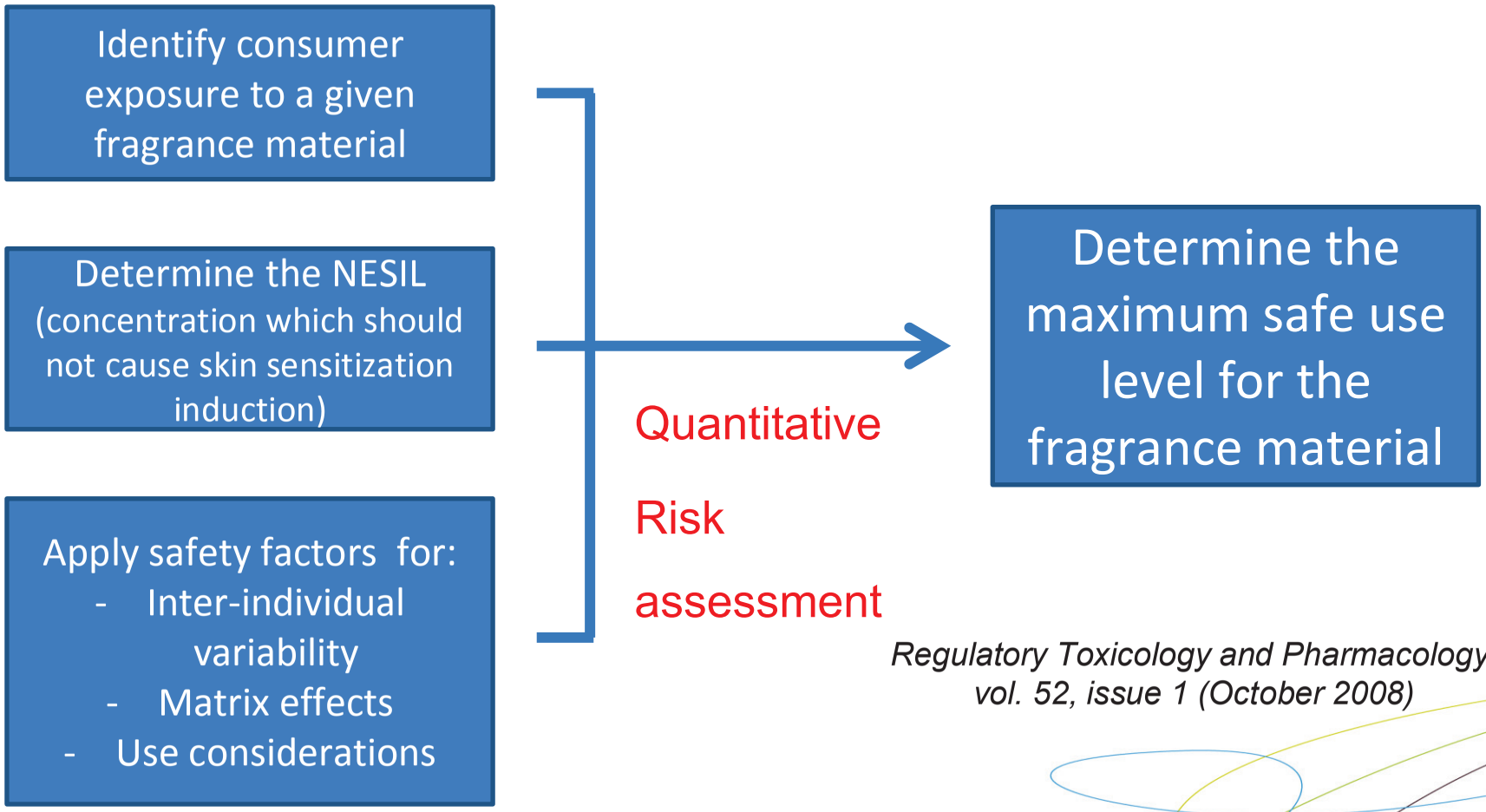


Prof. Jim Bridges
Chairman of the IDEA Supervisory Group

Principles of Allergic Contact Dermatitis

- ACD arises as the result of two essential stages:
  - an induction phase: primes and sensitizes the immune system (CA).
  - an elicitation phase: an immune response is triggered (ACD).
- Both stages appear to involve a thresholded mechanism and thus safe use levels could be derived from an appropriate risk assessment.
- Effective primary prevention (induction) would ultimately minimize the secondary issues (elicitation).
- QRA can be utilised to prevent induction.
- QRA uses the tools available for general RA.

Outline of the QRA methodology



Regulatory Toxicology and Pharmacology, vol. 52, issue 1 (October 2008)

Issues: Hazard identification / characterization

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- Relevance of tests and quality of studies determines the reliability and utility of the NESIL for establishing maximum safe use levels.

- Ban of animal testing is challenging for hazard assessment. New tools show promise. These should be included in the procedure for NESIL determination when properly validated.

Risk Assessment related issues

- Need for a “buffer zone” - technically termed the “Sensitization Assessment Factors” (SAFs) – to account for variability in individuals, differences in testing and using ingredients (matrix effects) and how finished products are used by consumers.

- While the QRA procedure is generally acceptable the SAFs need to be further substantiated.

SAF #1: Inter-individual variability factor

- The current QRA is **intended to protect the general population**.
- It uses a single factor of 10 to cover all sources of variability (age, gender, ethnicity, genetic effects, etc.). Additional allowance needs to be considered for people with compromised skin.
- *Understanding of inter-individual variability* should concentrate on (to be addressed at the next workshop):
  - The ability of skin to allow permeation to occur
  - The enzymatic / metabolic specificities
  - The genetic differences

Inter-individual variability: conclusion

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- This SAF, while based on general toxicological principles, is arbitrary and should be substantiated / reconsidered based on scientific data.

- However the NESIL is usually confirmed by HRIPT (tolerance study on humans) which adds additional precaution. Therefore, the overall approach might be viewed as already sufficiently conservative.

SAF #2: Vehicle or product matrix effects

- The existing scale of 1, 3 and 10 was based on scientific data comparing experimental conditions and real-life scenarios.
- Product matrix and skin permeation are important but **bioavailability** is key to estimating the risk of induction.
- Better consideration needs to be given to potential vehicle effects. (NB the solvents used for LLNA and HRIPT may enhance or lower the observed response).
- Presence of irritants in the matrix require careful consideration.

Conclusion: This SAF needs to be supported by additional scientific data.

SAF #3: Use considerations

- The existing scale was based on scientific data comparing experimental conditions and real-life scenarios.
- HRIPT is conducted under **full-occlusion**. This may result in an overly conservative safety factor depending on consumer product use.
- The assignment of use SAF should be reviewed in light of new scientific literature for potential update.

Refinement of exposure assessment

- **Professional** use of fragrance is currently not covered.
  - Include professional use of consumer products.
  - Give more emphasis to understand unregulated product types.
- The aggregate exposure model developed by RIFM was regarded appropriate and will be incorporated into the QRA:
  - Fine-tune how exposure can be aggregated at **different body areas.**
  - Substantiate the choice of an accumulation period of 24 hours.

Exposure assessment: further work

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- Investigate further the assumptions on **retention** (1% for rinse-off products) which are purely empirical.
- Consider potential **cross-reacting sensitizers** for the calculation of exposure.
- Evaluate the exposure at a global level (not limit to product categories of interest to the fragrance industry).

Documenting effectiveness of the QRA

- Need to carefully **monitor the effectiveness** of the QRA via the collection of clinical data and a broad dialogue between industry and dermatologists.

- Two sources of clinical data were identified:
  - **Retrospective analysis**
  - **Prospective analysis**

  These data could be developed in partnership with networks like ESSCA and IVDK.

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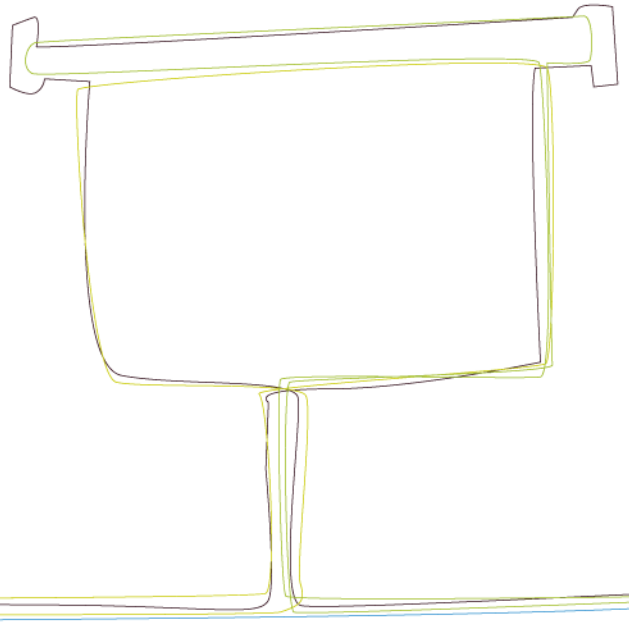
Progress report on actions taken

Validity of the QRA Methodology & Possibilities of Further Refinement



Process and timeframe

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- Recommendations from workshop:
  - pertaining to risk assessment will be addressed by RIFM.
  - pertaining to risk management and dialogue with trade associations / regulators will be addressed by IFRA.

- Preliminary results are already available and consolidated results will be presented at the next QRA workshop (March 2014).

General actions needed

- Skin sensitization is a general issue. QRA has limited value if not applied by everyone.
- Market trends and new fragrance ingredients need to be monitored to evaluate the risk of induction and dermatologists should be informed immediately.
- Ensure **compliance** with the IFRA Standards across the value chain.
- Other industries (OTC products, aromatherapy) should be sensitized to the problem of contact allergy.

Risk assessment

- RIFM reconvened its QRA Expert Group to:
  - **Substantiate the three SAFs.** (ONGOING)
  - Design **prospective studies** in collaboration with the dermatology community to measure the effectiveness of the QRA. (ONGOING)
  - Determine whether existing **retrospective data** can be used to build predictive models). (DONE)
  - Include **professional** exposure in the QRA methodology (ONGOING)
- With its Aggregate Exposure TF, RIFM continues to further develop the **aggregate exposure model** and incorporate it into the QRA methodology (ONGOING)

Improve the dialogue with the dermatologists

- RIFM is expanding its formal interactions with the international dermatology community. (ONGOING)
- IFRA is working on the improvement of the communication procedure between the dermatology community and the Industry (upstream and downstream).
- IFRA amended its **IFRA Standards development process** to include the dermatology community. The draft IFRA Standards will be shared for consultation with ESCD, ASCD, EADV and other relevant groups. (DONE)

Risk Management (ONGOING)

- IFRA is committed to **implement the refined QRA methodology**. The currently 81 IFRA Standards based on QRA will be progressively updated from the next Amendment to the IFRA Code of Practice.
- Work on **better informing the consumer** on the presence of fragrance allergens in consumer products going beyond QRA and targeting secondary prevention.
- IFRA is revamping its **compliance program** to ensure that its members apply the QRA methodology.

Dialogue with regulators/trade associations

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- Continue dialogue with regulators and explain that several markets are not properly regulated to prevent induction of skin sensitization to fragrance allergens. A dialogue has been established with **EMEA** (the European Medicines Agency). (ONGOING)

- Contact trade associations and strongly recommend the application of QRA to their industries. A dialogue has been established with **AESGP** (the Association of the European Self-Medication Industry) and CHPA in the USA. (ONGOING)

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Thank you for your attention

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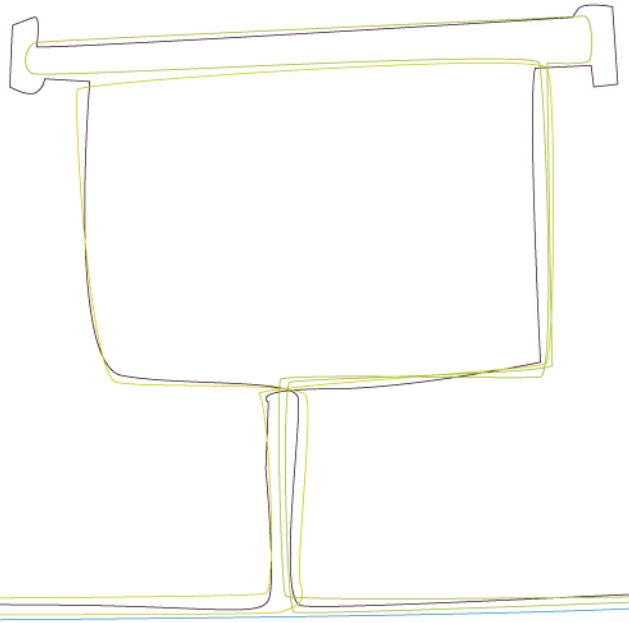

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