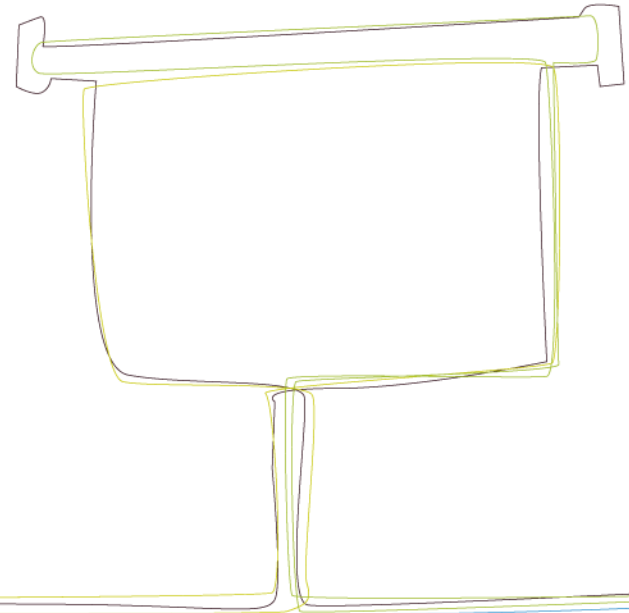


Risk Assessment of Pre- & Pro-Haptens

2015 Update

Dr. Alain Chaintreau
Chair of the IDEA Hydroperoxide TF

Dr. Matthias Vey
IDEA Management Team

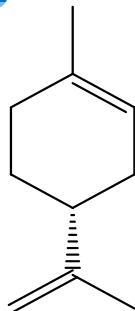


Risk Assessment of Pre- & Pro-Haptens

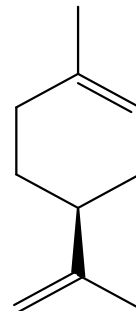
The concern about pre- and pro-haptens causing contact allergy through fragrances has been taken very seriously by IDEA, because some very prominent and widely used fragrance ingredients (Linalool and Limonene), while being themselves (if at all) only very mild sensitizers, can under certain conditions oxidise to potent allergens (haptens).

Limonene and Citrus oils

Key fragrance ingredients



R (*d*)-limonene

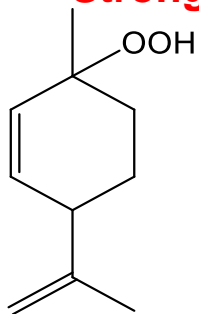


S (*l*)-limonene

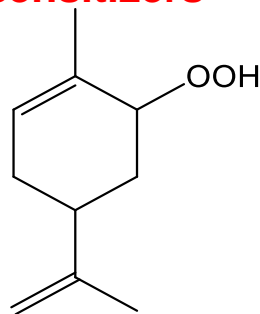
Low sensitizing potential

Primary oxidation products

Strong sensitizers

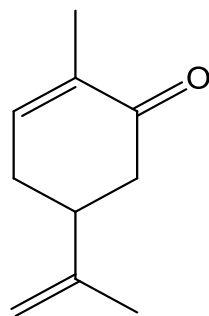


limonene-1-hydroperoxide

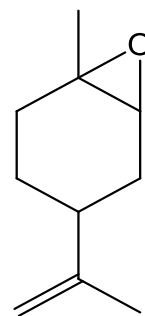


limonene-2-hydroperoxide

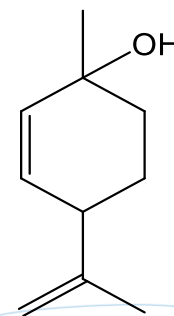
Secondary oxidation products



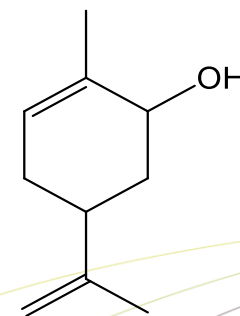
carvone



limonene epoxide

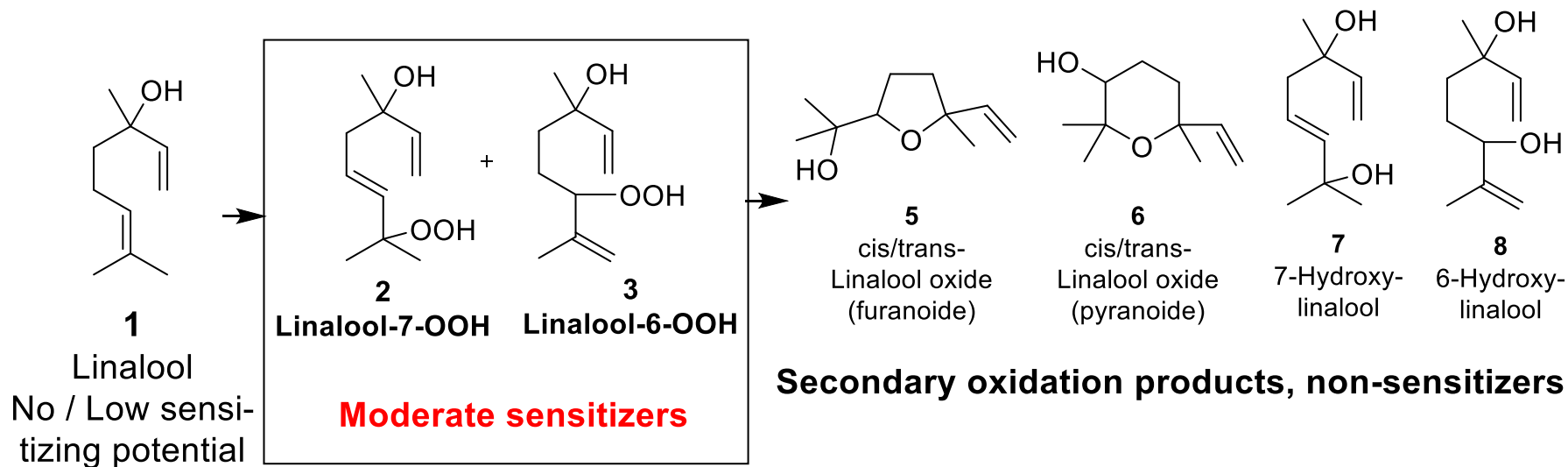


limonene alcohols



Lavender oil and Linalool

Key fragrance ingredients



Risk Assessment of Pre- & Pro-Haptens



The concern about formation of potent haptens has been fuelled by worrying clinical data, which is a high frequency of positive patch test reactions to 'oxidized Linalool or Limonene' (containing respective hydroperoxides).

The transition to potent haptens of Linalool and / or Limonene contained in fragranced products is a possible explanation for the clinical observations.

Risk Assessment of Pre- & Pro-Haptens

IDEA in a total of 3 workshops looked at:

- the clinical data, the hypothesized transformations (including hydrolysis),
- the question of significant exposure to hydroperoxides from fragranced products,
- the challenge of developing an analytical method to provide reliable analytical evidence.

It formulated a program that will drive analytical and mechanistic understanding of these potential reactions. It will eventually allow the development of a framework, broadly applicable to address the Pre/Pro-Hapten question.

Workshops on Pre- and Pro-Haptens



The workshops were designed to:

- Progress the analytical development for following hapten formation from pre-/pro- haptens in raw materials and finished products as well as on the skin.
- Obtain an agreement on what is known or unknown and lay out pathways to close the knowledge gaps.
- Work towards solid documentation of current knowledge and its implementation for risk management purposes.

Conclusions



- On the clinical side, high sensitization frequency to oxidized terpenes as shown by patch testing continues to be reported.
- Additional efforts are needed to bridge the knowledge gap between clinical observations and exposure to pre- and pro-haptens.
- On the investigative side, better understanding of skin metabolism should be a priority.
- The modelling of metabolic pathways via QSAR/SAR shows potential but requires further confirmation across a wider range of chemicals.
- QRA methodology can incorporate pre- and pro-haptens but will need further adaptation.

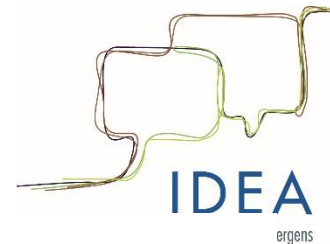
Next implementation steps

WG recommends integrating Pre- haptens (hydroperoxides) in the QRA.

Next investigative steps

- There is a need for a clear understanding of the contribution of the consumer products (under the scope of the QRA) to the clinical picture.
- Patch test materials used and consumer products retrieved from patients with a positive patch test for oxidized Linalool or Limonene should be analysed for hydroperoxide content.

Next investigative steps (II)

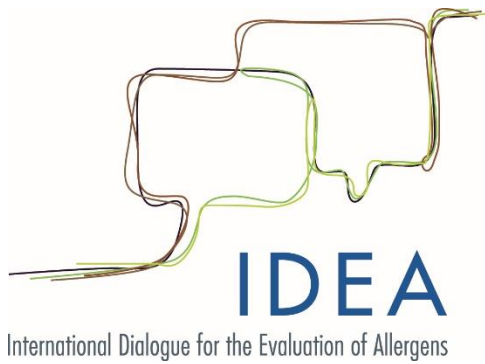


Pre-haptens (hydrolysis in product):

- Breakdown of hydrolysable precursors of potential sensitizers in the consumer products for risk assessment, e.g. Cinnamal diethylacetal which may be hydrolyzed to Cinnamic aldehyde under certain conditions.

Pro-haptens (hydrolysis on/in skin, through metabolic pathways):

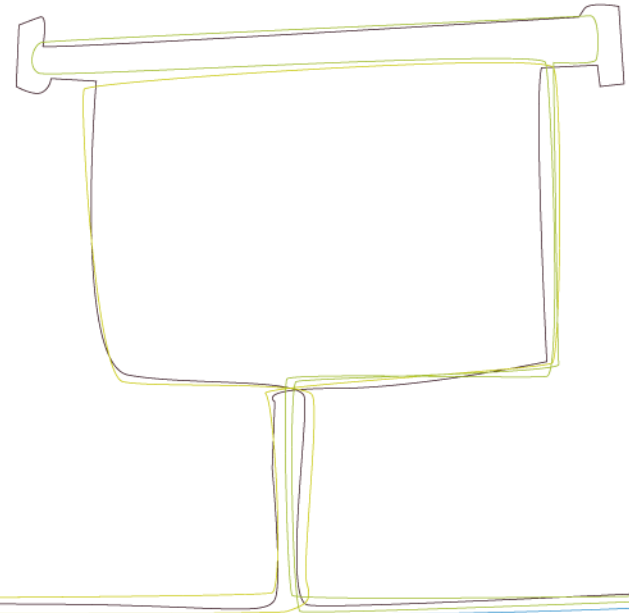
- Activation in the skin may contribute to hapten formation.
- Balance of activation / deactivation.
- Appropriate in-vitro test systems (e.g. metabolic activating systems).
- All of the above is largely covered by current HRIPT.



IDEA Annual Review 2015

Analytical efforts in support of pre-hapten assessment

IDEA Hydroperoxides TF



Purpose of the Hydroperoxides Task Force



- The purpose of the Task Force is to provide analytical data in support of interpretation of Patch Test reactions to materials containing the hydroperoxides of Limonene and Linalool*
- To achieve this, the ultimate objective is to provide methodology to enable the confirmation and quantitative measurement for Limonene and Linalool hydroperoxides in complex mixtures (including final consumer products) at 5000ppm and within agreed accuracy ranges; and to provide methodology for qualitative analysis (confirmatory purposes) at 500ppm.
- An intermediate objective is to provide methodology to achieve the above performance in fragrance ingredients and mixtures thereof.

*Pre-requisit: make available pure samples of each hydroperoxide.

- Indirect measurements to overcome the instability of hydroperoxides.
 - By reduction
 - By silylation
- Direct measurements under mild conditions.
 - Room temperature
- Testing on spiked samples.

Output of the Hydroperoxides Task Force



To apply QRA to haptens formed from pre-haptens over time, a solid analytical understanding is important:

- Qualified reference materials were made available to meet analytical needs.
- Concentrations of hydroperoxides have been measured in fragrance ingredients and a limited number of fine fragrances and deodorants.
- Further analytical work should focus on the actual hydroperoxide levels in different product matrices.
- Early leads for assessing hydroperoxides in consumer products.

The methods complement each other.

Next steps for the Hydroperoxides TF

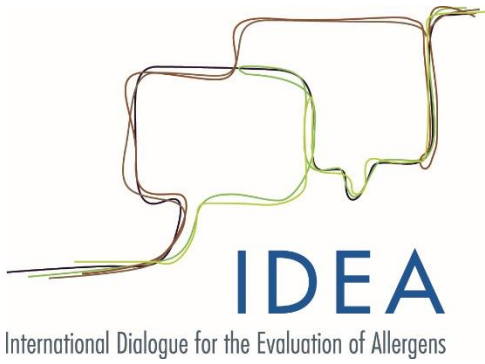
For routine use of these methods, we still need to:

- Assess the impact of analytical interferences on the quantification of hydroperoxides
- Assess the variability of selected methods
- Develop sample preparation methods to be compatible with these hydroperoxides and applicable to cosmetic products
- Confirm that methods are applicable to the various consumer product types
- Organize a ring test in consumer products

Involvement of the Hydroperoxides TF

The Standard development and qualification involved:

Academia	Industry
University of Lille (France)	Chanel
University of Gothenburg (Sweden)	IFF
University of Strasbourg (France)	Firmenich
University of Stockholm (Sweden)	Robertet
University of Liverpool (UK)	Givaudan
	DSM



Thank you for
your attention

