**International Dialogue for the Evaluation of Allergens (IDEA)**

# Fifth IDEA workshop on pre- and pro- haptens

## Key Conclusions

Brussels – October 16-17, 2019

## Fifth IDEA pre- and pro- haptens workshop

# Key conclusions – Day 1 (pre-haptens)

- The workshop took a deep dive into the extensive datasets generated both on the clinical and the analytical side to better understand positive patch test reactions to oxidized Limonene and Linalool.
- There is growing consensus that Limonene and Linalool containing products under the control of the fragrance industry may not be the main cause of the induction of contact allergy today. Other Limonene/Linalool exposure scenarios are more likely to be the major causes and need to be identified.
- Additional clinical studies are necessary:
  - ROAT with dilution series.
  - Use tests with suspected products.
  - Studies on exposure scenarios and confounding factors of affected patients (e.g. detailed and validated questioning).
- Further analytical work is needed:
  - On suspected products retrieved from patients to quantify elicitation levels.
  - On products with high terpene content to identify potential induction sources.
- Depending upon the outcome of the analytical work, the use of antioxidants and/or scavengers may be further optimized.
- Based on the above, further work may be needed to identify the circumstances involved in the induction of contact allergy to oxidized terpenes.

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# Key conclusions – Day 2 (pro-haptens)

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- To set the scene, the workshop reviewed current knowledge on phase I and phase II metabolism with a focus on skin.
- The terminology of pro- (and pre-) haptens was revisited, reminding that the differentiation is based on biotic and/or abiotic activation. However, a chemical may be activated in both ways. Among fragrance chemicals, there is a lack of concrete and well documented examples of pure pro- haptens.
- Discussion of pro- haptens (that may also be pre-haptens), relevant to the fragrance industry concluded that:
  - Animal models (e.g. LLNA) provide a good identification of hazard and a reasonable assessment of potency for use in risk assessment.
  - There is a good correlation between *in vitro* assays with LLNA and human data, even if the underlying mechanisms are not fully understood. While there is room for improvement, it is questionable whether there is an urgent need.
  - *In silico* tools are a useful complement in hazard identification and potency characterization, assuming the chemical domain is covered.
- Looking ahead we need:
  - Concrete case studies on pure pro- haptens that could serve as example for the modeling and the hazard/risk assessment as we currently do.
  - Continue to improve *in silico* models as new data get generated.
  - Further data on xenobiotic metabolism including phase III would be useful.
  - Further work to better understand the impact of oxidative stress on the activation of pro- haptens should be considered.

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# Thank you for your attention