IDEA Pre- and pro- haptens Workshop
October 16 and 17, 2019

Courtyard by Marriott Brussels Hotel
Avenue des Olympiades 6,
1140 Brussels, Belgium

Final Draft Agenda

OCTOBER 16, 2019 - SUGESTED TOPICS FOR DISCUSSION ON PRE-HAPTENS

Starting time: 09.15, Meeting room: Antwerp

9.15 – 9.30 Introduction into the 2 days by Hans Bender (IDEA Moderator) and Jim Bridges (Chair IDEA Supervisory Group)

Six years in IDEA – what is our progress in understanding and managing the pre-hapten question?
Spontaneous oxidation of terpenes in presence of air to form sensitising hydroperoxides was a potential risk highlighted by the SCCS opinion and investigated within IDEA. Over these six years many additional studies were published by dermatologists on patch test data and potential elicitation by hydroperoxides. In parallel IDEA developed, validated and applied analytical methods for hydroperoxide detection in products. These two parallel information streams do not yet match up and it is unclear how the clinical picture can be related to the analytical data.
The workshop brings together experts helping to interpret the data and define potential next steps to resolve this conundrum. Experts were invited to provide their view of the issue and include in their presentation a discussion of questions listed below, as far as they have a view on them.

Questions:

- **Clinical picture** – what does it tell us? How do we explain the high rates of positive reactions? What do we know on (i) reproducibility of the reactions? (ii) How to interpret high rate of irritant/doubtful reactions? (iii) How to interpret concomitant reactions to other allergens?
- **Breath of the problem:** What do we know clinically on other molecules next to Linalool and Limonene?
- **Analytical methods** – are the analytical methods reliable enough to answer the questions raised? If not, what needs to be done in addition?
- **Analytical data:** Do we trust the analytical data? Are there reasons that there might be underestimation of true HP levels? Would more analytical data change our interpretation, and if so on which products?

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- **Is our knowledge on induction and elicitation thresholds sufficient** (for linalool and limonene hydroperoxides)? What are, based on our data esp. from animal tests, the NESIL values for hydroperoxides?
- **Interpretation: How do we bring the clinical picture and the analytical data together?**
- **Which element are we missing and what next research steps are proposed?**

The following speakers (in alphabetical order) have been confirmed for sharing their view on one or more of the questions listed above.

09.30 – 11.00 Speaker group 1 (each speaker has about 30 minutes for presenting)
Johanna Bråred Christensson (University of Gothenburg), Carsten Goebel (Coty), Jean-Pierre Lepoittevin (University of Strasbourg)

11.00 - 11.15 Coffee break

11.15 – 12.45 Speaker group 2 (each speaker has about 30 minutes for presenting)
Andreas Natsch (Givaudan), Ahmed Ramzi (University of Stockholm), Axel Schnuch (University of Göttingen)

12.45 – 14.00 Lunch

14.00 – 15.30 General discussion
General discussion and key conclusions should focus on above questions and next steps to be taken under IDEA.
Moderated by Hans Bender

15.30 – 15.45 Coffee break

15.45 – 17.00 Key conclusions pre-haptens
Moderated by Hans Bender

19.30 Dinner location tbc

OCTOBER 17, 2019 - SUGESTED TOPICS FOR DISCUSSION ON PRO-HAPTENS

Starting time 9.00, Meeting room: Antwerp

9.00 – 9.15 Introduction into day 2 by Hans Bender and Jim Bridges

How to detect and evaluate pro-haptens in a reliable way with NAMs
It had been agreed at earlier workshops, that for pro-haptens the risk assessment can be done as for haptens, once a NESIL has been determined. When using animal tests, the NESIL is derived equally for pro-haptens and haptens. This brings the open questions re prohapten to the question how to assess them without animal testing using NAM.

9.15 – 09.45 Introduction: Reactive metabolites, their nature and toxicity
Speaker: Helmut Greim, Member IDEA Supervisory Group

Presentations:
9.45 – 10.30 Skin xenobiotic metabolism and review of structural consideration - What are the known fragrance prohaptens and their metabolic pathways leading to activation (including specific consideration of the mouse ear cf human skin) and other factors affecting it. How frequent are they in the fragrance universe?
Speaker: Jean-Pierre Lepoittevin, University Strasbourg

10.30 – 10.45 Coffee break

10.45 – 11.30 Xenobiotic metabolising capabilities of cell preparations used in KE1, KE2 and KE3 tests.
Speaker: Franz Oesch, Johannes Gutenberg University Mainz

11.30 – 12.15 How good are current NAMs to predict prohaptens – what do we miss and what do we miss in the fragrance universe?
Speaker: David Basketter, Consultant

12.15 – 13.30 Lunch

13.30 – 14.15 The effectiveness of in silico methods in predicting the formation of active metabolites.
Speaker: Steve Enoch, Liverpool John Moores University

14.15 – 15.15 General discussion
Considering the following questions:
Do we need to ensure that xenobiotic metabolism is adequately represented in in vitro tests?
How can we make sure pro-haptens are not missed in an ITS/defined approach applied to fragrance molecules?
Moderated by Hans Bender

15.15 - 15.30 Coffee break

15.30 - 17.00 Key conclusions pro-haptens
Moderated by Hans Bender

17.00 Closure of the workshop by Jim Bridges