IDEA
International Dialogue for the Evaluation of Allergens

Final Report on the IDEA Workshop on the

Quantitative Risk Assessment [QRA] based on New Approach Methodologies [NAMs]

December 10, 2019

The Dominican Hotel
Rue Léopold 9, 1000 Brussels, Belgium

This event was designed to build on progress that had been made a year earlier at an IDEA workshop titled: *Characterisation and Categorisation of Allergens* [December 12th, 2018].

A major aim of the 2019 workshop was to build on elements identified previously as being of pivotal importance for building a framework for the confident assessment of No Expected Sensitisation Induction Levels [NESILs] using NAMs.

Moderator: H Bender; **Rapporteur:** I Kimber

Also, in attendance:

A Api (by telephone), N Alépée, D Basketter, F Boislevé, B Blömeke, M Bruze, P-J Coenraads [SCCS observer], G Ellis, S Enoch, N Gilmour, C Goebel, C Gonzalez, H Greim, P Griem, A Irizar, M Klaric, G Manikas [DG Grow, observer], A Natsch, R Liska, P Kern, M Vey.

Presentations

Viable metabolic systems and how to assess pro-haptens and pre-haptens with NAMs: *David Basketter* [*for Jim Bridges*]

Quality assurance in NAMs and limitations for materials with limited solubility: *Andreas Natsch*

Confidence assessment: *Roman Liska*

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Criteria that should be applied to a reference chemical potency list [RCPL] for fragrance materials: *Amaia Irizar*

Case studies showing identification of NESIL with NAMs by RIFM: *Anne Marie Api*

Weight of individual parameters measured in NAMs: meta-analysis and how it can be applied to NESIL determination – case studies: *Andreas Natsch*

Take home messages

Viable metabolic systems and how to assess pro-haptens and pre-haptens with NAMs: *David Basketter [for Jim Bridges]*

- Substances that oxidise quickly to skin sensitising species are identified in predictive tests
- Substances that oxidise slowly to skin sensitising species can be important clinically, but there is a lack of in vivo or in vitro methods for their predictive identification
- Further work is necessary to characterise the mechanisms involved in the induction of skin sensitisation to oxidised terpenes
- There is little evidence that currently available NAMs fail to identify the hazard of fragrance sensitisation that is dependent upon indirect haptenation (pre- and pro-haptens)
- Perhaps all known indirect fragrance sensitisers can function as pre-haptens
- It may be that currently available NAMs do not properly assess skin sensitising potency, but metabolic competence failures are likely to be only a part of this problem

Quality assurance in NAMs and limitation for materials with limited solubility: *Andreas Natsch*

- The nature of NAMs facilitates the adoption of more rigorous quality assurance measures than were feasible for in vivo studies
- KeratinoSens, Direct Peptide Reactivity Assay (DPRA) and the kinetic DPRA (kDPRA) display reproducibility over time
- Fewer data are available for the human Cell Line Activation Test (hCLAT), but quantitative data appear to correlate well with KeratinoSens
- The use of 'proficiency chemicals' provides a mechanism for assuring the proficiency of laboratories
- Concerns have been expressed about variable solubility of test chemicals in NAMs. However, for KeratinoSens and hCLAT some, but few, false negative results appear to be attributable to limited solubility

- At the test concentration used in the DPRA (5mM) precipitation of some test chemicals is observed. However, it has been reported that this has little impact on predictive accuracy

Confidence assessment: *Roman Liska*

- Current approaches to evaluation of test performance have important limitations. There is, therefore, a need for a new approach
- An alternative performance assessment: reproducibility and predictive capacity should be based on probability – combined with expert judgement
- Such an approach would better facilitate comparison of methods and defined approaches, and characterisation of data variability

Criteria that should be applied to a reference chemical potency list [RCPL] for fragrance materials: *Amaia Irizar*

- A reliable RCPL would facilitate assessment of relative skin sensitising potency from NAMs, as well as providing a source of performance standards and positive controls
- It is possible to build upon, but improve, previously published approaches
- There is a need to agree objective criteria for animal (local lymph node assay) and human data
- It is proposed that a small task force is established to oversee development of an RPCL that would support the use of NAMs for both hazard identification and measurement of relative skin sensitising potency
- This task force would also be charged with addressing a number of considerations, including, for instance: whether reference chemicals other than fragrance materials should be included, and whether indirect haptens are included among reference chemicals

Case studies showing identification of NESIL with NAMs by RIFM: *Anne Marie Api*

- RIFM is committed to using NAMs for assessment of skin sensitising potency, and uses a Dermal Sensitisation Threshold (DST) metric to identify a level of exposure below which there is no appreciable risk of sensitisation
- RIFM has engaged in re-categorisation of skin sensitisation potency of reference chemicals based upon use of all available data
- Multiple sources of information are used when evaluating the sensitising activity of a fragrance material, including physico-chemical properties, including absorption and metabolism, in vitro/in chemico data, information from animal (mouse and guinea pig) studies and human data

- An illustrative example was provided using cinnamyl acetate as the chemical of interest

Weight of individual parameters measured in NAMs: meta-analysis and how it can be applied to NESIL determination – case studies: *Andreas Natsch*

- Quantitative parameters available from validated in vitro methods were described
- Combining data from different NAMs improves predictivity – and the combination of data on peptide reactivity with information from a cellular test appears to provide the most accurate predictions
- Case studies were provided that illustrated derivation of NESILs without animal data
- Assessments can be made using either domain models (for structurally closely related chemicals), or a global model
- For further information see: Natsch et al (2015) Predicting skin sensitizer potency based on in vitro data from KeratinoSens and kinetic peptide binding: global versus domain-based assessment. Toxicol Sci 143, 319-332; Natsch et al (2018) Deriving a no expected sensitization induction level for fragrance ingredients without animal testing: an integrated approach applied to specific case studies. Toxicol Sci 165, 170-185

Key Conclusions: Final Statement

- Reconfirming the outcome of the October 2019 IDEA workshop, hazard identification by NAMs of pre- and pro-haptens does not pose a significant problem
- The December 2019 workshop laid the foundation for creation of an industry-wide Reference Chemical Potency List (RCPL). This would provide a list of chemicals, ranked by skin sensitising potency based upon a consensus review of all available in vivo data (human and animal), together with chemical information
- The above is critical for the ultimate development of robust potency measurements based on the use of NAMs for the purposes of risk assessment
- Being able to interrogate the NAM approaches for potency assessment would facilitate the identification of key drivers of sensitising potency
- The workshop participants recommended that a small task force is established to develop the RCPL

Ian Kimber
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