IDEA
International Dialogue for the Evaluation of Allergens

IDEA Workshop on the

replacement of animal testing in QRA for skin sensitisation

Final Agenda

May 16-17, 2018

Hotel Amigo
Rue de l'Amigo 1, 1000 Brussels (Belgium)
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Defining a quantitative non animal testing framework for using information from case studies for skin sensitisation QRA for fragrance materials

Workshop objectives

To bring together different parties who have shown potentially promising methodologies for quantitative assessment of potency. IDEA provides the opportunity for companies/stakeholders to be part of a multi-stakeholder forum of experts working in a transparent process.

To share case studies explaining the application and current status of the approaches using only non-animal derived data for the determination of a non-expected sensitization induction level (NESIL) to serve as point of departure in quantitative risk assessment (QRA).

To facilitate open discussion on the shared approaches with the interest of further progression in this area.

Rationale

IDEA is committed to the integration of non-animal data to replace the LLNA for risk assessment. This is a goal shared by various stakeholders such as the EU Joint Research Centre (JRC), which is interested in liaising with the IDEA project. The workshop is intending to build on the OECD defined approaches with a focus on the use of these for deriving potency information.
The case studies presented should focus on NESIL derivation and not just cover the attribution of chemicals into potency classes (e.g. GHS 1A and 1B or ECETOC classes).

IDEA Management Team

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The final recommendation should be scientifically robust enough to gain endorsement from the wider scientific stakeholders and become an integral part of the methodology used to perform risk assessment for skin sensitisers through the QRA.

Guidelines for case studies

It is requested that participants present, through a case study they have been actively involved with, the approach they favour for the determination of a NESIL for use in risk assessment. This must include consideration of the level of uncertainty of the assessment and how this may be managed through the assessment process.

Speakers are expected to provide sufficient detail of their approach for all the participants to be able to understand how the NESIL is derived and to enable all to review the data gaps and possible synergies from the different approaches.

The case study (one or a few fragrance molecules of participants choice) should cover:
(1) The data relied on and its sources (in vitro, in silico, ...).
(2) Basis for dose selection and reason for benchmark selection.
(3) Basis for calculations used and whether the methodology of calculation is public, and if not, whether access will be given to the methodology of calculation or whether it will remain proprietory,
(4) The interpretation of the value derived and how it could be used for risk assessment. Note: The case studies presented should focus on NESIL derivation and not just cover the attribution of chemicals into potency classes (e.g. GHS 1A and 1B or ECETOC classes).
(5) Measure of the uncertainty involved / approach how uncertainty can be evaluated.

Principal outcome

The output of the workshop, including presentations, will be made publicly available within the IDEA platform (www.ideaproject.info). The workshop should lead towards a weight of evidence based integrated approach.
The workshop proceedings could further be helpful for the ongoing OECD project on the development of test guidelines in which the JRC is co-leading together with US and Canada.

Workshop participants:

Hans Bender (IDEA Management Team, Moderator of the workshop)
James Bridges (IDEA Supervisory Group, *Rapporteur* of the workshop)
Silvia Casati (JRC) (Speaker)
Federica De Gaetano (DG Grow) (Observer)
Bertrand Desprez (Cosmetics Europe) (Observer)
Graham Ellis (IDEA Management Team)
Nicola Gilmour (Unilever) (Speaker)
Carsten Goebel (Coty) (Speaker)
Cecile Gonzalez (IDEA Management Team)
Helmut Greim (IDEA Supervisory Group)
Hervé Groux (InmunoSearch) (Speaker)
Morihito Hirota (Shiseido) (Speaker)
Amaia Irizar (IFRA) (Consultant)
Petra Kern (P&G) (Speaker)
Charles Laroche (IDEA Management Team)
George Manika (DG Grow) (Observer)
Masaaki Miyazawa (Kao) (Speaker)
Andreas Natsch (Givaudan) (Speaker)
Devin O'Brien (RIFM) (Speaker)
Olga Tkachenko (DG Grow) (Observer)
Matthias Vey (IDEA Management Team)

Agenda:

May 16th, 2018

12:00 – 13:00 **Lunch**

13:00 - 13:10 **Workshop opening**

Matthias Vey and Hans Bender (IDEA Management Team)

13:10 – 13:25 **Status OECD activities**

Speaker: Silvia Casati (JRC)

13:25 – 14:10 **Case Study 1: Deriving a no expected sensitization induction level for fragrance ingredients without animal testing: An integrated approach applied to specific case studies**

Includes the approach using KeratinoSens and kinetic peptide reactivity data presented as OECD case study was used to derive NESIL; applied to 15 molecules with known LLNA EC3, human NOEL and human NOEL; applied to new molecules later tested in LLNA and new molecules no longer tested in LLNA and uncertainty analysis included with a read across approach.

Speaker: Andreas Natsch (Givaudan)

14:10 – 14:55 **Case Study 2: Derivation of skin sensitization potency using the Bayesian Net Integrated Testing Strategy**

The use of data addressing key events in the AOP combined with physical chemicals properties and in silico data to predict skin sensitization potency which can be used as a NESIL in a QRA. Information from analogue chemicals will be used to strengthen the prediction and uncertainties in the approach will be discussed.

Speaker: Petra Kern (P&G)

14:55 – 15:25 **Coffee break**

15:25 – 16:10 **Case Study 3: A Proposal using an artificial neural network (ANN) model predicting LLNA EC3 to support skin sensitization risk assessment**

In order to predict skin sensitization potency, a combined evaluation using parameters reflecting the key events in the AOP seems reasonable. In this workshop, skin sensitization risk assessment models based on the ANN analysis of parameters derived from multiple in vitro/in silico tests are proposed.

Speaker: Morihito Hirota (Shiseido)

16:10 – 16:55 **Case Study 4: AOP-based bottom-up approach using in vitro tests and Bayesian network for skin sensitization risk assessment**

Binary test battery of KeratinoSens and h-CLAT is first used to classify a non-sensitizer as a part of bottom-up approach. Then, if a test chemical is considered a sensitizer, a modified potency classification from Bayesian network ITS-3 is used to derive an EC3 value, taking into account uncertainties like under-predictions for potency classification.

Speaker: Masaaki Miyazawa (Kao)

16:55 – 17:30 **Wrap up of Day 1**

Hans Bender

Dinner

19:30 – 22:00 **Brussels – Amigo Hotel**

May 17th, 2018

08:30 – 09:00 **Coffee**

09:00 – 09:15 **Introduction and objectives of Day 2**

Hans Bender

09:15 – 10:00 **Case Study 5: Non-animal skin sensitization risk assessment for fragrance ingredients – a Weight-of-Evidence approach using in silico, in vitro and read-across data.**

The approach predicts the skin sensitization potency class using the DC ITS SkinSens online tool. It follows the Bayesian integrated testing strategy (Jaworska et al 2015) and further includes running the OECD toolbox for analogues. At the end all available information is used in a WoE approach, including analogue and human data, to come to a prediction of a surrogate EC3/NESIL and to dimension uncertainty.

Speaker: Carsten Goebel (Coty)

10:00 – 10:45 **Case Study 6: Next generation Integrated Strategy for Skin Allergy Risk Assessment (SARA)**

Our next generation integrated approach to skin allergy risk assessment (SARA) is a tiered model-based approach that predicts the probability of human skin sensitisation occurring following a given product exposure, with explicit uncertainty. The first tier is a probabilistic, weight of evidence (WoE) human potency model designed to use historical in vivo (HRIPT), in vitro (DPRA, Keratinosens, hCLAT, SENS-IS and U-SENS) and in silico (DEREK-NEXUS) hazard information to inform an initial prediction of human skin allergy risk which can be combined with an applied dose model. A skin toxicokinetic (TK) model may also

be utilised as an additional tier that can further reduce uncertainty in the risk prediction from the clinical potency model by extrapolating from the HRIPT exposure to a market scenario.

Speaker: Nicola Gilmour (Unilever)

10:45 – 11:15 **Coffee break**

11:15 – 12:00 **Case Study 7: Using the SENS-IS assay to evaluate fragrance ingredients' no expected sensitization induction level (NESIL). A comparison to LLNA derived EC3 data**

The SENS-IS assay provides a way to measure skin sensitization potency by deriving a no sensitization signal dose on human 3D epidermis model. Using a group of 20 fragrance ingredients with known LLNA EC3 and human data we analysed the correlation between in vivo and in vitro measured NESIL. The importance of vehicle and uncertainty analysis will be discussed.

Speaker: Hervé Groux (ImmunoSearch)

12:00 – 12:30 **An interim report of the RIFM AAT Dermal Sensitization Research Program**

Speaker: Devin O'Brien (RIFM)

12:30 – 13:30 **Lunch break**

13:30 – 16:00 **Brainstorming - Analysis of synergies, data gaps, uncertainties, next steps**

Rapporteur of the IDEA workshop: Prof. Jim Bridges

16:00 – 16:15 **Coffee break**

16:15 – 16:45 **Key conclusions and recommended actions**

Hans Bender, All

16:45 – 17:00 **End of Day 2 and workshop closing**

Matthias Vey