IDEA WORKSHOP

PROJECT: Skin Sensitisation Risk Assessment: NAMs and Derivation of NESILs

Working towards non-animal risk assessment for skin sensitising chemicals- developing the IDEA strategy

OCTOBER 10, 2024 (online)

A SUMMARY

(Final December 10, 2024)

Attendees

Nathalie Alépée (L'Oréal), Anne Marie Api (RIFM), Hans Bender (IDEA MT), Fanny Boislève (Chanel), Jim Bridges (IDEA SG Chair), Silvia Casati (JRC), Peter Jan Coenraads (SCCS Observer), Emanuela Corsini (University of Milan), Jennifer Dorts (IFRA), Chaima Elyamadi (IFRA), Andy Forreryd (SenzaGen), Nicola Gilmour (Unilever), Anna Giusti (BfR), Peter Griem (Symrise; IDEA MT), Hervé Groux (ImmunoSearch), Christina Hickey (DSM-Firmenich); Amaia Irizar (IDEA MT), Petra Kern (P&G), Ian Kimber (University of Manchester; IDEA SG), Isabelle Lee (RIFM), Rizos-Georgios Manikas (DG Grow Observer), Andreas Natsch (Givaudan), Brian Palmer (P&G), Aurélie Perrichet (IDEA MT), Laura Rossi (ECHA), Thomas Rustemeyer (University of Amsterdam; IDEA SG), Chunli Shao (DSM-Firmenich), Katherina Siewert (BfR), Anna Sonnenburg (BfR), Matthias Vey (IDEA MT)

The Workshop Programme:

Welcome and purpose of the Workshop in the context of the European regulatory environment (J Bridges)

Purpose, objectives and challenges of the IDEA NAMs project and development of the RCPL (I Kimber)

The RIFM in vitro test program with quantitative endpoints (I Lee)

In vitro data and prediction approaches: initial results comparing the RCPL with data from the GARD-DR and Linear Regression models (P Griem)

Extending the RCPL (A Irizar)

Outlook: how to tailor considerations of uncertainty into risk assessment (A Natsch)

Key conclusions and next steps (H Bender, M Vey)

Background and Introduction (*J Bridges, I Kimber)*

The primary objective of this project is to work with others in support of the assessment of New Approach Methodologies (NAMs) that will permit the development of effective skin sensitisation risk assessments without recourse to animal data.

In addressing this objective 2 key challenges have been identified:

- *Measures of potency.* In recent years considerable progress has been made in the identification of NAMs that provide a reliable identification of skin sensitisation hazards. However, for the accurate assessment of potency it is necessary that test methods should be based on markers or measures that are causally AND quantitatively associated with the acquisition of skin sensitisation. Two promising approaches were considered during the Workshop (GARDskin-Dose Response and Linear Regression models).

- *Assessment of NAMs for potency predictions.* It is necessary that there are in place mechanisms for the determination of whether a NAM provides an accurate measurement of skin sensitising potency. One approach, the Reference Chemical Potency List (RCPL), has been discussed at previous IDEA Workshops.

The RCPL

The RCPL has the following characteristics: (a) presently, it comprises 33 readily available chemicals (fragrance and non-fragrance materials) comprising a wide range of chemistry and skin sensitising potency, (b) includes direct haptens and indirect haptens (both pre- and pro-haptens), (c) skin sensitising potency is expressed as a Potency Value (PV) derived from the best available human and animal (LLNA) data, (d) PVs do not include consideration of *in vitro* or *in silico* data, (e) chemicals are ranked according to PV, without the use of potency categories (Irizar et al., 2022).

The RCPL: next steps (*A Irizar*)

Plans include:

- An increase in the number of chemicals included in the RCPL, with an emphasis on fragrance materials. The aim is to introduce up to 90 additional new chemicals
- A re-examination of how best to apply human data from HRIPT in derivation of PVs
- Develop criteria to confirm the absence of sensitising activity based upon LLNA data

The extended RCPL, including any modifications to the way in which PVs are derived will be used to further evaluate methods for measurement of skin sensitising potency.

NAMs for the measurement of skin sensitising potency (*I Lee and P Griem*)

Two NAMs approaches were considered:

- GARDskin Dose-Response (GARD-DR) (Donthamsetty et al., 2024; Gradin et al., 2024*)*
- Linear Regression models (Lee et al., 2024)

These methods were evaluated using two databases: (a) a reference database of fragrance materials developed by RIFM for evaluation of NAMs based on potency categories (Na et al., 2022) (described by *I Lee)* and the RCPL based on PVs (Irizar et al., 2022) (described by *P Griem).*

Using these reference databases both methods performed very well. However, some under-predictions and over-predictions were noted and these will be the subject of further investigations. It was noted that an extension of the RCPL with additional chemicals, together with application of the RIFM database, would facilitate more detailed investigations of outliers.

Considerations of uncertainty (*A Natsch*)

The nature and sources of uncertainty in hazard identification, hazard characterisation and risk assessment were described and examples provided. More specifically, options to address uncertainty in developing risk assessments based on NAMs data were discussed. It was agreed that incorporation of uncertainty analysis into NAMs-based risk assessment would be an important component of the next IDEA Workshop.

Key conclusions agreed at the Workshop

The following key conclusions were agreed at the end of the Workshop against the overall aim of providing the SCCS with a dossier on NAMs-based risk assessments

- *RCPL next steps*

The Workshop participants agreed on an extension and refinement of the RCPL towards a more diverse reference dataset to evaluate NAMs and allowing more confidence in predictions.

- *Assessment of NAMs*

The preliminary analyses of the GARD dose response and Linear Regression models versus the RCPL look promising. However, some outliers require follow-up.

It was recommended to expand the scope of NAMs comparisons with the (extended) RCPL, in the first instance by including SARA ICE.

- *Considerations of uncertainty*

Characterisation of areas of additional uncertainty that might be associated with the incorporation of NAMs into the risk assessment process needs to be a key topic at the next Workshop.

- *Dealing with very weak sensitisers*

To progress the topic the draft commentary using benzyl alcohol as an example will be shared with Workshop participants for comments

References

Donthamsetty S, Forreryd A, Sterchele P, Huang X, Gradin R, Johansson H, Mattson U, Lee I, Api AM, Ladics G (2024) GARDskin dose-response assay and its application in conducting quantitative risk assessment (QRA) for fragrance materials using a next generation risk assessment (NGRA) framework. Regul. Toxicol. Pharmacol. 149, 105597

Gradin R, Tourneix F, Mattson U, Andersson J, Amaral F, Forreryd A, Alepee N, Johansson H (2024) In vitro prediction of skin sensitizing potency using the GARDskin dose response assay: a simple regression approach. Toxics 17, 626.

Irizar A, Bender H, Griem P, Natsch A, Vey M, Kimber I (2022) Reference Chemical Potency List: A new tool for evaluating the accuracy of skin sensitisation potency measurements by New Approach Methodologies (NAMs) Regul. Toxicol. Pharmacol. 134, 105244.

Lee I, Na M, Lavelle M, Schember I, Ryan C, Gerberick GF, Natsch A, Api AM (2024) Predicting points of departute and potency for fragrance ingredients by integrating OECD in vitro models. Fd. Chem. Toxicol. 193:114998

Na M, O'Brien D, Lavelle M, Lee I, Gerberick GF, Api AM (2022) Weight of evidence approach for skin sensitization potency categorization of fragrance ingredients. Dermatitis 33, 161-175.