



IDEA Reference Chemical Potency List (RCPL)

2nd RCPL Workshop

Brussels, September 22, 2023

A Summary

(Final December 18, 2023)

Attendees

Nathalie Alépée (L’Oreal), David Basketter (DABMEB Consultancy), Hans Bender (IDEA MT), Fanny Boislève (Chanel), Jim Bridges (IDEA SG), Peter Jan Coenraads (SCCS), Jennifer Dorts (IFRA), Chaima Elyamadi (IFRA), Andy Forreryd (SenzaGen), Peter Griem (Symrise; IDEA MT), Hervé Groux (ImmunoSearch), Amaia Irizar (IDEA MT), Petra Kern (P&G), Ian Kimber (IDEA SG), Andreas Natsch (Givaudan), Aurélie Perrichet (IDEA MT), Katherina Siewert (BfR), Matthias Vey (IDEA MT)

Attendees (virtual)

Anne Marie Api (RIFM), Silvia Casati (JRC), Nicola Gilmour (Unilever), Tiina Lantto (DSM-Firmenich), Isabelle Lee (RIFM), George Manikas (DG Grow), Vera Rogiers (SCCS), Thomas Rustemeyer (IDES SG), Pamina Suzuki (Cosmetics Europe), Ian White (IDEA SG)

Background

The RCPL was developed to contribute to the development, evaluation and adoption of New Approach Methodologies (NAMs) for assessment of the skin sensitising potency of chemicals, with a particular focus on fragrance ingredients. The importance of this is that skin sensitising potency is a key element in the development of effective risk assessments.

The fragrance industry has developed, and relies heavily upon, quantitative risk assessment (QRA) for skin sensitisation. For conduct of a QRA derivation of a No Expected Sensitisation



Induction Level (NESIL) is required as a Point of Departure (PoD). Historically, PoDs have been derived using human data, in some cases supported by confirmatory human data.

IDEA has sought, for the purposes of QRA, to develop a framework that supports evaluation of methods (NAMs) that been developed for measurement of skin sensitisation potency and the derivation determination NESILs (No Expected Sensitisation Induction Levels) without recourse to animal data.

The development of NAMs that can be used reliably for potency assessment will provide confidence that effective QRAs for skin sensitisation can be conducted without reliance on data derived from studies using animals.

Against this background the RCPL was developed to provide a resource with which to evaluate the ability of NAMs, or combinations of NAMs, to measure the potency of skin sensitising chemicals.

RCPL

The RCPL is comprised of 33 chemicals, known to cover a wide range of skin sensitising potency, that are all readily available commercially. For each of these chemicals a Potency Value (PV) has been assigned based upon analysis of the best available animal and human data. Non-animal data (data from *in vitro* or *in silico* evaluations) were not used in the derivation of PVs so that the RCPL training set was not influenced by sources of data it was designed to evaluate. Finally, the RCPL includes complete haptens, as well as pre-haptens and pro-haptens (Irizar et al., 2022).

The first IDEA workshop on the RCPL was held in Brussels on October 7 2022. That workshop focused on the development, roll-out and proposed applications of the RCPL. The key conclusions were that: (a) the RCPL represented an important step forward in the development, evaluation and adoption of NAM-based methods for the assessment of skin sensitising potency, and (b) that it would be of value to undertake an informal evaluation of performance of one or more NAMs with respect to potency assessment using the RCPL.



The second IDEA workshop on the RCPL, which is the subject of this brief report, had the following objectives;

- To compare, using invited case studies selected by IDEA, PoDs/PVs derived using selected NAMs with the RCPL
- On the basis of the above to consider whether there are any changes that should be made to the RCPL, and/or to the way in which it is used in practice.

Following a brief introduction to the RCPL, and the aims of the workshop, the following case studies were presented:

- *Linear Regression Defined Approach: Prediction of PV Values:* Dr Andreas Natsch, Givaudan
- *GARD – Genomic Allergen Rapid Detection: GARDskin Dose Response – performance on the Reference Chemical Potency List:* Dr Andy Forreryd, SenzaGen
- *The SENS-IS assay:* Dr Hervé Groux, ImmunoSearch Labs
- *Bayesian Network- Integrated Testing Strategy Evaluation of the RCPL:* Dr Petra Kern and Dr Els DeConinck, Procter & Gamble
- *Skin Allergy Risk Assessment (SARA) Defined Approach (DA) and RCPL:* Dr Nicola Gilmour, Unilever
- *Towards Next Generation Risk Assessment for Skin Sensitisation – Case Study on Diethanolamine:* Dr Nathalie Alépée, International Collaboration on Cosmetic Safety Skin Sensitisation Working Group

Key conclusions agreed at the conclusion of the Workshop

1. Value of the RCPL

The workshop saw the RCPL as an important contribution for assessing potency with New Approach Methodologies (NAMs). At this stage there is no further work planned for the RCPL.

2. Assessment of NAMs

- *The NAMs reviewed at the workshop were generally viewed positively in their ability to predict potency values in line with the RCPL, and thus can determine the Point of Departure for Risk Assessment.*
- *For the methods reviewed at the workshop, there was good correlation between RCPL Potency Values (PVs) and predictions made with NAMs with some exceptions, possibly due to differences in applicability domain.*
- *Refinement should now focus on evaluation of weak/very weak sensitisers considering their widespread use in fragrances. (see below; annex 1)*

3. Consequences for skin sensitisation risk assessments with NAMs (Next Generation Risk Assessments)

- *Progress is needed in quantifying any additional uncertainty when using NAMs instead of in vivo data*
- *A structured approach is needed to deal with chemicals outside the applicability domain of certain NAMs*
- *Nevertheless, we now have the ability to do risk assessment for skin sensitisation without the use of newly-generated animal and human data*

Strategic considerations

It is clear from the work presented at the Workshop that significant progress has been made in the development of NAMs that can provide a reliable assessment of skin



sensitising potency for derivation of NESILs required for QRA, and for Next Generation Risk Assessments (NGRA). There can be little doubt that in the near future there will be described other test methods for skin sensitisation potency assessment, and other approaches to risk assessment. The RCPL can play an important role in evaluating the performance of such new methods.

The important point is that collectively the scientific community as a whole has responded vigorously (and successfully) to the challenge of developing robust methods that provide reliable assessments of skin sensitising potency, and effective risk assessments, without recourse to animal data. The availability of such approaches, and the prospect of the development of additional experimental strategies in the future, indicates clearly that reliable risk assessments of skin sensitisation can be achieved without reliance on data from studies in animals.

Annex 1. Weak/very weak sensitisers

There was some discussion during the workshop regarding issues associated with the identification, potency assessment and relevance of weak/very weak skin sensitisers. Following the workshop, it was decided that the IDEA SG – with others – would address this issue, with particular reference to benzyl alcohol – one of the chemicals within the RCPL.

Reference

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) 134, 105244.