

## **IDEA - Workshop on the application of the RCPL**

**Hybrid Event coordinated out of IFRA Offices, 6 Avenue des Arts, 1210 Brussels**

**Date: October 7, 2022**

**The WS started with a tour de table of all physical and online participants as detailed below.**

### **Participants in the Workshop (\*virtual)**

**IDEA:**

Hans Bender (IDEA Moderator), Jim Bridges (Chair IDEA SG), Amaia Irizar (IDEA MT), Ian Kimber (IDEA SG), Matthias Vey (IDEA MT), Peter Griem (IDEA MT)

*Fragrance industry:*

Christina Hickey (Firmenich)\*, Gregory Ladics (IFF), Andreas Natsch (Givaudan),

*Customer industry:*

Nathalie Alépée (L'Oréal), Fanny Boislève (Chanel), Nicky Gilmour (Unilever), Petra Kern (P&G), Brian Palmer (P&G)\*

*IFRA / RIFM:*

Anne Marie Api (RIFM)\*, Jennifer Dorts (IFRA), Aurelie Perichet (IFRA)

*Other experts:*

Brunhilde Bloemeke (University of Trier, Germany), Juan-Carlos Carrillo (Shell), Silvia Casati (JRC)\*, Emanuela Corsini (Toxicologist, Milan, Italy) \*, Nicole Kleinstreuer (NICEATM)\*, Emily Reinke (NICEATM)\*, Laura Rossi (ECHA)\*, Katherina Siewert (BfR), Anna Sonnenburg (BfR)\*

*Observers*

Pieter-Jan Coenraads (SCCS), Arianna Giusti (Cosmetics Europe), Pamina Suzuki (Cosmetics Europe)

HB reminded the participants of the larger context of IDEA and how the structure was established. The critical review of the Quantitative Risk Assessment (QRA) for skin sensitisers, leading to QRA2, was in the focus of a series of IDEA WS since it was established in 2013.

Given that there remained a lot of reliance on historical data, including animal data, for deriving a NESIL as starting point in the QRA, follow up activities focused on NAMs and how to derive a point of departure for risk assessment from NAMs. As a first step the development of the Reference Chemicals Potency List (RCPL) was recommended as a key conclusion from previous workshops.

### **Proposed objectives of the Workshop**

1. Now that the RCPL has been developed and published, it is critical that a detailed consideration is given to exactly how it can be used in practice, and what performance criteria will be required of candidate NAMs (or combinations of NAMs) to provide assurance that there is the ability to measure skin sensitising potency to an acceptable degree.
2. For a later roll-out and to promote acceptance and use of the RCPL, it will be helpful if the WS leads to an outcome that can be disseminated in a peer-reviewed publication explaining the practical application and merits of the RCPL for assessment of the ability of NAMs to measure skin sensitising potency and how best it can be used in practice.
3. In this context it will be important to have the RCPL used to evaluate at least one NAM approach designed for potency assessment (and preferably more than one). This will require effective liaison and collaboration with the relevant scientific community and industrial laboratories. It is hoped (but cannot be guaranteed) that, using the RCPL as a template for assessment, at least one NAM can be shown to provide a reliable assessment of skin sensitising potency for all (or most) of the 33 reference chemicals in the RPCL list. The WS should consider this follow-up step and, if deemed pertinent, propose some follow-up actions.

In summary the WS was therefore designed to

- i) broaden stakeholder input to the relevance of the RCPL, including from industry, academia, and regulatory bodies,
- ii) discuss how the RCPL can be used in practice,
- iii) review presented assessments of sample NAMs with the RCPL
- iv) discuss roll-out of RCPL as a prime evaluation tool for NAMs.

## **Agenda followed for the Workshop**

The first part of the WS was structured into

- i) a landscape assessment of key NAMs
- ii) an overview on key objectives of the RCPL
- iii) a detailed review of the RCPL itself as well as
- iv) a review of one NAM evaluation through the RCPL

The second part of the WS comprised the discussion around the themes of suitability, systematic use and thoughts beyond the RCPL, which laid the foundation for the creation of key conclusions by the group as key outcome of the WS.

## **Take home messages from the individual presentations**

(Respective presentations are attached)

### Landscape (P. Kern)

A broad variety of NAMs is available and used to different degrees for hazard categorization but also to derive potency categories or values as points of departure (POD) that can be used for risk assessment. Most use animal data as reference – an integrated human / animal database as provided by the RCPL seems absent so far. It was recognized that there are also other approaches

for risk assessment for skin sensitisers, which do not go via prediction of a potency value as an interim step.

#### Background on RCPL (I. Kimber)

The important overall objective is to have available at least one NAM (or combination of NAM approaches) that provides a credible and reliable method that can be used with confidence to measure the skin sensitising potency of chemicals. This would permit NAM data to be incorporated into QRA2 to provide an effective risk assessment of skin sensitisation without recourse to animal studies. To facilitate this, a Reference Chemical Potency List (RCPL) has been developed that provides a template against which the performance of NAM approaches in evaluating skin sensitising potency can be judged. The RCPL has been developed by integrating the best available human and animal data (but not in vitro or in silico data) which makes it unique and valuable.

It was pointed out that if it cannot be shown that at least one NAM approach can provide a credible assessment of skin sensitising potency, then the proposed drive towards hazard-based, rather than risk-based, safety assessment will be reinforced.

#### Details on the RCPL (A. Irizar)

Following a recommendation of earlier WS, an IDEA WG has supported the creation of the RCPL and the output of the work has been published.

A large number of sensitisers (mainly fragrance materials) was reviewed to eventually arrive at 33 materials displaying a wide range of potencies for which high quality animal and/or human data are available. The review and decision processes through which materials and corresponding data were selected was displayed with underlying studies referenced. The final list and corresponding publication were shared [Irizar A, Bender H, Griem P, Natsch A, Vey M, Kimber I (2022) Reference Chemical Potency List (RCPL): a new tool for evaluating the accuracy of skin sensitisation potency measurements by new approach methodologies (NAMs) Regul Toxicol Pharmacol doi: 10.1016/j.yrtph.2022.105244].

### Evaluation of NAMs with RCPL (A. Natsch)

Exemplary NAMs such as the combination of KeratinoSens with kDPRA, kDPRA with hCLAT or all three assays as Defined Approach show a good correlation in a multiple regression model, trained on animal data only (EC3). The correlation is similarly good versus the PV values of the RCPL particularly for molecules in the chemical space and potency range of fragrance molecules, while there is some underestimation of extreme (non-fragrance) sensitisers. Given some outliers and numerical differences, the models do require correction factors to account for uncertainty as has been the case all along in QRA done with animal data. Net, an encouraging result for these combinations of NAMs in a Defined Approach and support for the application of the RCPL with its incorporation of human data versus historical comparisons with EC3 or human data (DS04) only.

### Discussion

#### Which NAMs seem most suitable for evaluation by the RCPL in determining potency of fragrance materials? How do we encourage systemic use of the RCPL?

Given encouraging results with initial NAMs assessments (see above), the group encouraged widening the application of the RCPL to assess a broad range of NAMs. Collection of these assessments under the auspices of IDEA was encouraged. Both the determination of individual PVs as well as the ranking compared with the RCPL were supported as metrics to arrive at a rather complete NAM assessment.

The anticipation is that the RCPL will provide a flexible and reliable template for evaluating the accuracy of NAMs for measuring skin sensitising potency.

#### Are there other things to be considered in the assessment of NAMs?

The suggestion to make the RCPL part of an OECD standard by submitting a SPSF to the OECD to propose these chemicals as the reference list for the new section of the DASS GL on QRA was generally supported by the group. The discussion whether this would require an extension of the

list of 33 materials was not answered finally, but it was felt that this was an adequate number to start with.

## **Key Conclusions**

(Details attached)

The RCPL was received well by the WS participants. Little if any criticism was expressed to its form and content. It was seen as a major step forward in enabling skin sensitisation risk assessment without the use of animals. This is of particular importance in a regulatory environment, where a hazard-based assessment has been advocated – partly due to its simplicity but also due to a lack of validated NAMs. With the creation of the RCPL and its application in practice, there is now an improved basis for a position to challenge this regulatory approach.

Going forward, the WS encouraged widespread use of the RCPL in the evaluation of NAMs under the auspices of IDEA and active advocacy of this work, starting with a scientific paper on the outcome of this WS. The increased use of the RCPL is expected to reveal to what extent further guidance on the use of the RCPL is required.

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