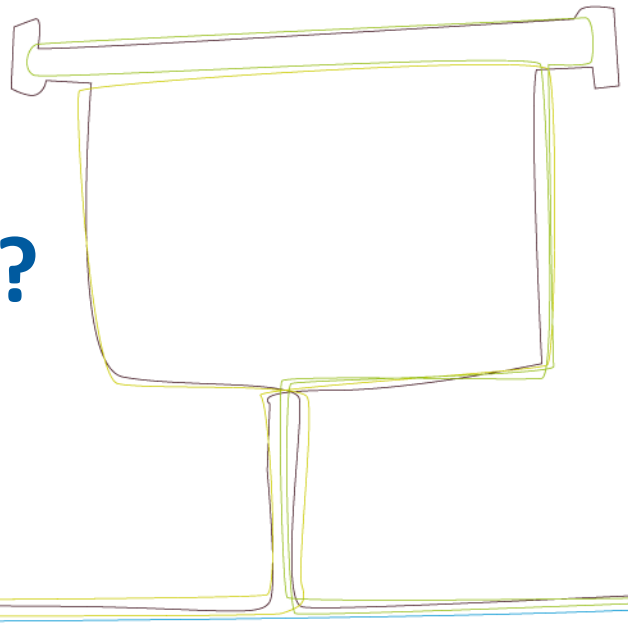
IDEA

International Dialogue for the Evaluation of Allergens

CRITERIA FOR A REFERENCE CHEMICAL POTENCY LIST (RCPL): WHAT'S LEFT TO BE DONE?



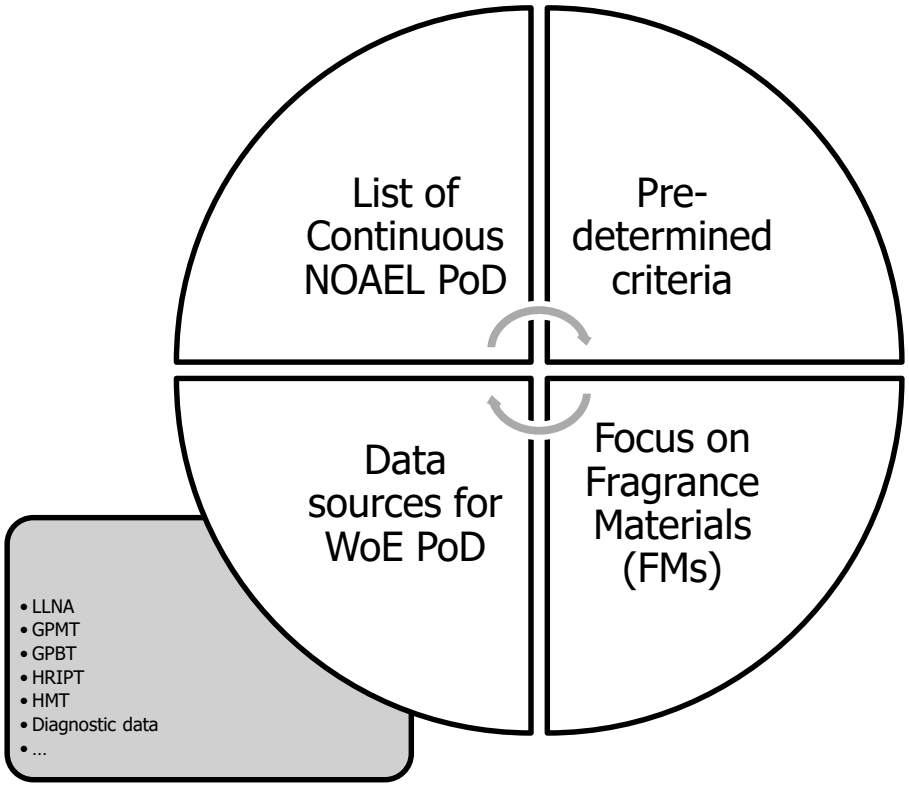
Amaia Irizar,

IFRA

Key Conclusions IDEA WS December 12th, 2018

- To set the scene, the group reemphasized that potency assessment (for definition of a point of departure in risk assessment e.g. NESIL) is such a complex task that all relevant data (weight of evidence) need to be considered to address the nature and degree of uncertainty.
- Doing potency assessment without animal testing, logically requires the same weight of evidence approach and reference needs to be made equally to LLNA EC3 and/or to human data on intrinsic potency.
- **For the development of non-animal alternatives for potency assessment, there is a need for a reference chemical potency database integrating human, animal and in vitro evidence.**

What do we mean by a Reference Chemical Potency List (RCPL)?



Why do we need a RCPL?

- The RCPL could be used:
  - as performance standards in new assays
  - as positive controls in assays
  - To help validate PoD output of Define Approaches and IATAs
  - as basis for Read-Across
- The requirements for each need to be considered separately

Other Databases:
Published and in Development

- Several in peer-review literature over the last few years
- Various degrees of data curation
- Much overlap of chemicals
- Three DB will be covered:
  i. Urbisch, et al 2015, RTP 71: 337-351
  ii. Hoffman et al 2018, Crit RevToxicol. 2018 May; 48(5):344-358
  iii. OECD DASS EG Database

Urbisch, et al 2015, RTP 71: 337-351

- DB of 213 chemicals
- QSAR Toolbox alerts
- In vitro, (DPRA, KeratinoSens, LuSens, h-CLAT, (m)MUSST)
- LLNA EC3
- Human data (HRIPT, HMT, potency category)
- Define Approach 2 out of 3 prediction

Hoffman et al 2018, Crit RevToxicol. 2018 May; 48(5):344-358

- Known as ‘Cosmetics Europe database’
- based on the NICEATM/ICCVAM LLNA database and data from Cosmetics Europe
- Used for the initial assessment of DAs (in Kleinstreuer et al 2018 Crit Rev Tox)
- 128 chemicals
- Approx. 60 Fragrance materials, including 6 UVCBs
- Comprehensive database
- For each individual chemical data given in an excel sheet

Hoffman et al 2018- Information for Each Chemical

- Name
- CAS No.
- Smiles
- Mechanistic domain and reference
- Pre/Pro-hapten and reference
- LogP, LogS, BP, MP, Log VP, LogBCF
- For each individual LLNA study
  - Individual EC3%
  - Maximum dose tested in LLNA
  - Vehicle
  - Reference for the study

- In vitro data
  - DPRA, KeratinoSens, hCLAT, U-SENS, SENS-IS
- Human potency (1-6) according to Basketter et al 2014

Relevant notes from the discussions for the purposes of building IDEA RCPL

- This exclude aspects regarding categorization of potency GHS 1A/1B
- **NEGATIVES** – what is the minimum acceptable concentration tested in LLNA and Human studies? (100%? 50%? 25%?)
  - Only 4 LLNA negatives tested up to 100%, 4 to 50%, remaining 31 <30% max concentration (of references found re validation LLNA)
  - LLNA was not validated between 25-100% max concentration
  - Not known whether higher doses were not tested due to irritation
  - Reality that GHS guideline mandates 100%...otherwise, not wanting to know answer.
  - 44/315 LLNA results show EC3> 20%, hence we may miss weak sensitisers
  - Lack of dose-response relationship at doses <50% - speculative about higher doses

Relevant notes from the discussions for the purposes of building IDEA RCPL

- **Meta-analyses** of all the LLNA studies taking into account
  - Revised dataset, and papers such as Urbisch et al 2015, Hirota et al 2015,Otsubo et al 2017 etc.
  - Leave the rule-based mindset and look at the false-negatives regulators are so concerned about and see what we miss and the associated risk– and not numbers on proxy values (EC3).
  - Similar assessment to be made for the false-positives. All positive LLNA results up to 100% were taken as positives.
  - Conclusion on a single Human patch test study but rejection when ample clinical evidence from e.g. epidemiology
- **Transparency** of separate LLNA and human DBs (for the same chemicals), vs. Weight of Evidence of all human and animal data
- **Borderline results** and how to deal with them. The implications may be different whether it is for classification or PoD
- **Solvent** effect: LLNA TG AOO and DMF, vs EtOH:DEP
- **Isomer mixtures** e.g. Lyral no, Citral? , Anethole yes.

Can’t IDEA just take the existing CE or OECD database or the RIFM NESIL list?

- **Difference of the IDEA database vs. the NESIL database used for risk assessment of skin sensitizers:**

i. For risk assessment many data are based on NOEL only – NOEL may be significantly lower than true threshold
   - When doing risk assessment, we can be very conservative driven principally by uncertainties in the assessment. The RA itself should be based on the best available science
   - However, too conservative NESIL assumptions are not appropriate to evaluate NAM approaches

ii. For current RIFM risk assessments, human data overrule LLNA data

=> For the IDEA database a WoE based on animal and human data may be made

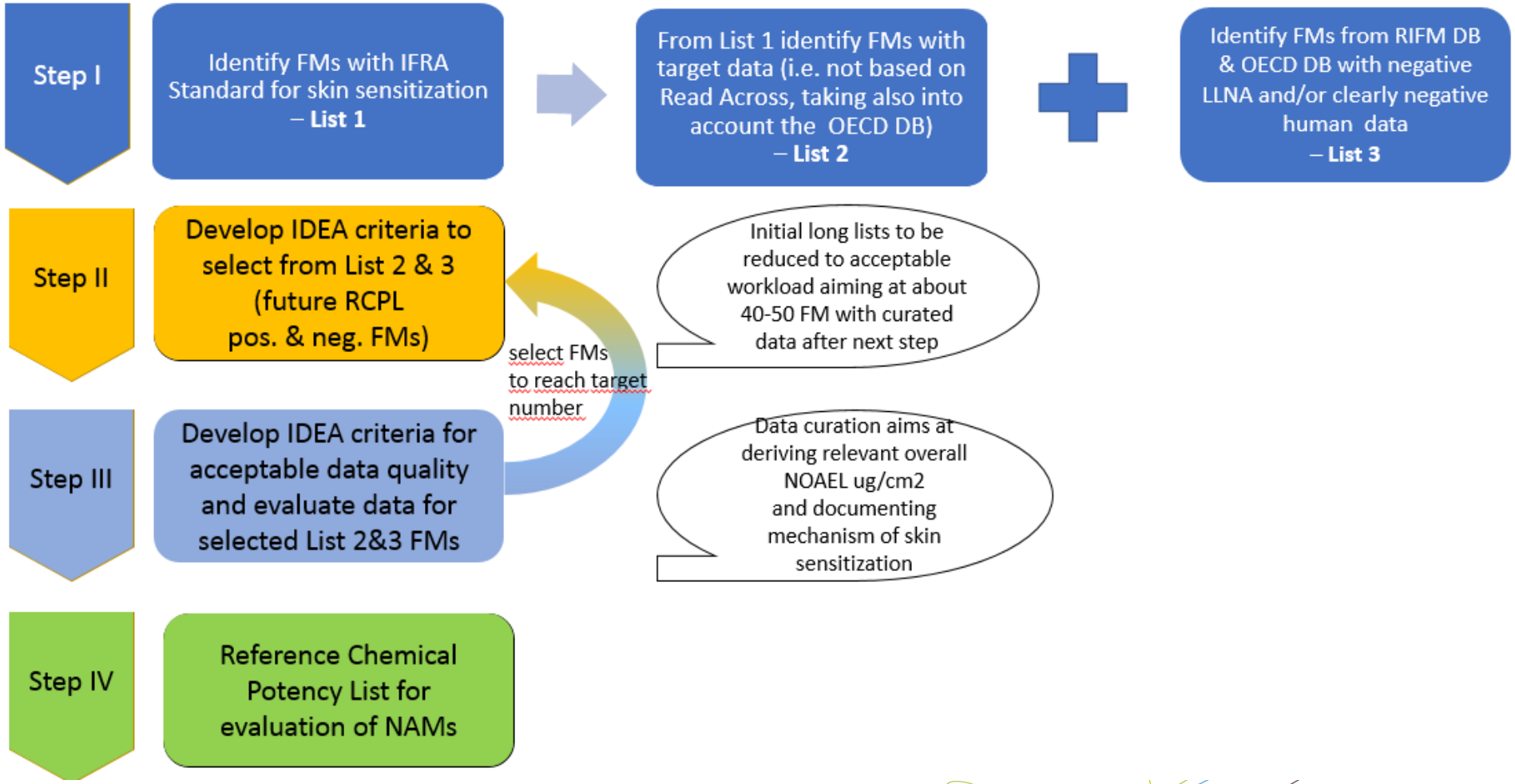
Can’t we just take the existing CE or OECD database or the RIFM NESIL list?

Difference vs. Cosmetics Europe and OECD databases

- Focus on fragrance materials – we want to know how NAMs work for fragrance materials
- Include WoE animal and human data – most other databases focus on LLNA or Human data

The IDEA database to evaluate NAMs can be smaller than other databases – but high quality data / judgement of NESIL is needed.

Proposed Workflow for the Preparation of the RCPL



Proposed Workflow of IDEA Criteria for RCPL (1)

- **Purpose** of reference chemicals (RCs) is to serve as reliable benchmarks for comparison purposes in assays for the potential of individual fragrance materials to induce dermal sensitisation in consumers (i.e. identification and potency) .
- **Requirements**

i. Access to a complete data set on the physical and chemical properties of each candidate RC

ii. Access to complete details of the LLNA tests and other animal tests used, and the findings to conclude on their dermal induction potential.

iii. Both positive reaction and negative reaction RCs are needed.

iv. RC selection should incorporate a range of quantitative potencies

Proposed Workflow of IDEA Criteria for RCPL (2)

- **Further considerations**

i. Should essential oils and extracts be excluded a priori?

ii. Do we need to include RC's that are known/likely to undergo metabolic transformation to more reactive metabolites?

iii. Even though RCs other than FM (which are also applied dermally) might be viewed as useful for RCPL purposes, it is proposed that the priority for harvesting data and initial focus is on FMs.

iv. Do we need to break down the RCPL into different structures, physical chemistry and reactivity domains.

v. …….more to be added……

Proposal to define a TF to develop the RCPL

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THANK YOU!