Extending the RCPL

IDEA Workshop: Working towards non-animal risk assessment for skin sensitising materials – developing the IDEA strategy

October 10, 2024

Amaia Irizar

RCPL Extension Plan

- The RCPL[*] work established:
  - A workflow to apply a **structured WoE** to combine human and animal data
  - **Strict criteria** for the selection of animal and human data
  - Currently **33 chemicals** are included in the RCPL
  - All **fragrance materials** except for 6 extreme sensitisers
- Plan to **extend RCPL** - initially with additional fragrance materials
- Why focus on fragrance materials
  - **Availability of data** – not only from NAMs but also robust historical animal and human meeting the established criteria to derive a PV
  - **SCCS interest** in receiving sensitisation dossiers for fragrance materials
  - However, this does not exclude the application of the workflow **to chemicals outside the fragrance industry** in the future

Work in Progress

- Aim to use the **extended RCPL for the assessment of the models** ahead of the next IDEA Workshop (early Q2 2025 tbc)

- Starting point is the fragrance materials for which **GARD DR** and **Linear Regression data** are available

- **Systematic data curation** of the available historical LLNA EC3, and human NOEL and LOEL values
  - This means that certain existing values may not be acceptable for meeting the current RCPL criteria
  - It also excludes values based on Read Across and UVCBs
  - How to manage some pre-haptens (e.g. hydroperoxides of linalool and limonene)
  - For those accepted, the RCPL workflow is applied to derive a Potency Value

- We are currently working with a total of **about 90 chemicals in addition to the 33 chemicals in the current RCPL**.

IDEA

Additional Chemicals

Established RCPL Workflow/Data criteria

Updated RCPL Workflow/Data criteria?
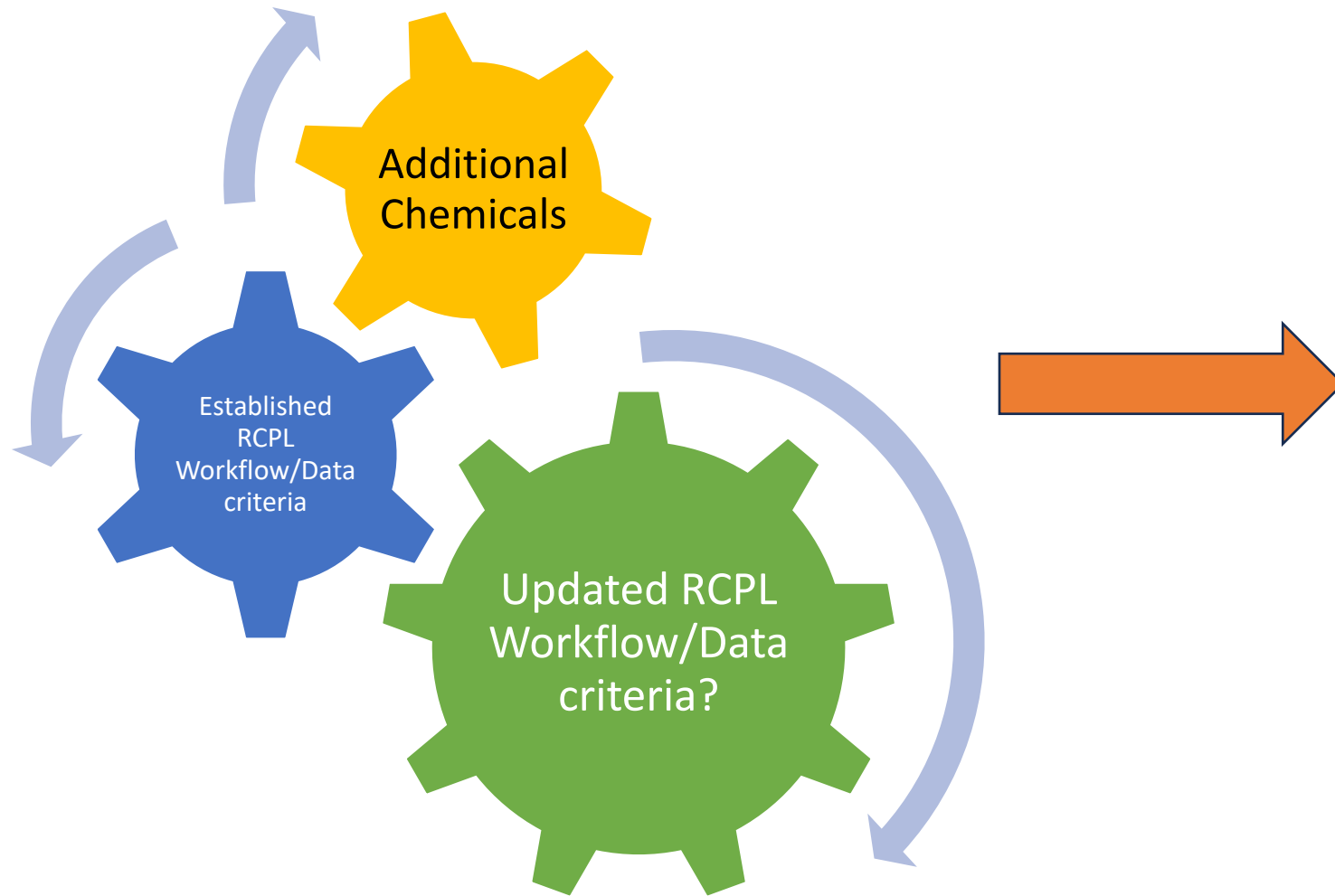
- **So far, no need**
- **Analysis of new considerations for potential further refinement**

4

Criteria to Consider LLNA Negatives

- Criteria to qualify a historical LLNA as negative – what should be **the highest dose tested**
- Not many examples for the development of the RCPL – not an issue at the time
- In the **validation of the LLNA very few chemicals** were tested at 50% or 100%
- **OECD criteria** to qualify as negative 100% dose should be tested – without validation on whether this does not lead to false positive
- We have **many negative LLNAs** (10-15 out of the 90 candidates) with max test concentration of 20% - 40%
- Whether the rejection of a LLNA, **tested at less than 100% for classification as negative** for hazard assessment, is appropriate
- When developing a PV, a measure of potency, there might be **value in utilising negatives at <100%** dose tested
- **For example**, if for a chemical the human NOEL (single or maximal concentration tested) is 1500 ug/cm2, and LLNA is negative at 20% (5000 ug/cm2), shouldn't the LLNA result have some weight in the derivation of PV?

Human Data

- The RCPL workflow **weights in the potency information derived from human LOELs and/or LLNA EC3, vs the human NOEL** as the latter is generally not a reflection of potency

- **If only a human NOEL is available for a chemical, no PV will be derived** on that basis, i.e. it must have in addition a human LOEL and/or LLNA EC3

- **Criteria to conclude a very weak/non-sensitiser** if only a human NOEL is available needs further refinement

- Both the human LOELs and NOELs are derived from **HRIPTs with around 100 subjects**.

- The **human LOEL is converted into DSA04** as a closer potency measure of sensitisation in humans similarly to the LLNA EC3 in animals

- **HMTs may be used as supporting evidence only** as the protocol includes SDS making them more sensitive

- Review of additional chemicals will **help further consolidate/refine the criteria** established previously

Next Steps

- **Complete curation** of human and animal data

- Derive a**dditional PVs**

- Evaluate whether a **revision of RCPL workflow and/or data criteria** are needed

- Confirm **final Extended RCPL**

- **Apply the Extended RCPL PVs** to the models

- Sharing of results in **next IDEA Workshop** (Q2 2025 tbc)

- **Publication** of Extended RCPL?