The Reference Chemical Potency List (RCPL): original development, recent extension and benefits

IDEA Workshop: Skin sensitisation potency measurement and Risk Assessment without a requirement for animals

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RCPL Original Development

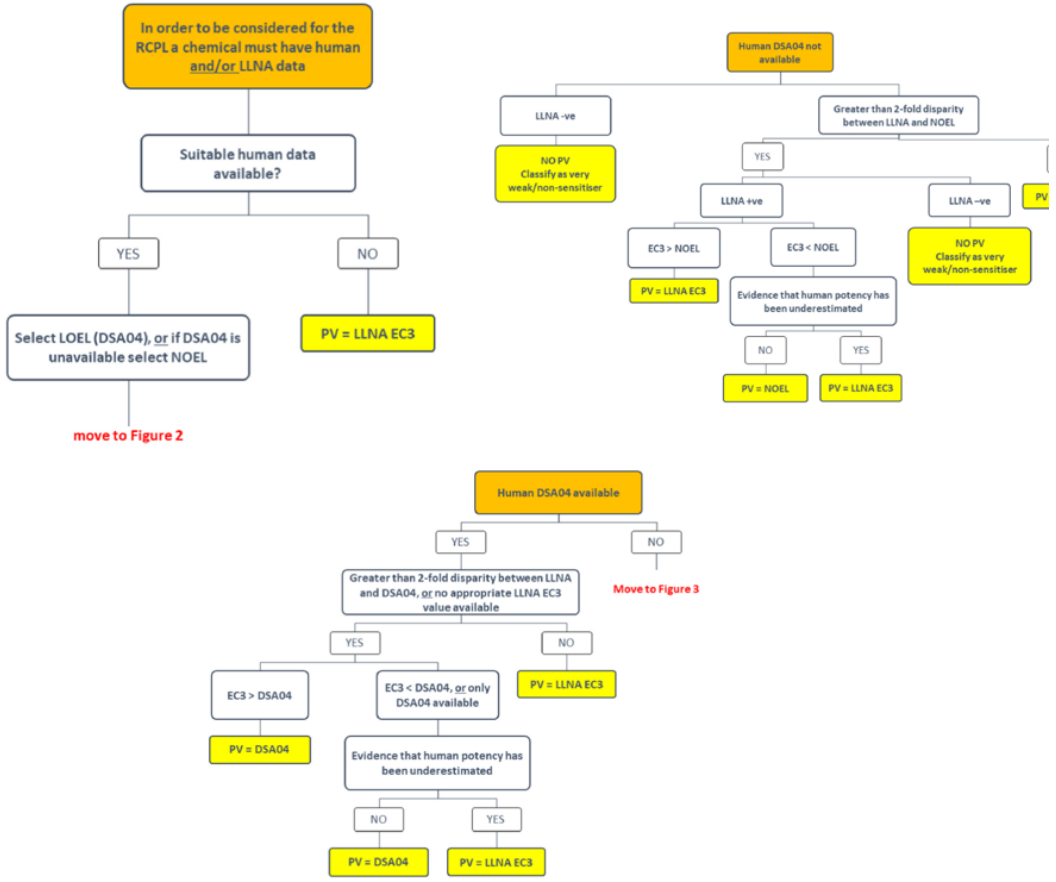
- When addressing a **NAMs-based QRA**, the **challenge has been to define a 'NESIL** – No Expected Sensitisation Level' from the outputs of NAMs.
- Therefore, **characterisation of the potency output** from NAMs by deriving a discrete value is key for the application of QRA.
- The question then is **accuracy of NAMs' output** compared with reference animal and/or human data.
- Therefore, in an early IDEA WS it was concluded that a **carefully curated reference based on consideration of the best available human and animal data** should be established for this purpose.
- Hence, the **RCPL* – Reference Chemical Potency List** was developed.

*Irizar et al 2022, https://doi.org/10.1016/j.yrtph.2022.105244

RCPL Original Development

➢ **The RCPL work established:**

- A **workflow** to apply a **structured WoE** to combine **human and animal** data.
- The concept of **Potency Value (PV):** the estimated concentration (dose per unit area) at which skin sensitisation is first induced, based on available human and animal data; it represents the inflection point for sensitisation initiation for that chemical.
- **Strict criteria** for the selection of animal and human data.
- PVs which were assigned to **33 chemicals.**
- PVs which do **not** include consideration of **in vitro or in silico** data.
- **Chemicals ranked** according to PV, without the use of potency categories.
- All **fragrance materials** except for 6 strong sensitisers.



RCPL Application – IDEA WS

➢**Oct 2022 IDEA WS Conclusions**

- The RCPL represents an **important advance** in developing, evaluating, and adopting NAM-based methods for assessing skin sensitisation potency.
- An **informal evaluation of NAMs using the RCPL** could provide useful insights into their performance.

➢**Sep 2023 IDEA WS Conclusions**

- NAMs (five) reviewed at the workshop were **generally seen as effective** in predicting potency values aligned with RCPL Potency Values (PVs).
- Some **exceptions** were noted, possibly due to differences in applicability domains.

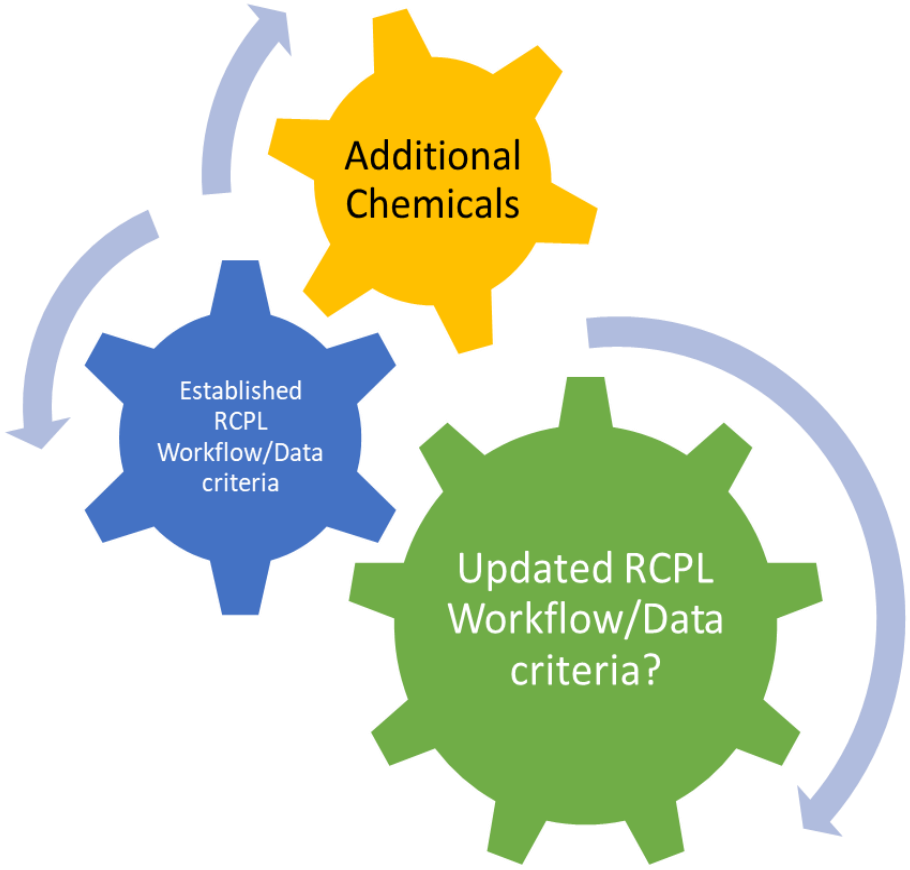
RCPL Application – IDEA WS

➢**Oct 2024 IDEA WS Conclusions**

- **Extend and refine the RCPL** with a more diverse dataset to improve evaluation of NAMs.
- **Preliminary results** for GARD-DR and Linear Regression models appear promising, though some outliers require further investigation.
- **Include SARA-ICE** (Skin Sensitization Risk Assessment – Integrated Chemical Environment) in future NAM comparisons with the (extended) RCPL.
- Prioritise **characterisation of uncertainties** associated with incorporating NAMs into risk assessment at the next workshop.

RCPL Extension

- The RCPL Extension is now completed with **110 chemicals** in total.
- Selection of chemicals based on **systematic data curation** of the available historical LLNA EC3, and human NOEL and LOEL values
- This means that certain existing values were not acceptable for meeting the **RCPL criteria set previously**
- It excludes values based on **Read Across and UVCBs**
- **Structural isomers** were excluded except for in one case where purity is well defined (2,4-Dimethyl-3-cyclohexen-1-carboxaldehyde).
- The same **workflows** previously established were applied.
- Analysis of new considerations for potential further refinement **did not lead to changes** to the workflows.
- For those accepted, the RCPL workflow was applied to derive a Potency Value.



RCPL Extension – further considerations

- Several chemicals had **negative LLNA results** at doses up to or exceeding 25% (6,250 µg/cm²).
- **A minimum tested concentration of 25% was set as the threshold for considering an LLNA study valid for PV derivation**.
- LLNA studies with all stimulation indices (SI) <3 and highest tested concentration <25% were excluded as non-informative.
  - In the ICCVAM interlaboratory LLNA validation, 25% with SI <3 was also classified as negative (ICCVAM, 2009).
  - Most negative chemicals in ICCVAM LLNA validation for GPMT or human patch test prediction were not tested above 25% (Kolle et al., 2020).

ICCVAM (2009). NIH Publication No. 09-7357
Kolle et al., (2020) doi: 10.1016/j.yrtph.2020.104713

RCPL Extension – further considerations

- If the **LLNA was negative at ≥25% and no human data were available, workflow 1** was applied.
  - Based on the negative LLNA, the PV was derived as very weak/non-sensitiser.
  - This applied to Octanoic acid, Benzoic acid 2-methyl-, methyl ester, and 6-Methyl coumarin.
- **If the PV was based on a human NOEL or DSA04 >25,000 µg/cm²**, it was reported as >25,000 µg/cm².
- **If the PV was based on a negative LLNA up to 100% (25,000 µg/cm²)**, the PV was reported as very weak/non-sensitiser. This reflects the upper dosing limit in the LLNA.

Extended RCPL

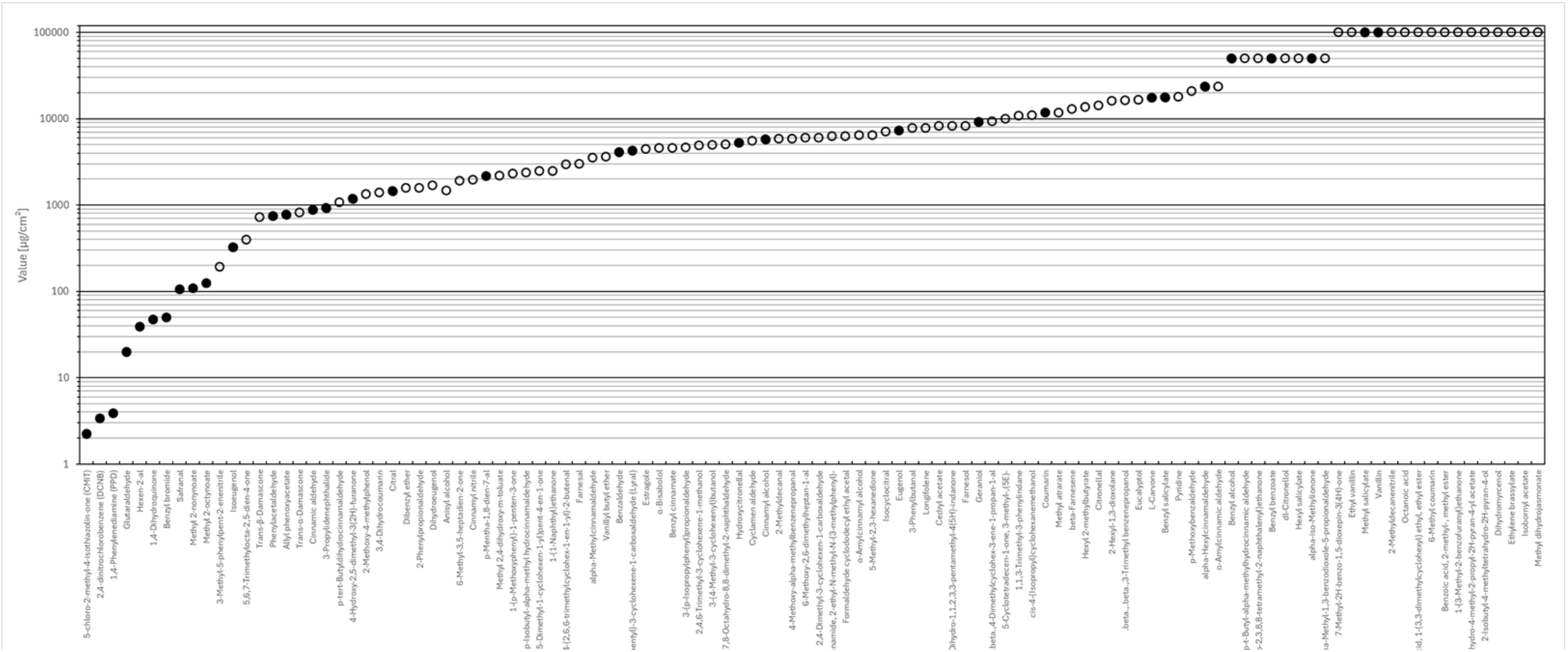
Source data translating to final PV following weight of evidence workflows

Source data	Number of PVs per source data		
	Total	RCPL extension	RCPL (Irizar et al 2022)
DSA04	21[1)]	9	12
Human NOEL	17	12	5
LLNA	55	41	14
Human NOEL/LLNA	17 (Very weak/non-sensitiser)	15	2
Total	110	77	33

1) Indicates that for 21 chemicals, the value chosen according the workflows as final PV is the DSA04. However, all available and curated data was used in the derivation of PV.

Extended RCPL

Range of PVs in the full RCPL with 110 chemicals



Chemicals were ordered by increasing PV values. Filled circles represent PV values of chemicals already published in the first RCPL publication (Irizar et al., 2022). Chemicals with a PV set as “>25,000 µg/cm²” or “very weak/non-sensitizer” were arbitrarily assigned values of 50,000 and 100,000 in order to represent them in the figure

Extended RCPL benefits

- Ranking of 110 chemicals in a **potency value scale** derived with the best available human and/or animal data.
- Formed mostly of fragrance ingredients, however, enabling **comprehensive coverage of sensitisation mechanisms across chemical domains**.
    - It encompasses diverse chemical classes, including direct haptens and pre-/pro-haptens, with functional groups characteristic of fragrance allergens such as esters, alcohols, aldehydes, ketones, and aromatic hydrocarbons. It also includes non-fragrance strong sensitisers bearing reactive moieties such as isothiazolinones, substituted benzenes, diamines, and quinones.
- **In vitro and/or in silico data are not used** in its derivation, and **it avoids potency categorisation**
- Expected to provide **a more powerful tool** that can be applied to assess the strengths and weaknesses of NAMs that deliver a discrete value for skin sensitisation potency as PoD
- The larger number of well-characterised chemicals allows for certain **statistical analyses.** Such an analysis will be shared in this IDEA Workshop
- Final goal is to obtain **insights of the NAM-PoDs for incorporation into QRA**

RCPL Application towards NAMs based QRA