Reference **C**hemical **P**otency **L**ist
RCPL

Skin Sensitisation Potency

Ian Kimber and Amaia Irizar

What is potency?

- **Vigour of response** *Immunology*

- **Concentration/dose required to give biologically/clinically meaningful effect** *Toxicology*

- **What dose/level of exposure is safe?** *Regulatory Science*

What is skin sensitisation potency?

The ease with which a chemical (contact allergen) is able to induce skin sensitisation

A reflection of the local concentration of the chemical that will be required to initiate the process of skin sensitisation

The more potent the contact allergen, the lower will be the concentration required for the acquisition of skin sensitisation

What drives skin sensitisation potency?

- **VIGOUR** of T lymphocyte responses
- **QUALITY** of T lymphocyte responses
- **BREADTH** of T lymphocyte responses

Why is measurement of skin sensitising potency important?

- **It builds upon the significant achievements that have been made in the development, validation and deployment of non-animal methods (NAMs) for skin sensitisation hazard identification**

- **In the absence of effective and validated methods for the measurement of skin sensitising potency based on NAMs (or combinations of NAMs) then hazard-based, rather than risk-based, regulation will be encouraged.**

Risk = Hazard × Exposure

Philippus Aureolus Theophrastus Bombastus von Hohenheim

1493 – 1541

'Paracelsus' : the 'first' toxicologist

"The dose makes the poison"

The Challenge

Markers of potency should be causally AND quantitatively associated with the relevant end-point

(acquisition of skin sensitisation)

Assessment of skin sensitising potency

A key question:

What is/are the event(s) that correlate quantitatively with the effectiveness/potency of sensitisation?

Candidate NAM approaches for assessment of skin sensitisation potency
How can these be evaluated for accuracy and reliability?

- *Animal data (guinea pig/local lymph node assay)*
- *Human data*
- *In vitro data*

RCPL

Integration of best available human data and animal data (primarily LLNA data)

RCPL Characteristics

- *33 readily available chemicals comprising a wide range of chemistry, and skin sensitising potency*

- *Includes direct haptens and indirect [both pre- and pro-] haptens*

- *Potency expressed as a Potency Value (PV) derived from the best available human and animal (LLNA) data*

- *PVs do not include consideration of in vitro or in silico data*

- *Chemicals ranked according to PV without the use of potency categories*

IDEA

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Reference Chemical Potency List (RCPL): A new tool for evaluating the accuracy of skin sensitisation potency measurements by New Approach Methodologies (NAMs)

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A R T I C L E   I N F O

A B S T R A C T

Considerable progress has been made in the design of New Approach Methodologies (NAMs) for the hazard identification of skin sensitising chemicals. However, effective risk assessment requires accurate measurement of sensitising potency, and this has proven more difficult to achieve without recourse to animal tests.

One important requirement for the development and adoption of novel approaches for this purpose is the availability of reliable databases for determining the accuracy with which sensitising potency can be predicted. Some previous approaches have relied on comparisons with potency estimates based on either human or animal (local lymph node assay) data. In contrast, we here describe the development of a carefully curated Reference Chemical Potency List (RCPL) which is based on consideration of the best available human and animal data.

The RCPL is comprised of 33 readily available chemicals that span a wide range of chemistry and sensitising potency, and contain examples of both direct and indirect (pre- and pro-) haptens. For each chemical a potency
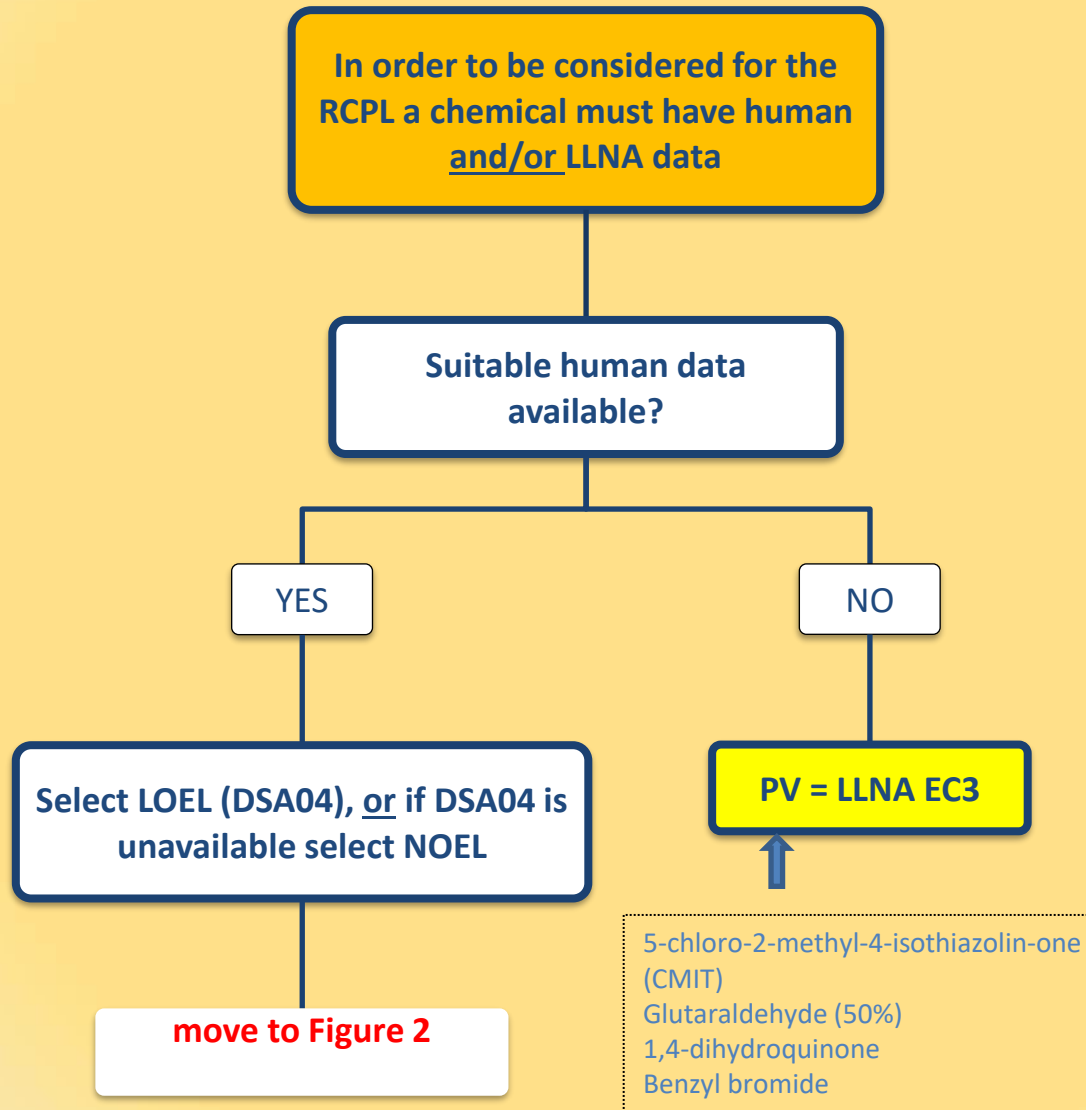
PV: a definition

The PV provides an estimate of the lowest concentration of chemical (measured as µg/cm2 of skin) that is necessary to initiate the development of skin sensitisation
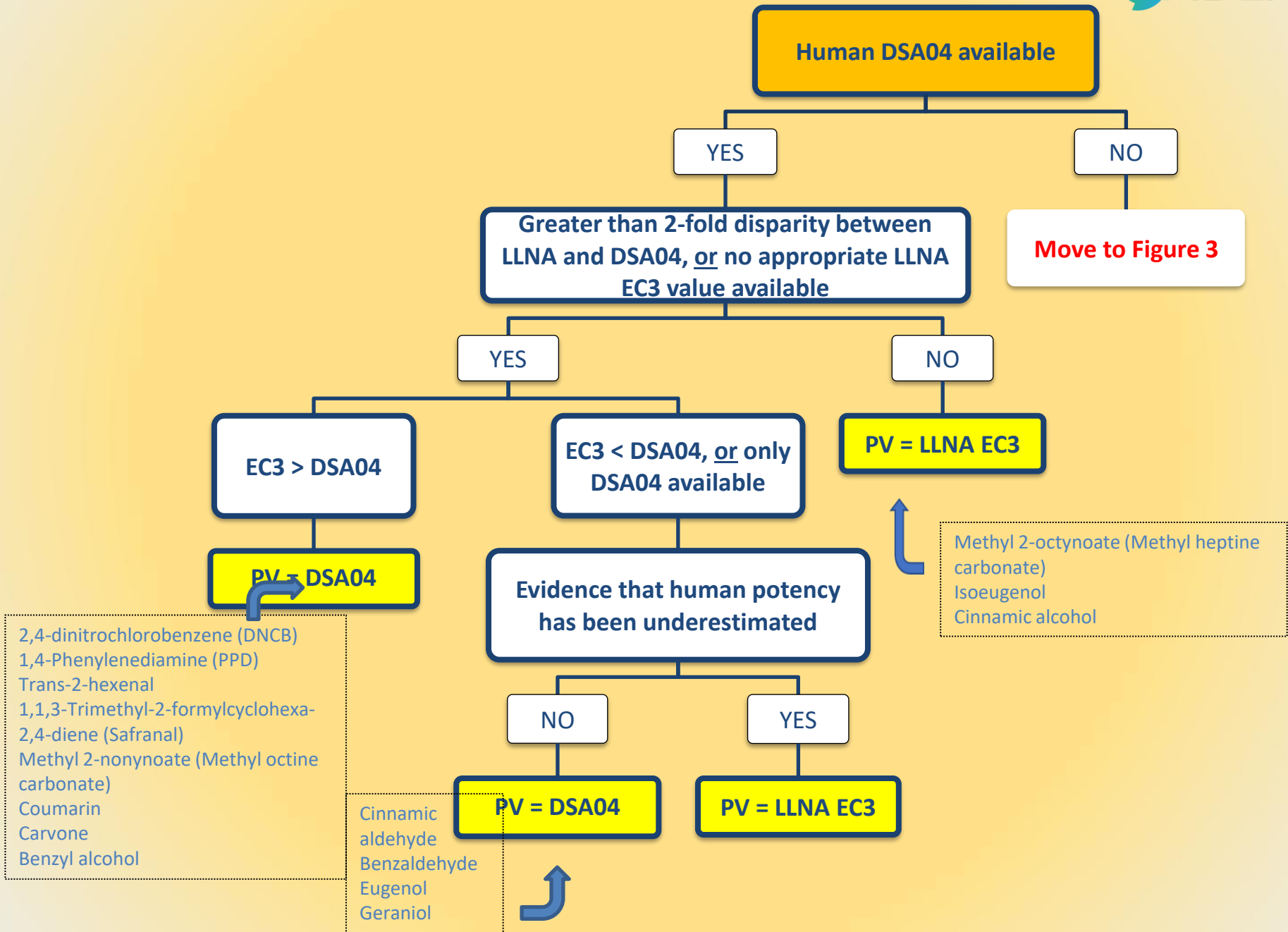
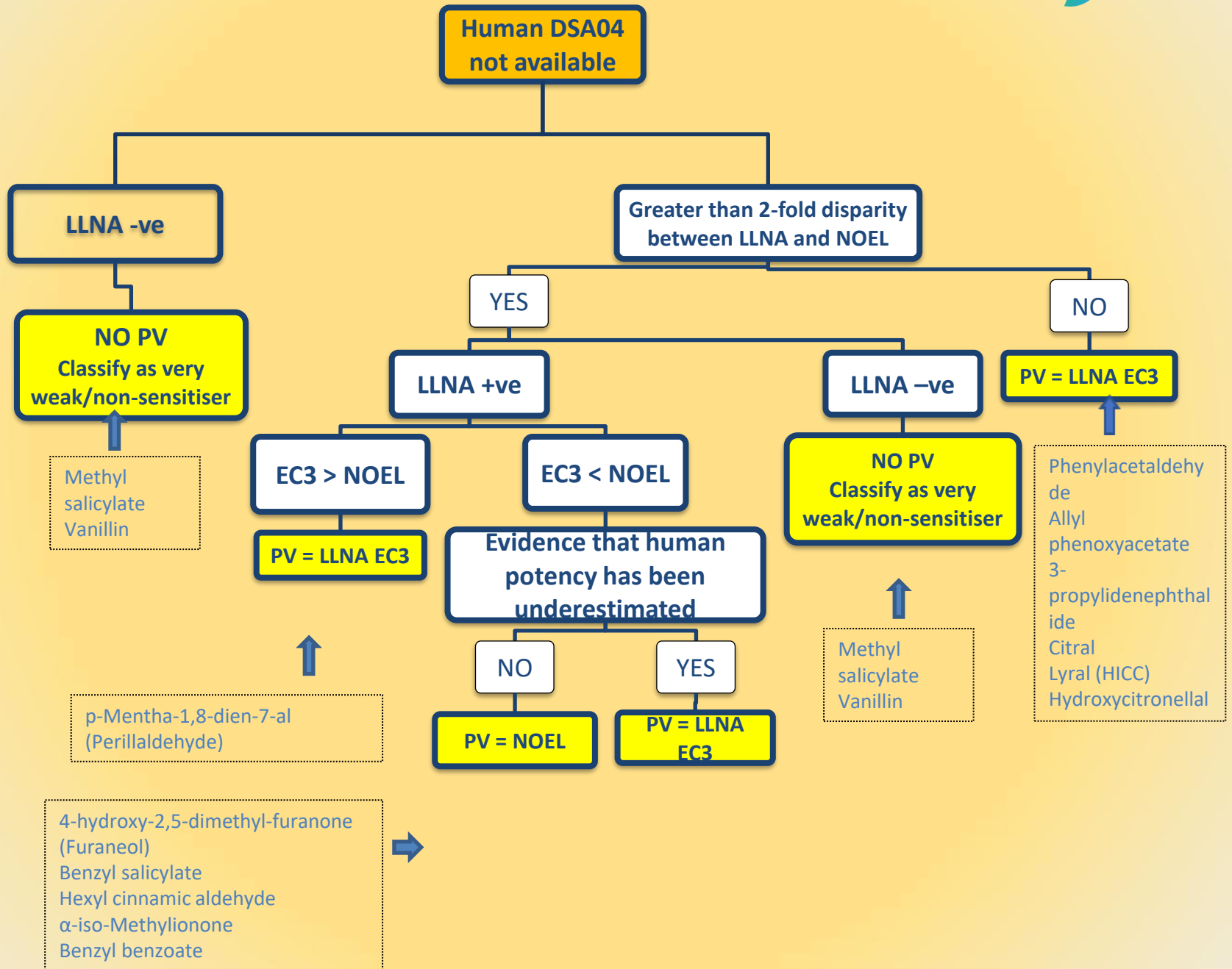*(an inflection point for the initiation of skin sensitisation)*

Key elements of the RCPL

1. Definitions: Potency Value (PV)

2. Guidance for the derivation of LLNA EC3 values

3. Guidance for the derivation of human NOEL and LOEL (DSA04) values

4. Derivation of Potency Values WoE Workflow

5. Review of the PVs derived

Derivation of PVs: 1, 2 and 3

In order to be considered for the RCPL a chemical must have human _and/or_ LLNA data

Suitable human data available?

YES

NO

Select LOEL (DSA04), _or_ if DSA04 is unavailable select NOEL

PV = LLNA EC3

move to Figure 2

5-chloro-2-methyl-4-isothiazolin-one (CMIT)
Glutaraldehyde (50%)
1,4-dihydroquinone
Benzyl bromide

Final output: Potency Values

Name	Pre / Pro - Hapten	Potency Value [µg/cm²]
5-Chloro-2-methyl-4-isothiazolin-one (CMIT)		2.3
2,4-Dinitrochlorobenzene (DCNB)		3.4
1,4-Phenylenediamine (PPD)	Pre	3.9
Glutaraldehyde		20.0
trans-2-Hexenal		39.3
1,4-Dihydroquinone	Pre	47.5
Benzyl bromide		50.0
1,1,3-Trimethyl-2-formylcyclohexa-2,4-diene (Safranal)		106
Methyl 2-nonynoate (Methyl octine carbonate)		109
Methyl 2-octynoate (Methyl heptine carbonate)		125
Isoeugenol	Pre	325
Phenylacetaldehyde		750
Allyl phenoxyacetate		775
Cinnamic aldehyde		885
3-Propylidenephthalide	Pre	925
4-Hydroxy-2,5-dimethyl-3(2H)-furanone (Furaneol)		1181

Name	Pre / Pro - Hapten	Potency Value [µg/cm²]
Citral		1450
p-Mentha-1,8-dien-7-al (Perillaldehyde)		2175
Benzaldehyde		4094
Lyral (HICC)		4275
Hydroxycitronellal		5275
Cinnamic alcohol	Pre / Pro	5775
Eugenol	Pre / Pro	7357
Geraniol	Pre / Pro	9197
Coumarin		11792
Carvone		17573
Benzyl salicylate		17715
Hexyl cinnamic aldehyde		23620
Benzyl Alcohol	Pro	>25000
Benzyl benzoate		>25000
Isomethylionone (α-)		>25000
Methyl salicylate		No PV derived- very weak/non-sensitiser
Vanillin		No PV derived - very weak/non-sensitiser

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Conclusions

- Candidate methods for this purpose must be shown to be accurate and reliable so that they can be used with confidence

- The development of non-animal methods that permit reliable assessment of skin sensitisation potency are necessary for effective risk assessment using QRA-2

- The RCPL provides a new resource for the evaluation of candidate NAM methods for potency assessment based on the best available human and animal (LLNA) data

Next Steps

- Promote the use of the RCPL among stakeholders and the relevant scientific community

- Encourage the use of the RCPL for the evaluation of candidate methods for skin sensitisation potency assessment

- In due course provide a review of the value of the RCPL in practice and of the need for any modifications or extensions