Scientific advances in skin sensitisation assessment:

Progress on integrating non-animal scientific tools (New Approach Methodologies) into QRA methodology
&
Perspectives on practical implementation

IDEA 7th Regular Review, Brussels

January 29, 2026

Presenters:

Dr Peter Griem, IDEA MT

Dr Amaia Irizar, IDEA MT

The International Dialogue on the Evaluation of Allergens

https://ideaproject.info

IDEA Supervisory Group:

Professor James Bridges (Chair)

Professor Ian Kimber

Professor Thomas Rustemeyer

Dr Ian White

Role: Ensure transparency, independence and scientific integrity

Project IDEA – Setup and Organization

- **Global Framework:** Provides a transparent, widely agreed framework for assessing fragrance skin sensitizers
- **EU Commission Partnership:** Developed in collaboration with the EU Commission
- **Expert Workshops:** Series of workshops with international experts to improve methodologies
- **Multi-Stakeholder Approach:** Open exchange of diverse perspectives on fragrance skin sensitization
- **Public Review:** Regular reviews under the auspices of the Commission

MC Escher (1898 – 1972)

Skin Sensitization and Allergic Contact Dermatitis (ACD)

Skin Sensitization

INDUCTION

↓

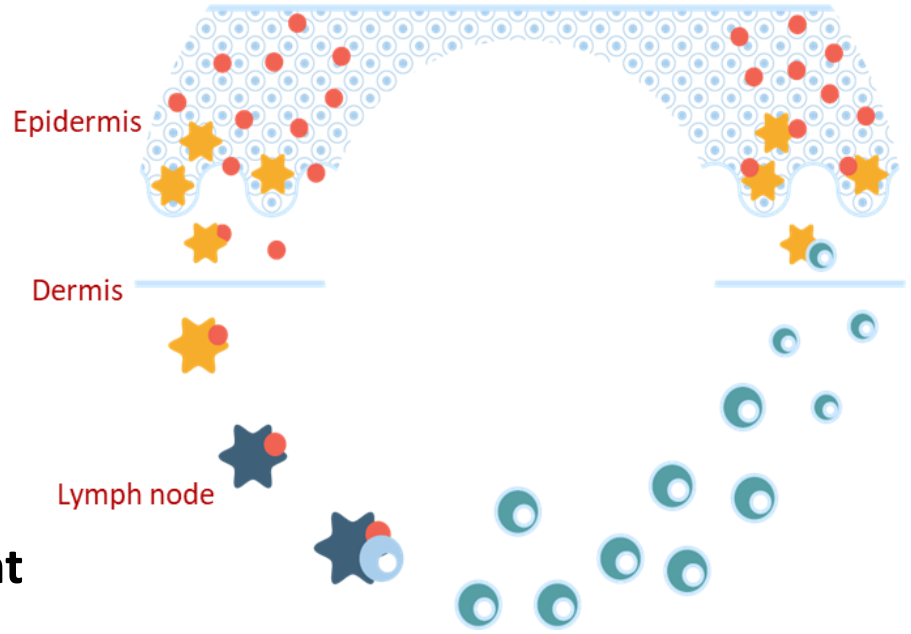
Risk Management:

Prevent induction

↓

Fragrance industry tool:

Quantitative Risk Assessment (QRA)



Allergic Contact Dermatitis

ELICITATION

↓

Risk Management:

Prevent elicitation

↓

Regulatory tool:

Fragrance Allergen Labelling

2008: QRA (version 1) launched as fragrance industry standard

- Skin sensitization = threshold phenomenon
- Induction thresholds can be determined with a higher level of reliability than elicitation thresholds
- Development of QRA for skin sensitizers by a crossover industry expert group to provide use levels in consumer products that will not cause induction of skin sensitization (for most of the population)
- Based on peer-reviewed publications

Available online at www.sciencedirect.com
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Regulatory Toxicology and Pharmacology 52 (2008) 3–23
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Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients

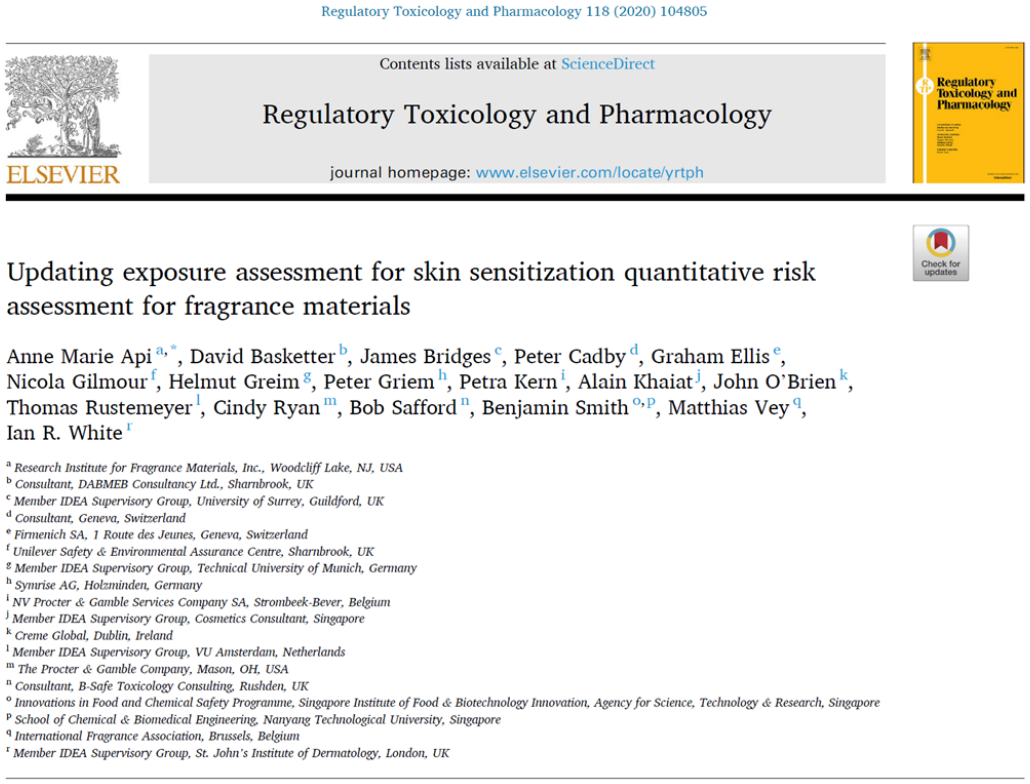
Anne Marie Api [a,*], David A. Basketter [b,1], Peter A. Cadby [c], Marie-France Cano [d,2], Graham Ellis [e], G. Frank Gerberick [f], Peter Griem [g], Pauline M. McNamee [h], Cindy A. Ryan [f], Robert Safford [b]

[a] Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, USA
[b] Unilever SEAC, Colworth House, Sharnbrook, Bedford MK44 1LQ, United Kingdom
[c] Firmenich SA, Corporate Product Safety & Regulatory Affairs, Case Postale 239, 1, Route des Jeunes/de la Jonction, Geneva 8 CH-1211, Switzerland
[d] LVMH, Fragrance Safety and Regulatory Affairs, 185 Avenue de Verdun, Saint Jean de Braye Cedex F-45804, France
[e] Givaudan Suisse SA, 5 chemin de la parfumerie, Vernier CH 1214, Switzerland
[f] The Procter & Gamble Company, Miami Valley Laboratories, 11810 East Miami River Road, Cincinnati, OH 45252, USA
[g] Clariant Produkte (Deutschland) GmbH, Corporate Product Safety, Am Unisys-Park 1, 65843 Sulzbach, Germany

Regulatory, Toxicology and Pharmacology 52 (2008) 2-23

QRA progress by multistakeholder participation

- 2012 SCCS Opinion on Fragrance Allergens
- A sequence of IDEA multistakeholder workshops resulting in:
  - Additional validation of the sensitisation assessment factors (SAFs) applied in QRA1 by reassessing uncertainties where necessary and reviewing the scientific rationale behind the assigned factors.
  - Integration of an aggregate exposure model within the QRA framework.
- Publication of QRA version 2 in 2020



Regulatory Toxicology and Pharmacology 118 (2020) 104805

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials

Anne Marie Api [a,*], David Basketter [b], James Bridges [c], Peter Cadby [d], Graham Ellis [e], Nicola Gilmour [f], Helmut Greim [g], Peter Griem [h], Petra Kern [i], Alain Khaiat [j], John O'Brien [k], Thomas Rustemeyer [l], Cindy Ryan [m], Bob Safford [n], Benjamin Smith [o,p], Matthias Vey [q], Ian R. White [r]

[a] Research Institute for Fragrance Materials, Inc., Woodcliff Lake, NJ, USA
[b] Consultant, DABMEB Consultancy Ltd., Sharnbrook, UK
[c] Member IDEA Supervisory Group, University of Surrey, Guildford, UK
[d] Consultant, Geneva, Switzerland
[e] Firmenich SA, 1 Route des Jeunes, Geneva, Switzerland
[f] Unilever Safety & Environmental Assurance Centre, Sharnbrook, UK
[g] Member IDEA Supervisory Group, Technical University of Munich, Germany
[h] Symrise AG, Holzminden, Germany
[i] NV Procter & Gamble Services Company SA, Strombeek-Bever, Belgium
[j] Member IDEA Supervisory Group, Cosmetics Consultant, Singapore
[k] Creme Global, Dublin, Ireland
[l] Member IDEA Supervisory Group, VU Amsterdam, Netherlands
[m] The Procter & Gamble Company, Mason, OH, USA
[n] Consultant, B-Safe Toxicology Consulting, Rushden, UK
[o] Innovations in Food and Chemical Safety Programme, Singapore Institute of Food & Biotechnology Innovation, Agency for Science, Technology & Research, Singapore
[p] School of Chemical & Biomedical Engineering, Nanyang Technological University, Singapore
[q] International Fragrance Association, Brussels, Belgium
[r] Member IDEA Supervisory Group, St. John's Institute of Dermatology, London, UK

IFRA Standards Setting Process - Transparency & Independence

IFRA, RIFM and the Expert Panel for Fragrance Safety are at the heart of a multi-stakeholder Standard Setting Process performed in close collaboration

www.ifrafragrance.org

www.rifm.org

fragrancesafetypanel.org

IFRA Standards Setting Process for a fragrance material

Executive summary contained in the Guidance for the Use of IFRA Standards; https://ifrafragrance.org/safe-use/introduction

Step 1
Fragrance manufacturers and customers share with IFRA / RIFM information on use and exposure (concentrations & variety of use, volume of use); chemical composition; Industry also shares studies into RIFM DB

Step 2
RIFM drafts a safety assessment (SA) by combining exposure info with toxicological data

Step 3
Expert Panel evaluates draft SA and assesses safety of current reported use (exposure)

Step 4
RIFM publishes the SA and provides IFRA with maximum acceptable concentrations (MACs), identifying those that require limits

Step 5
IFRA prepares an IFRA standard as a risk management measure to address SA concerns

Step 6
Consultation phase with broad stakeholder community

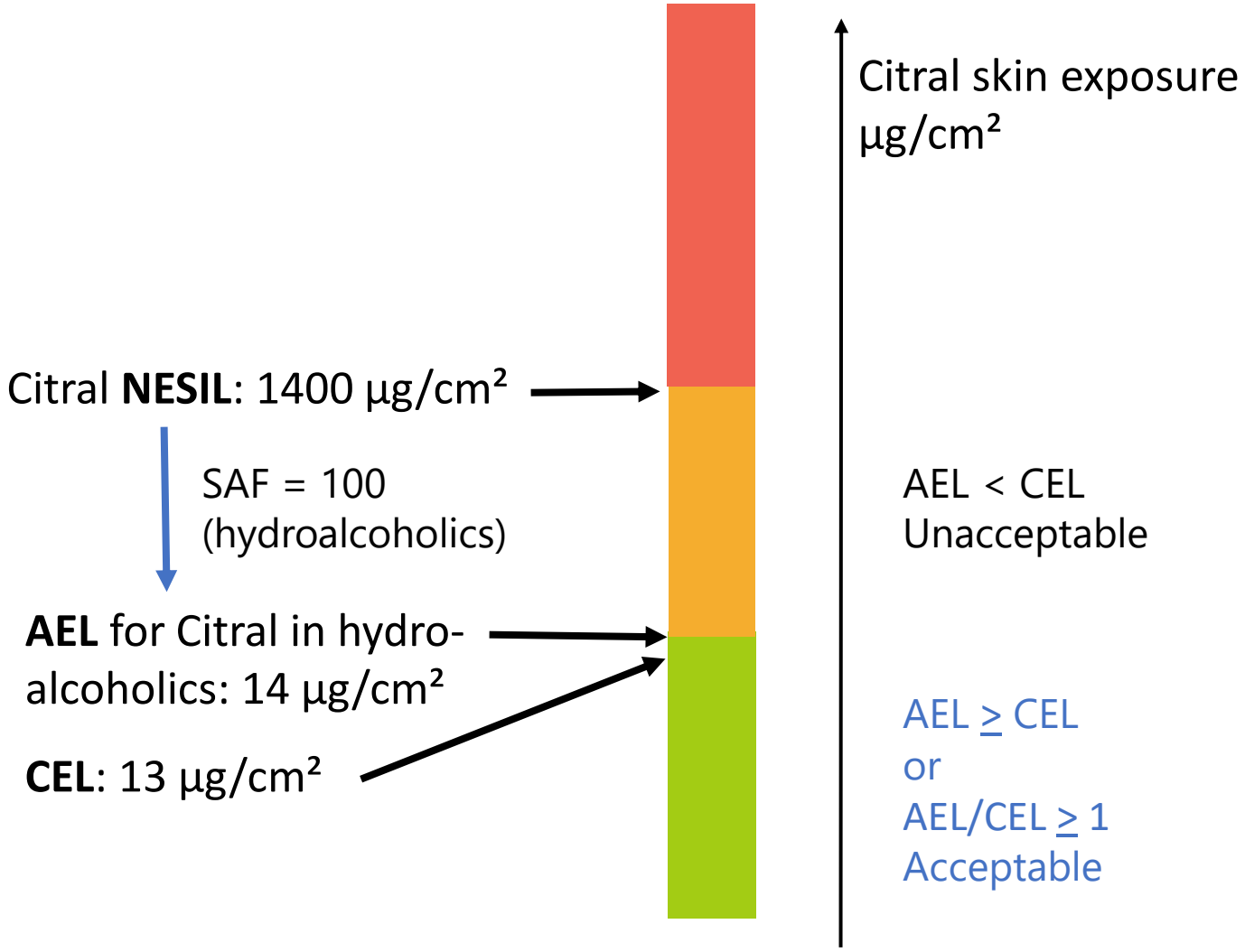
Step 7
Publication and implementation of industry-wide Standard by IFRA

QRA Dermal Sensitization Risk Characterisation: *Citral in hydroalcoholic products*

Acceptable Exposure Levels (AELs) to sensitizing fragrance ingredients can be determined for consumer product types:

AEL = NESIL / SAF

Estimated/modelled/measured Consumer Exposure Level (CEL) is compared against AEL to determine safety of exposure/use



Ongoing IDEA activities on QRA2

- Establish a monitoring system to follow trends in contact allergy by patch testing of consecutive patients to certain fragrance ingredients in a Europe-wide network of dermatology clinics

- Work on regulatory acceptance of incorporation of NAMs into QRA2 by interaction with authorities in all global regions and submission of methodology and single substance SCCS dossiers

- Implement the use of NAMs for NESIL derivation to make QRA in the future independent of studies on animal or humans

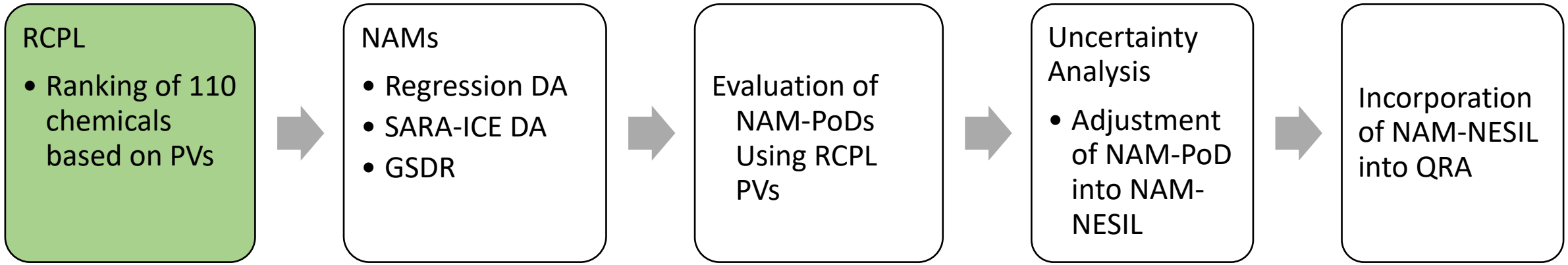
Working towards the regulatory acceptance of QRA based on NAMs

- Establishing a framework for integrating non-animal new approach methodologies (NAMs) into risk assessment is essential.
- This involves **accurate determination of NESIL using NAMs** rather than depending on animal and human data.
- Since 2016, a series of IDEA workshops has focused on incorporating NAMs into quantitative risk assessment (QRA).
- One outcome was the creation of a Reference Chemical Potency List (RCPL), published in 2022 and 2025, serving as a benchmark for assessing NAM effectiveness.

Working towards the regulatory acceptance of QRA based on NAMs

- Three established NAM approaches that provide potency values (PV) for skin sensitizers were assessed and deemed appropriate for deriving NESIL values for sensitizing fragrance ingredients.
- This topic will be elaborated upon further, as it constitutes the central focus of this presentation.

Project steps for deriving a NAM-based QRA framework



RCPL – Reference Chemical Potency List

- **A ranking of 110 chemicals based on skin sensitization potency values** was developed using the most reliable human and/or animal data available.
- The RCPL initiative achieved:
  - A **workflow** designed to implement a **structured Weight of Evidence (WoE)** approach integrating both **human and animal** data.
  - The introduction of the **Potency Value (PV):** defined as the estimated concentration (dose per unit area) at which skin sensitization is first triggered, derived from human and animal data; this value marks the inflection point on the dose-response curve for the initiation of sensitization for each chemical.
  - The establishment of **rigorous quality standards** for selecting both animal and human data.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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)

Amaia Irizar [a,*], Hans Bender [b], Peter Griem [c], Andreas Natsch [d], Matthias Vey [a], Ian Kimber [e]

[a] The International Fragrance Association (IFRA), Switzerland
[b] hjb Consulting, Bonn, Germany
[c] Symrise AG, Holzminden, Germany
[d] Givaudan Suisse SA, Switzerland
[e] Faculty of Biology, Medicine and Health, University of Manchester, UK

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


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journal homepage: www.elsevier.com/locate/yrtph

An extended Reference Chemical Potency List (RCPL) for characterising the performance of New Approach Methodologies (NAMs) in measuring the skin sensitisation potency of fragrance chemicals

Amaia Irizar [a,*], Hans Bender [b], James W. Bridges [c], Peter Griem [d], Andreas Natsch [e], Matthias Vey [a], Ian Kimber [f]

[a] The International Fragrance Association (IFRA), Switzerland
[b] hjb Consulting, Bonn, Germany
[c] Faculty of Health and Medical Sciences, University of Surrey, UK
[d] Symrise AG, Holzminden, Germany
[e] Givaudan Suisse SA, Switzerland
[f] Faculty of Biology, Medicine and Health, University of Manchester, UK

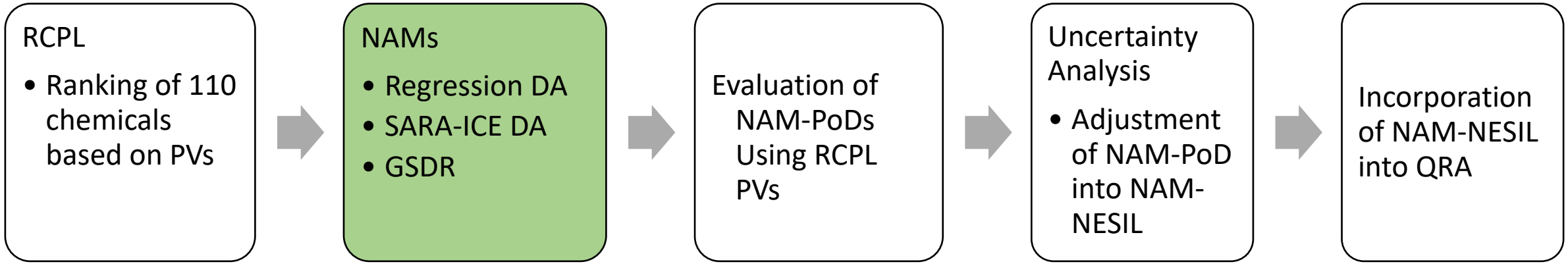
Irizar et al 2025, https://doi.org/10.1016/j.yrtph.2025.105944

Benefits of the RCPL

- RCPL PVs were developed as a tool to assess NAM-based predictions, serving as points of departure (PoD) for QRA.
- These RCPL PVs were established using well-curated human data (e.g., HRIPT) and animal data (e.g., LLNA).
- NAM data, whether in vitro or in silico, were excluded to specifically evaluate the predictivity of NAM approaches.
- The majority (100 out of 110) of RCPL chemicals are fragrance ingredients, with additional substances included to cover the full potency range of chemical sensitizers.
- PVs are primarily expressed numerically on a continuous scale, minimizing the use of potency categories wherever possible.

The following slides will demonstrate the application of RCPL.

Process flow for deriving the NAM-based QRA framework



The three approaches to derive a NAM-PoD

- **Regression Defined Approach (DA)**: integrates data from KeratinoSens, kinetic DPRA and human cell line activation assay (h-CLAT) in a fixed flow encoded in an Excel sheet to determine a PoD in µg/cm²

- **The SARA-ICE DA** is a Bayesian statistics-based software
  - It uses the same input data as the regression-based DA (KS, h-CLAT and kDPRA), in addition, DPRA and optionally U-SENS and LLNA can be used
  - Gives a probability distribution, the latest online version also gives PoD in µg/cm²

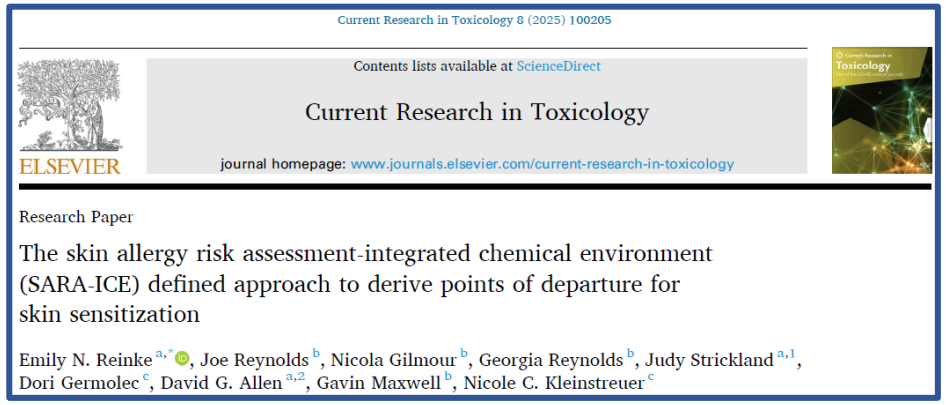
- **GSDR** (GARD-dose response assay) – same method as GARD, but conducted in dose-response mode to determine concentration for changed genomic signature, linear transformation leads to a PoD in µg/cm²

Research Article

Integrated Skin Sensitization Assessment Based on OECD Methods (I): Deriving a Point of Departure for Risk Assessment

Andreas Natsch[1] and George Frank Gerberick[2]

[1]Fragrances S&T, Ingredients Research, Givaudan Schweiz AG, Kemptthal, Switzerland; [2]GF3 Consultancy, LLC, Cincinnati, OH, USA



Current Research in Toxicology 8 (2025) 100205

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Current Research in Toxicology

journal homepage: www.journals.elsevier.com/current-research-in-toxicology

Research Paper

The skin allergy risk assessment-integrated chemical environment (SARA-ICE) defined approach to derive points of departure for skin sensitization

Emily N. Reinke[a,*], Joe Reynolds[b], Nicola Gilmour[b], Georgia Reynolds[b], Judy Strickland[a,1], Dori Germolec[c], David G. Allen[a,2], Gavin Maxwell[b], Nicole C. Kleinstreuer[c]

Regulatory Toxicology and Pharmacology 149 (2024) 105597

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

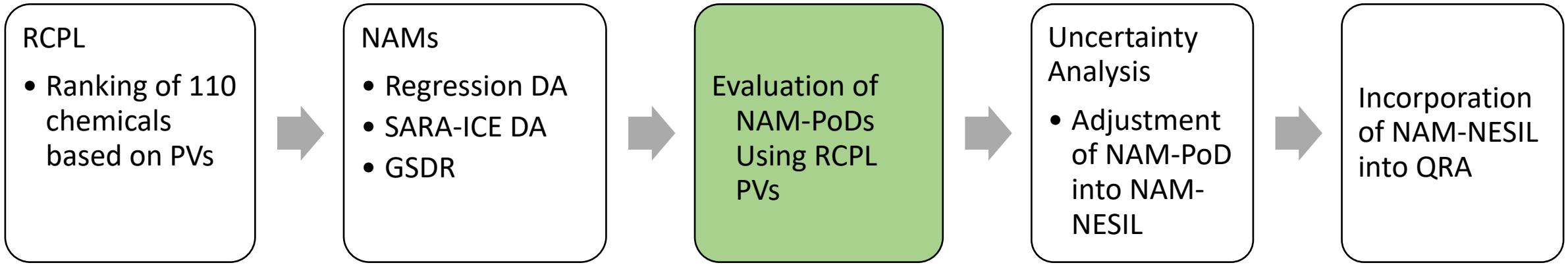
GARDskin dose-response assay and its application in conducting Quantitative Risk Assessment (QRA) for fragrance materials using a Next Generation Risk Assessment (NGRA) framework

Shashikiran Donthamsetty[a,1,*], Andy Forreryd[b,1], Paul Sterchele[a], Xiao Huang[a], Robin Gradin[b], Henrik Johansson[b], Ulrika Mattson[b], Isabelle Lee[c], Anne Marie Api[c], Gregory Ladics[d,**]

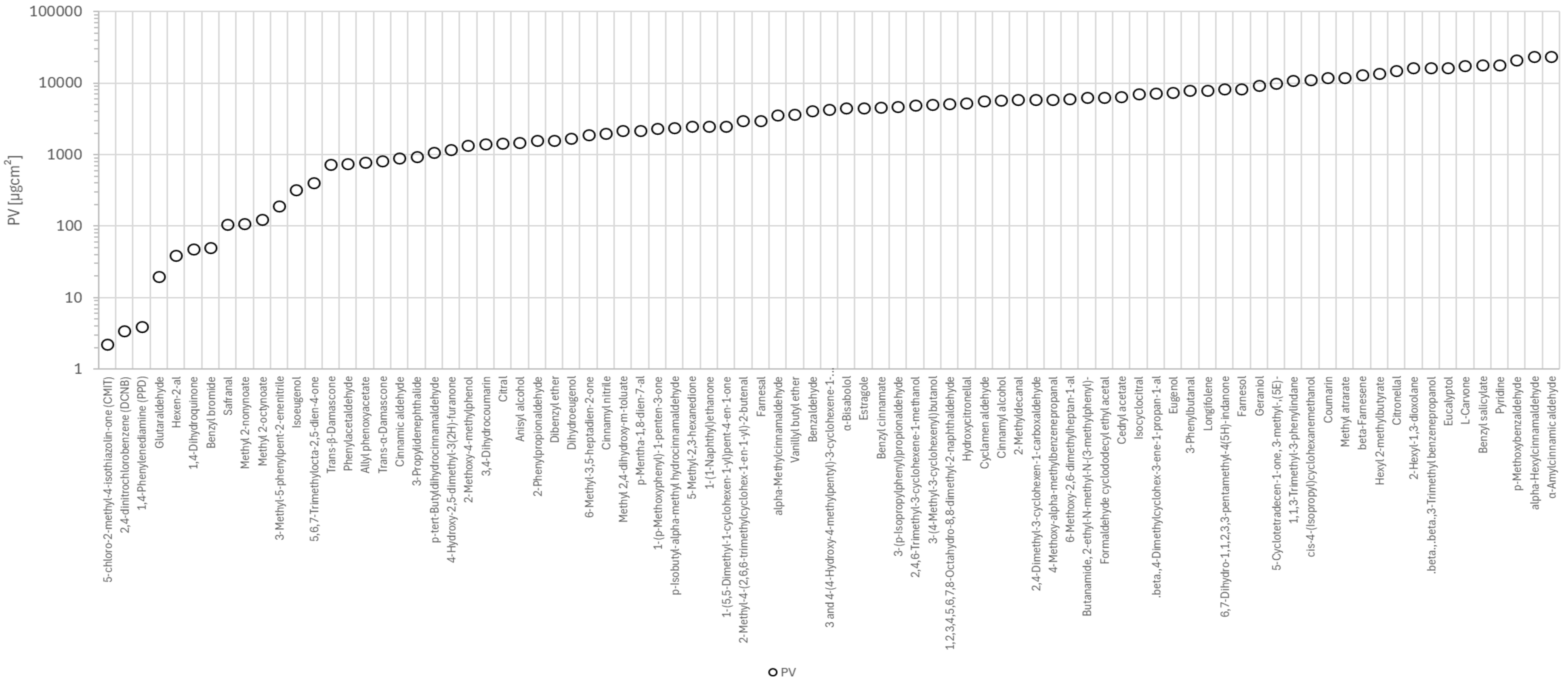
Prediction target of the different approaches

- Fundamentally, all three methods estimate a **point of departure (PoD)** using the same unit of measurement, **µg/cm²**.
- Nevertheless, they are calibrated against different **metrics**. Since each method targets distinct **reference points**, the **NAM-PoD**, although expressed in the same unit, is not inherently equivalent across approaches.
- As a result, certain methods are expected to yield lower **PoD values**, which must be taken into account when assessing **uncertainty** and adjusting **NAM-PoDs**.
- For this initial evaluation, however, we accept these varying **NAM-PoDs** at face value and proceed to compare them against the **RCPL PV**.

Process flow for deriving the NAM-based QRA framework

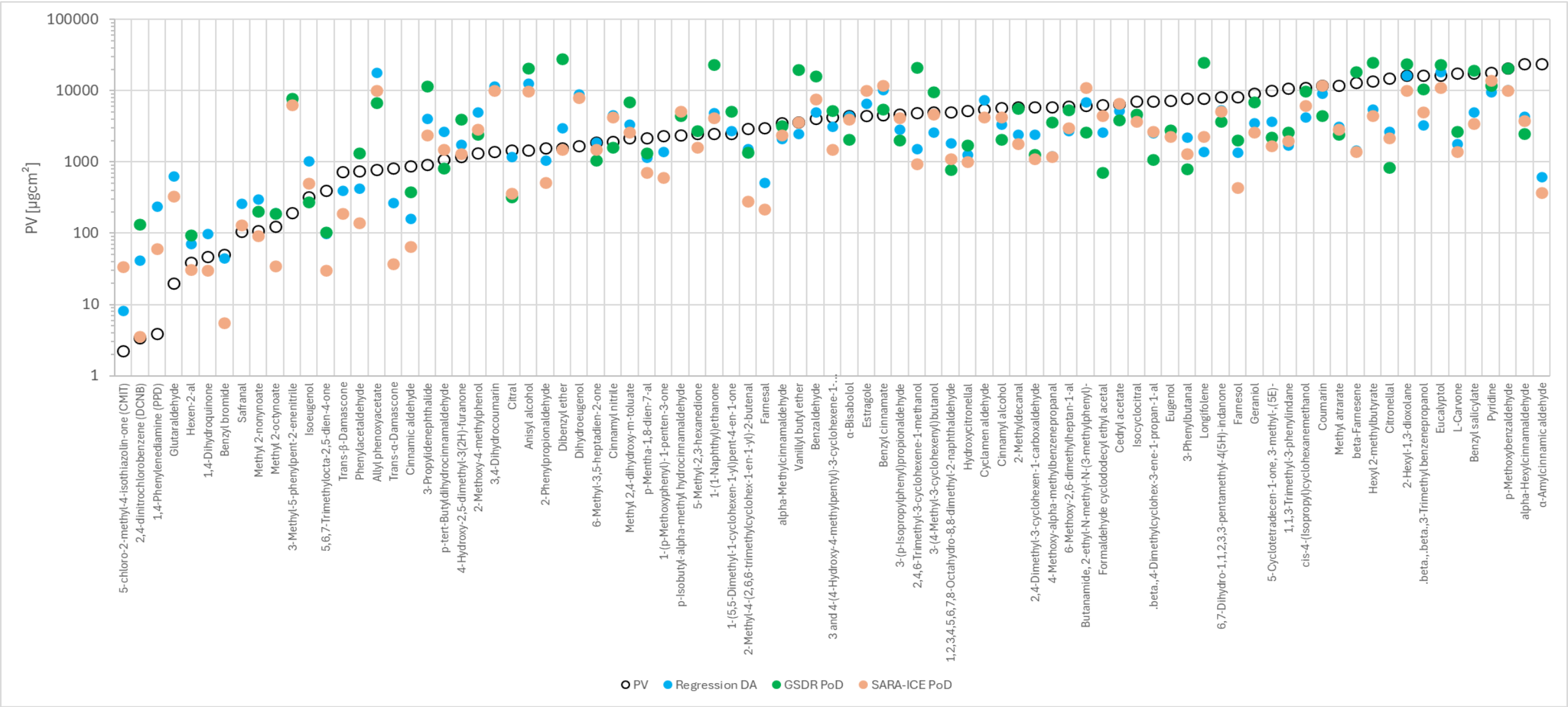


RCPL PVs



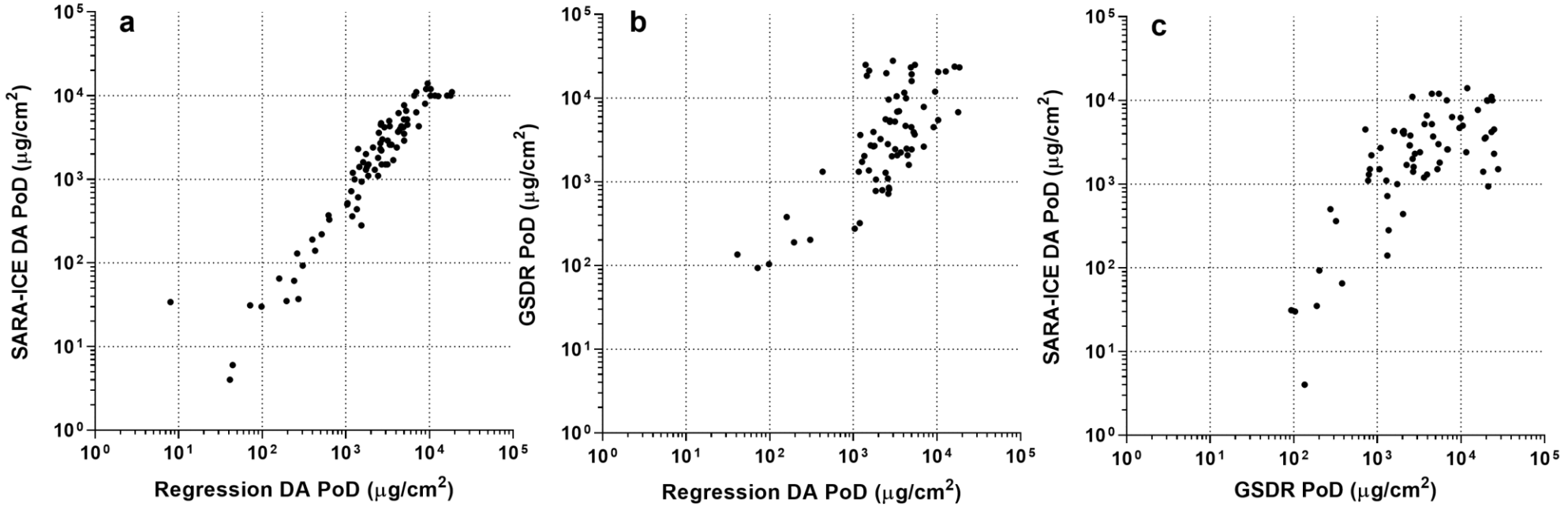
100000
10000
1000
100
10
1
PV [μgcm^{2}]
5-chloro-2-methyl-4-isothiazolin-one (CMIT)
2,4-dinitrochlorobenzene (DCNB)
1,4-Phenylenediamine (PPD)
Glutaraldehyde
Hexen-2-al
1,4-Dihydroquinone
Benzyl bromide
Safranal
Methyl 2-nonynoate
Methyl 2-octynoate
3-Methyl-5-phenylpent-2-enenitrile
Isoeugenol
5,6,7-Trimethylocta-2,5-dien-4-one
Trans-β-Damascone
Phenylacetaldehyde
Allyl phenoxyacetate
Trans-α-Damascone
Cinnamic aldehyde
3-Propylidenephthalide
p-tert-Butyldihydrocinnamaldehyde
4-Hydroxy-2,5-dimethyl-3(2H)-furanone
2-Methoxy-4-methylphenol
3,4-Dihydrocoumarin
Citral
Anisyl alcohol
2-Phenylpropionaldehyde
Dibenzyl ether
Dihydroeugenol
6-Methyl-3,5-heptadien-2-one
Cinnamyl nitrile
Methyl 2,4-dihydroxy-m-toluate
p-Mentha-1,8-dien-7-al
1-(p-Methoxyphenyl)-1-penten-3-one
p-Isobutyl-alpha-methyl hydrocinnamaldehyde
5-Methyl-2,3-hexanedione
1-(1-Naphthyl)ethanone
1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one
2-Methyl-4-(2,6,6-trimethylcyclohex-1-en-1-yl)-2-butenal
Farnesal
alpha-Methylcinnamaldehyde
Vanillyl butyl ether
Benzaldehyde
3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-...
α-Bisabolol
Estragole
Benzyl cinnamate
3-(p-Isopropylphenyl)propionaldehyde
2,4,6-Trimethyl-3-cyclohexene-1-methanol
3-(4-Methyl-3-cyclohexenyl)butanol
1,2,3,4,5,6,7,8-Octahydro-8,8-dimethyl-2-naphthaldehyde
Hydroxycitronellal
Cyclamen aldehyde
Cinnamyl alcohol
2-Methyldecanal
2,4-Dimethyl-3-cyclohexen-1-carboxaldehyde
4-Methoxy-alpha-methylbenzenepropanal
6-Methoxy-2,6-dimethylheptan-1-al
Butanamide, 2-ethyl-N-methyl-N-(3-methylphenyl)-
Formaldehyde cyclododecyl ethyl acetal
Cedryl acetate
Isocyclocitral
.beta.,4-Dimethylcyclohex-3-ene-1-propan-1-al
Eugenol
3-Phenylbutanal
Longifolene
6,7-Dihydro-1,1,2,3,3-pentamethyl-4(5H)-indanone
Farnesol
Geraniol
5-Cyclotetradecen-1-one, 3-methyl-,(5E)-
1,1,3-Trimethyl-3-phenylindane
cis-4-(Isopropyl)cyclohexanemethanol
Coumarin
Methyl atrarate
beta-Farnesene
Hexyl 2-methylbutyrate
Citronellal
2-Hexyl-1,3-dioxolane
.beta.,.beta.,3-Trimethylbenzenepropanol
Eucalyptol
L-Carvone
Benzyl salicylate
Pyridine
p-Methoxybenzaldehyde
alpha-Hexylcinnamaldehyde
α-Amylcinnamic aldehyde
PV

RCPL PVs and 3 NAM approaches



Skin sensitizers: correlation between NAMs

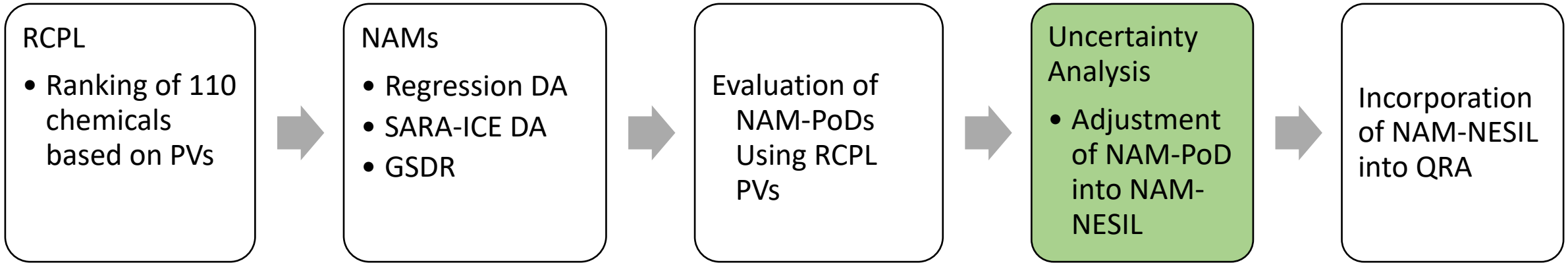
- The output of SARA-ICE DA is strongly correlated with the output of the Regression DA, which is not surprising as they use the same input data
  - ➢ However, the slope is steeper than 1, and hence strong sensitizers are predicted more strongly by SARA-ICE DA – again in line with the prediction target
- A more even correlation exists between GSDR-PoD and Regression DA-PoD, although we lack data on very strong sensitizers
- In general correlation is weaker between GSDR and the other DAs – but this is due to GSDR data coming from an independent experimental approach



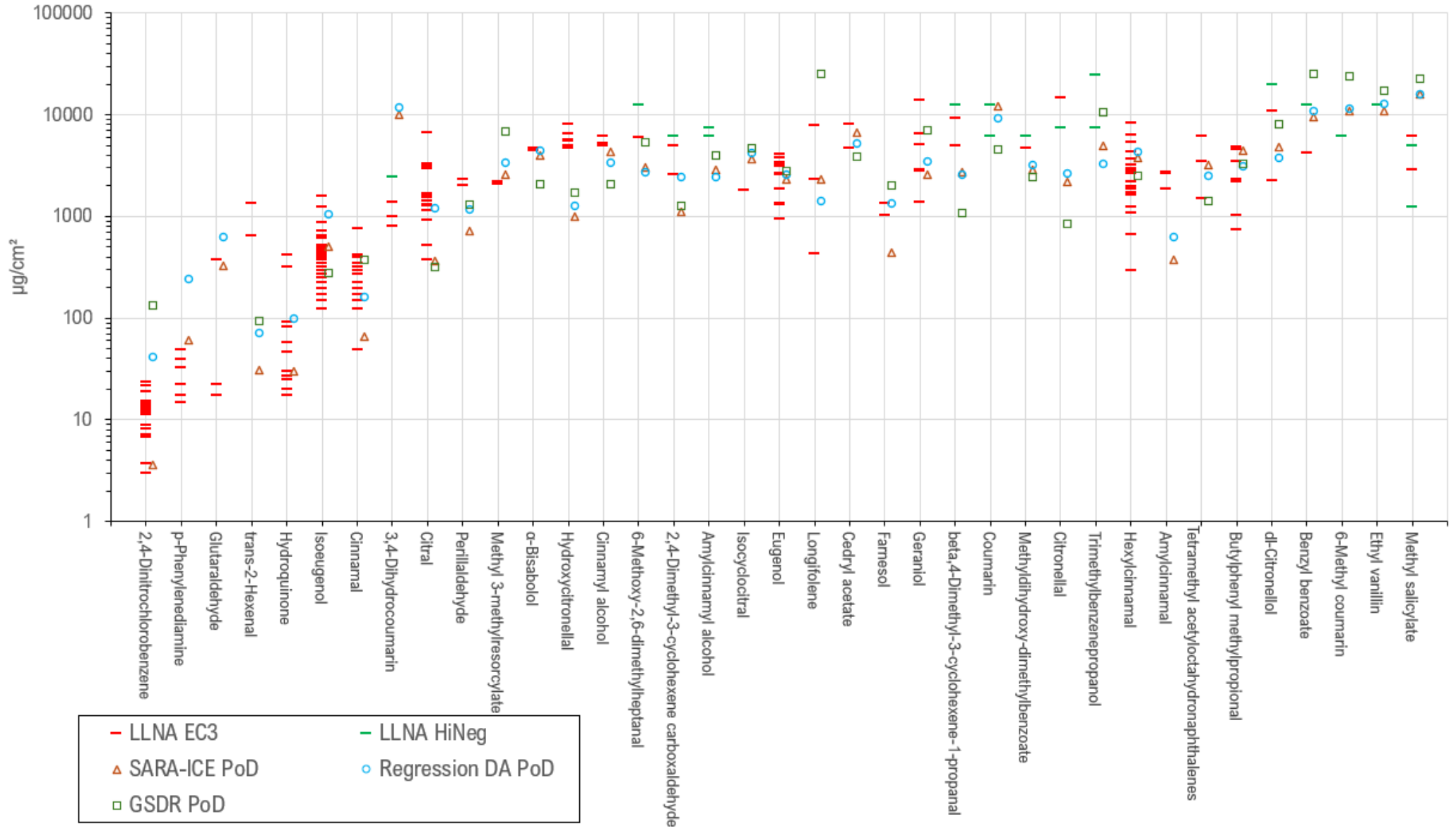
Summary statistics for comparison of NAM-PoD with RCPL PVs

- **Three currently available NAM approaches** Regression DA, SARA-ICE DA and GSDR were evaluated.
- For about **100 chemicals**, the NAM-PoDs were compared to PVs based on animal/human data (RCPL)
  - **Potency predictions from all three approaches correlate well with PVs,** with a geometric mean of the fold-difference on either direction close to three
- Regression DA and GSDR, on average, predict slightly higher values than SARA-ICE DA
  - explained by the different prediction target the models were trained on

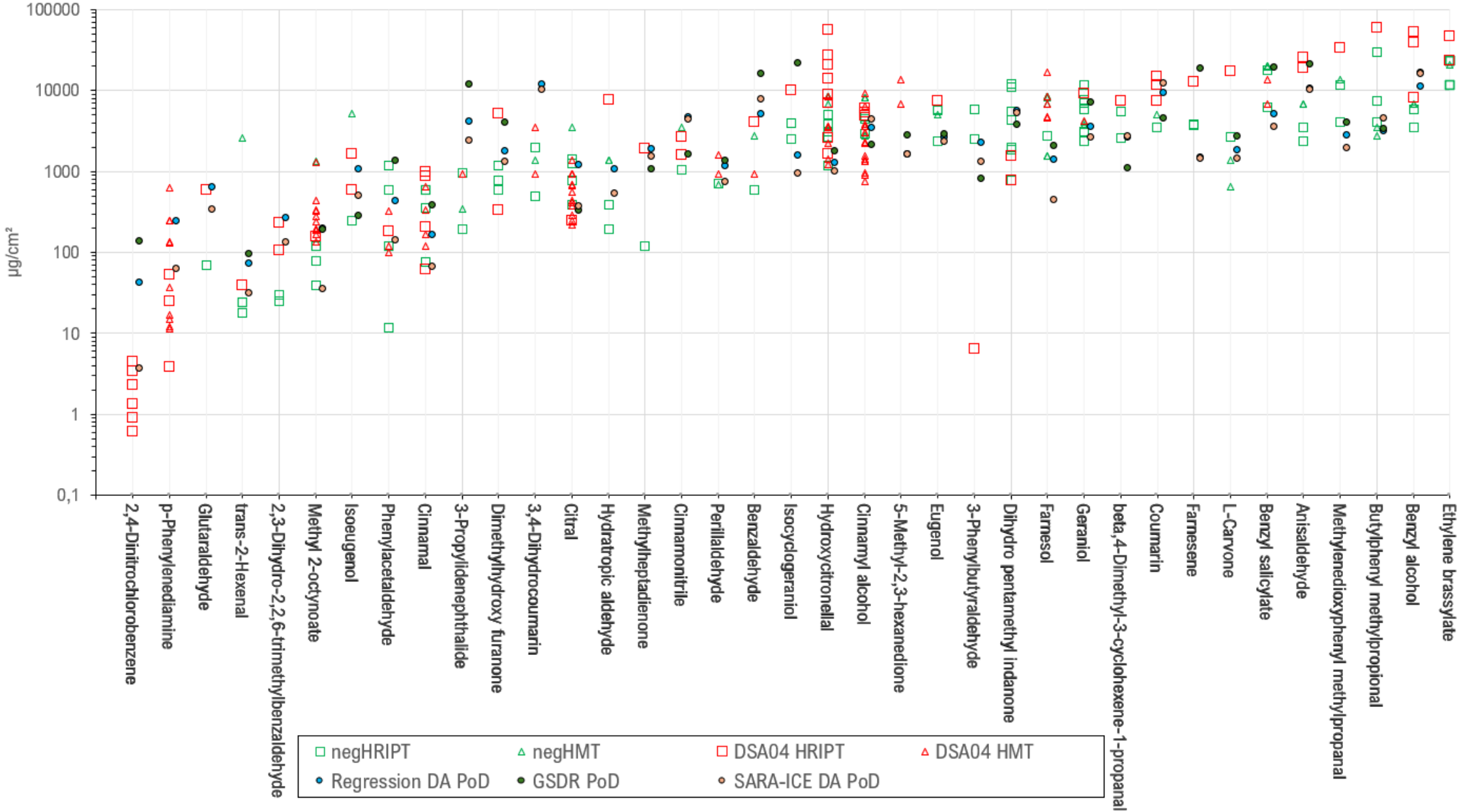
Process flow for deriving the NAM-based QRA framework



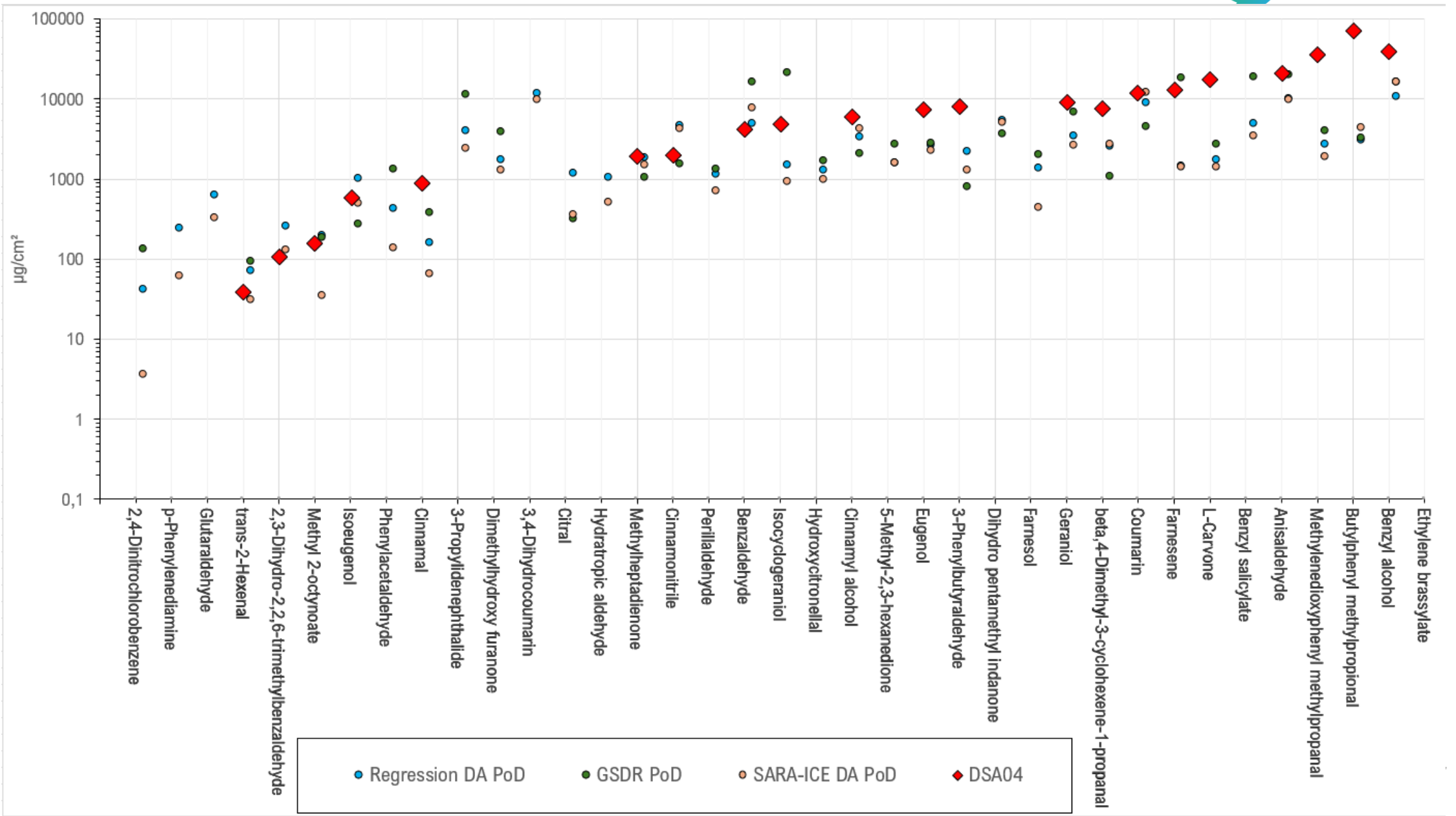
Variability of LLNA EC3 values used in the derivation of RCPL PVs



Variability of human data used in the derivation of RCPL PV



Human DSA04 vs. NAM PoD

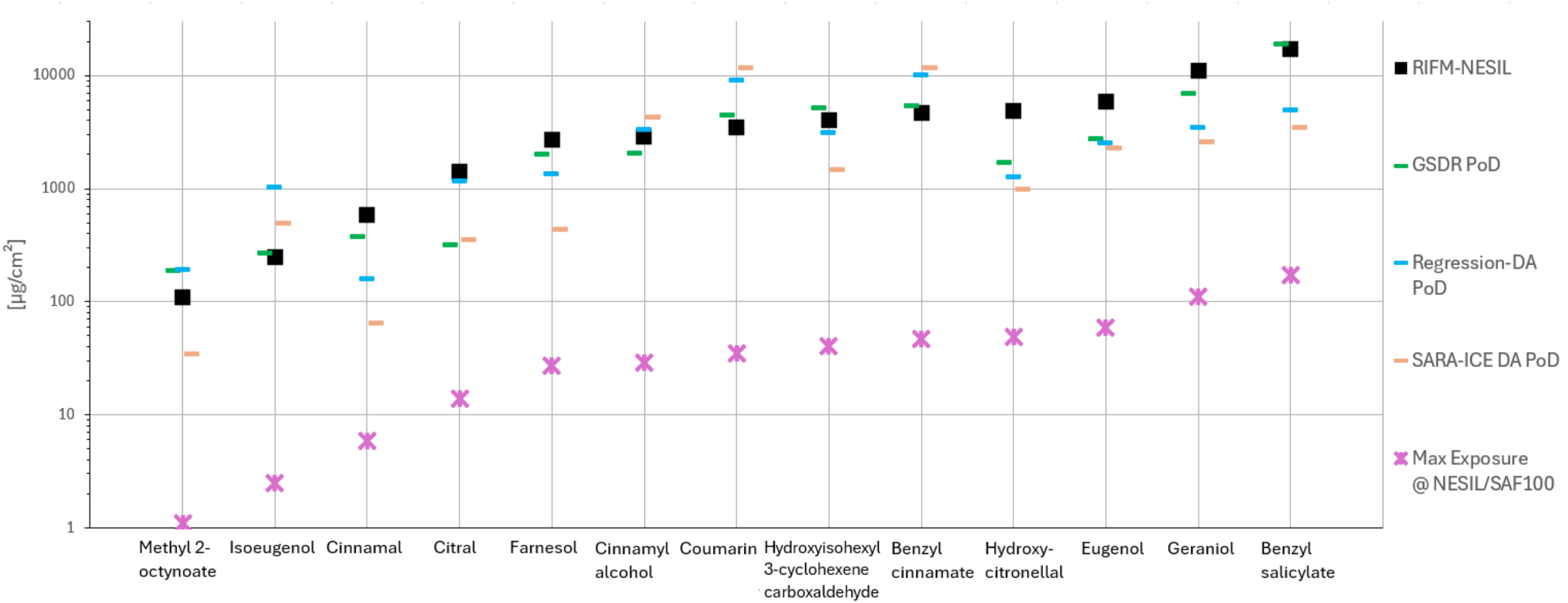


Deriving method-specific Adjustment Factors

Chemical	GSDR-PoD/DSA04	Chemical	Regression DA-PoD/DSA04	Chemical	SARA-ICE DA-PoD/DSA04
Isocyclogeraniol	4,33	Methyl 2-nonynoate	2,80	Cinnamonitrile	2,19
Benzaldehyde	3,91	2,3-Dihydro-2,2,6-tri-methylbenzaldehyde	2,47	Benzaldehyde	1,88
Trans-2-Hexenal	2,38	Cinnamonitrile	2,35	2,3-Dihydro-2,2,6-tri-methylbenzaldehyde	1,23
Methyl 2-nonynoate	1,86	Trans-2-Hexenal	1,82	Coumarin	1,02
Farnesene	1,43	Isoeugenol	1,77		
Methyl 2-octynoate	1,19	Methyl 2-octynoate	1,23		
		Benzaldehyde	1,22		
Mean of two highest values	4,12		2,63		2,04
Rounded to closest half value	4		2,5		2

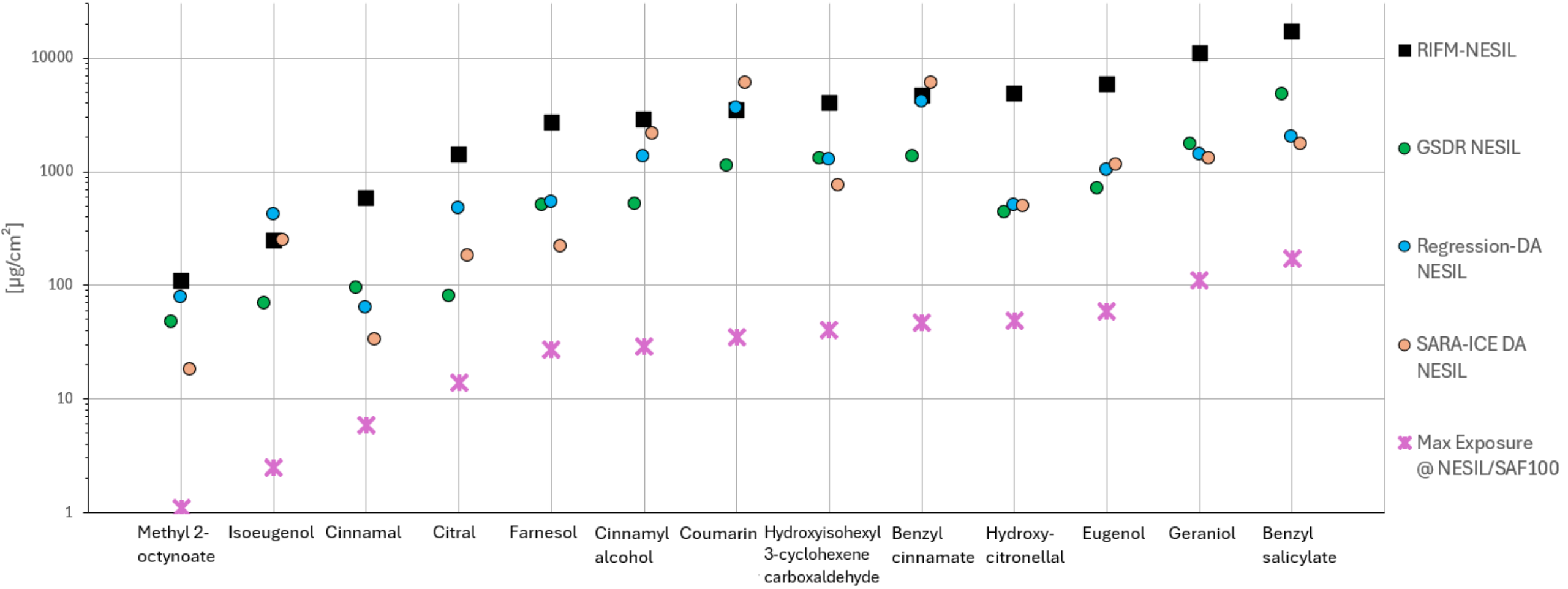
Case studies: Some clinically relevant allergens

- **NAM-PoDs** for some clinically relevant fragrance allergens which are frequently used in patch testing
- RIFM-NESILs are starting points for assessments (usually from/supported by human studies) used for setting current IFRA standards (max. exposure from cosmetic products with 100x safety factor)



Case studies: Some clinically relevant allergens

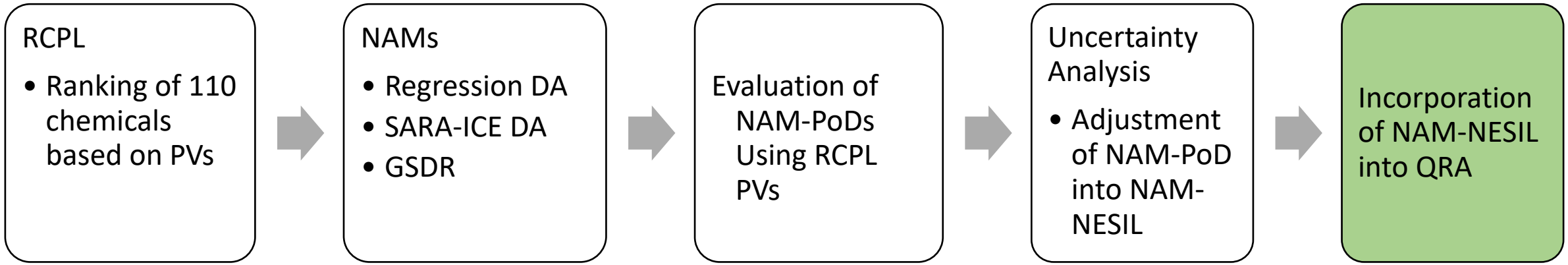
- **NAM-NESILs** are NAM-PoDs divided by the NAM adjustment factor
- NAM-NESILs are at or below the current RIFM-NESIL values
- ***This means that if only NAM data were available to derive the NESIL, the NAM-NESILs would be conservative.***



Summary of uncertainty analysis

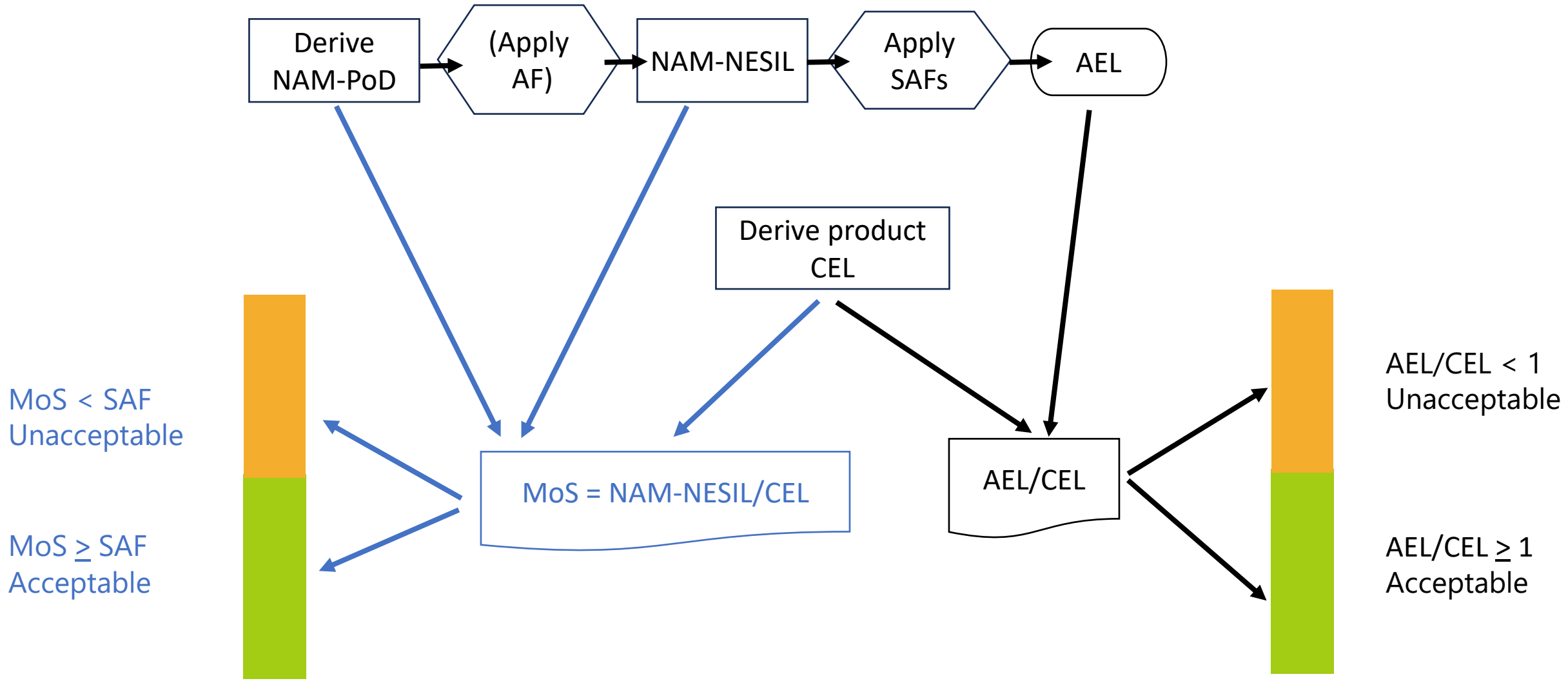
- For a given skin sensitizer each, human and animal in vivo potency values from independent experiments tend to vary about 3-fold from the mean
- For all sensitisers, potency values from all three NAM approaches, similarly, vary about 3-fold from the RCPL PV
- From comparison of NAM PoDs with human DSA04s and NOELs **adjustment factors** for each NAM may be derived:
  - **2.5 for Regression DA**
  - **2 for SARA-ICE DA**
  - **4 for GSDR**
- Since NAM PoDs vary rather less than the mouse and human data used to derive current NESIL values, use of the adjustment factors is not considered a must, especially when data supporting the NAM PoD are available

Process flow for deriving the NAM-based QRA framework



Perspectives on Practical Implementation

Process to conduct QRA for NEW fragrance materials based only on NAM data (adjustment factor OR margin of safety approach)



Summary

- **Three currently available NAM approaches** Regression DA, SARA-ICE DA and GSDR were evaluated
- **Potency predictions from all three approaches correlate well** with Reference Chemical Potency List (RCPL)
- **Adjustment Factors** may **not be considered necessary** if NAM-PoD is supported by additional evidence
- For new materials with no other data available **adjustment factors** of **2.5 for Regression DA, 2 for SARA-ICE and 4 for GSDR** may be applied
- **NAM-NESIL derived from any of the three NAM approaches may be used in** Quantitative Risk Assessment **(QRA) for NEW fragrance materials** with identified skin sensitisation hazard
- **Future skin** sensitisation risk assessment **(QRA)** should be **possible without** need for **animal** or **human** studies

Publication: Andreas Natsch, Peter Griem, Amaia Irizar, James Bridges, Matthias Vey, Isabelle Lee, Anne Marie Api, Petra Kern, Ian Kimber, Derivation of a Point of Departure using NAMs for application in Quantitative Risk Assessment of fragrance materials, Regulatory Toxicology and Pharmacology, 2026, https://doi.org/10.1016/j.yrtph.2026.106052