Application of a next generation risk assessment framework for skin sensitisation using non-animal data: geraniol case study

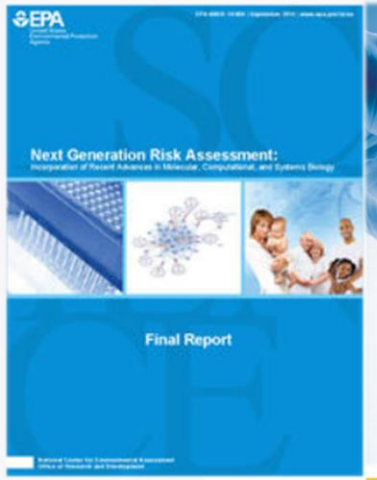
Nicola Gilmour, Nora Aptula, Katarzyna Przybylak, Georgia Reynolds, Joe Reynolds, Maja Aleksic, Ramya Rajagopal and Gavin Maxwell.

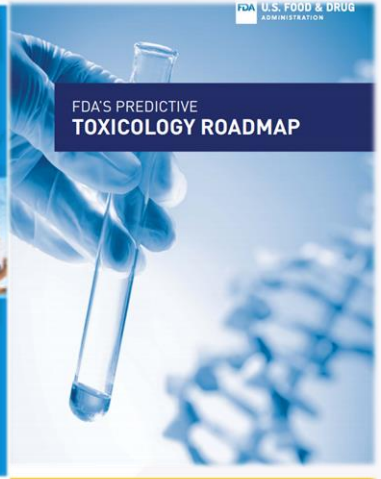
ESCD Amsterdam 8-10th June 2022

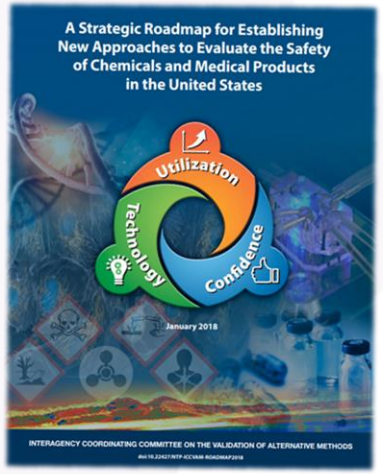
Unilever

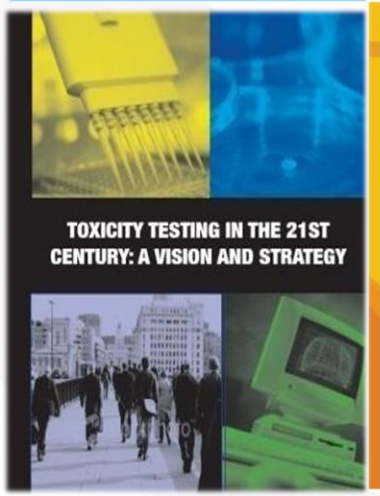
Assessing ingredient & product safety without animal testing

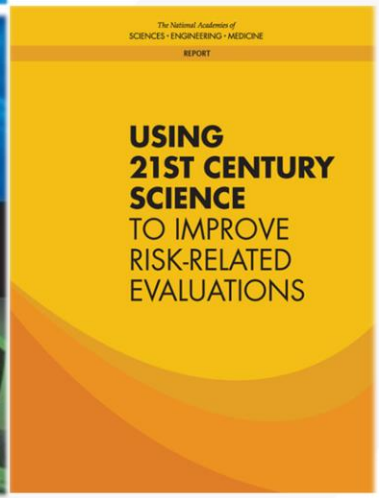
Next Generation Risk Assessment (NGRA)











Is it safe to include x% of chemical y in product z?

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Skin allergy risk assessment evolution

Increased mechanistic understanding

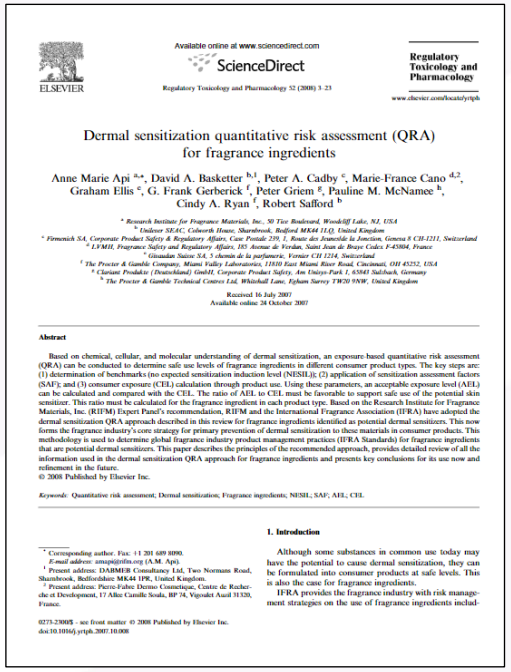
GPMT / Buehler → LLNA → Non-animal test methods

More accurate exposure assessments

Rinse off / Leave on → Individual Products → Aggregate exposure models; new exposure metrics

Increased transparency in risk assessment

Risk benchmarking → QRA → Computational / informatics approaches



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www.elsevier.com/locate/yrtph

Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients

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Abstract

Based on chemical, cellular, and molecular understanding of dermal sensitization, an exposure based quantitative risk assessment (QRA) can be conducted to determine safe use levels of fragrance ingredients in different consumer product types. The key steps are: (1) determination of benchmarks (no expected sensitization induction level (NESIL)); (2) application of sensitization assessment factors (SAF); and (3) consumer exposure (CEL) calculation through product use. Using these parameters, an acceptable exposure level (AEL) can be calculated and compared with the CEL. The ratio of AEL to CEL must be favorable to support safe use of the potential skin sensitizer. This ratio must be calculated for the fragrance ingredient in each product type. Based on the Research Institute for Fragrance Materials, Inc. (RIFM) Expert Panel's recommendation, RIFM and the International Fragrance Association (IFRA) have adopted the dermal sensitization QRA approach described in this review for fragrance ingredients identified as potential dermal sensitizers. This now forms the fragrance industry's core strategy for primary prevention of dermal sensitization to these materials in consumer products. This methodology is used to determine global fragrance industry product management practices (IFRA Standards) for fragrance ingredients that are potential dermal sensitizers. This paper describes the principles of the recommended approach, provides detailed review of all the information used in the dermal sensitization QRA approach for fragrance ingredients and presents key conclusions for its use now and refinement in the future.
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Keywords: Quantitative risk assessment; Dermal sensitization; Fragrance ingredients; NESIL; SAF; AEL; CEL

1. Introduction

Although some substances in common use today may have the potential to cause dermal sensitization, they can be formulated into consumer products at safe levels. This is also the case for fragrance ingredients.

IFRA provides the fragrance industry with risk management strategies on the use of fragrance ingredients includ-

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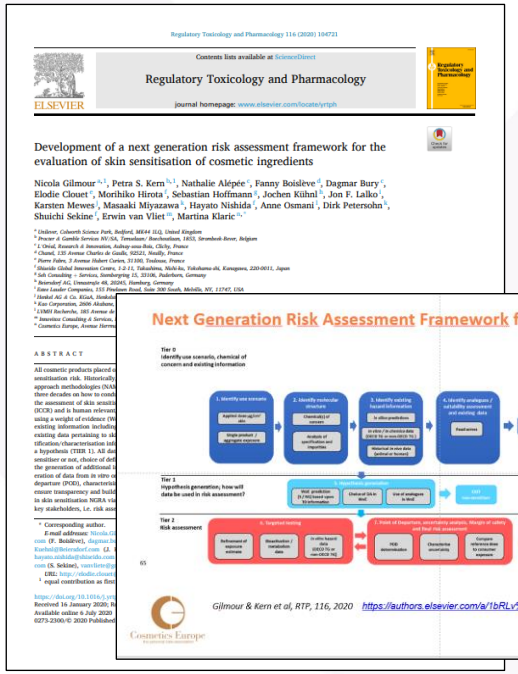
Updating exposure assessment for skin sensitization quantitative risk assessment for fragrance materials

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]

ARTICLE INFO

ABSTRACT

1. Introduction



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Development of a next generation risk assessment framework for the evaluation of skin sensitisation of cosmetic ingredients

Nicola Gilmour [a,1], Petra S. Kern [b,1], Nathalie Alépée [c], Fanny Boislève [d], Dagmar Bury [e], Elodie Clouet [f], Morihiko Hirota [g], Sebastian Hoffmann [h], Jochen Kühnl [b], Jon F. Lalko [i], Karsten Mewes [j], Masaaki Miyazawa [k], Hayato Nishida [l], Anne Osmani [f], Dirk Petersohn [b], Shuichi Sekine [l], Erwin van Vliet [m], Martina Klaric [n,*]

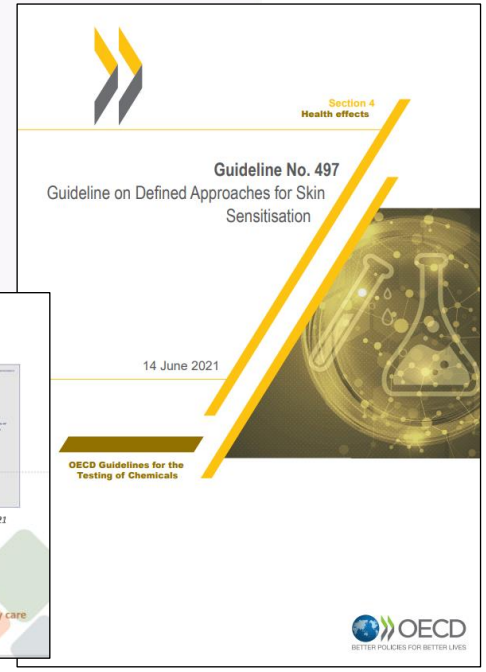
ABSTRACT

Next Generation Risk Assessment Framework for Skin Sensitisation

Gilmour & Kern et al, RTP, 116, 2020 https://authors.elsevier.com/a/1bRLv%7E81JLAV

SCCS 11th NoG 2021

We personally care



Section 4
Health effects

Guideline No. 497
Guideline on Defined Approaches for Skin Sensitisation

14 June 2021

OECD Guidelines for the Testing of Chemicals

OECD
BETTER POLICIES FOR BETTER LIVES

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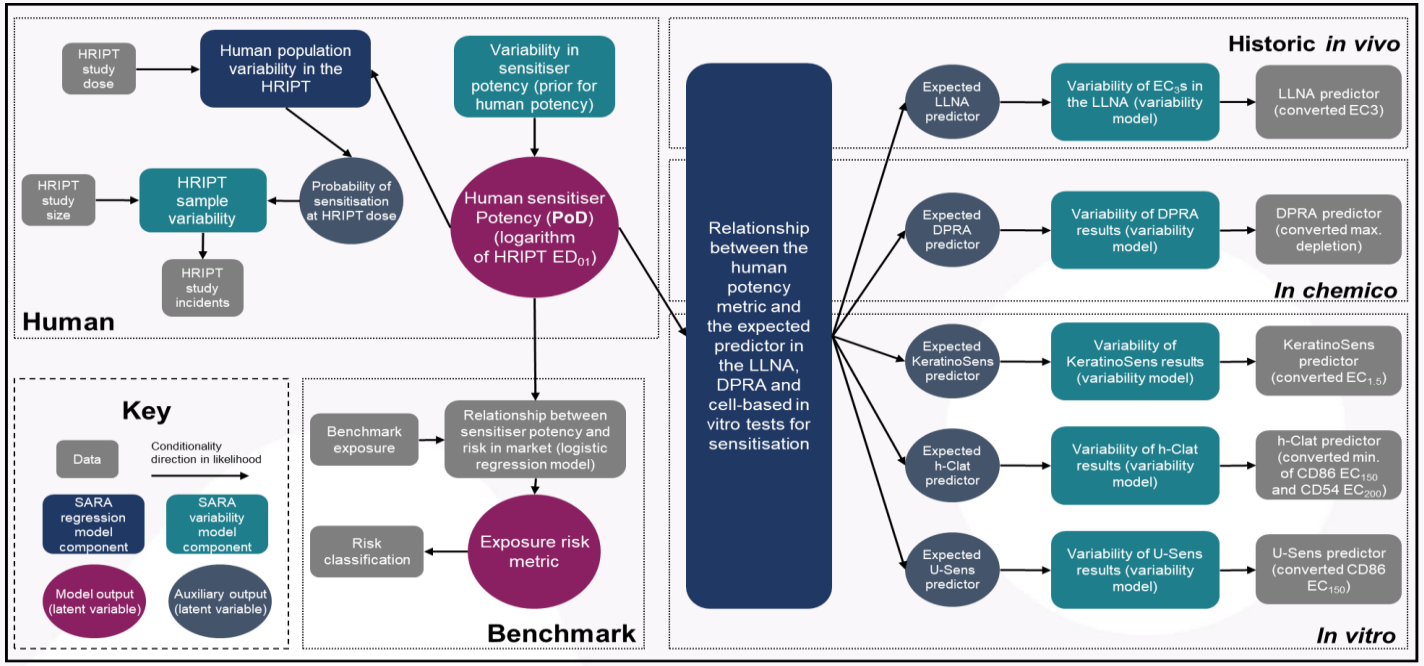
SARA Model – a defined approach to provide potency and risk information based upon New Approach Methodologies



- SARA model is a Bayesian statistical approach which can make potency and risk predictions using any combination of historical *in vivo* (LLNA, HRIPT) or NAM (DPRA, KeratinoSens™, h-CLAT and U-SENS™)
- Skin sensitser potency is expressed as the ED_{01}, the dose estimated to induce sensitisation in 1% of a HRIPT population. This is the Point of departure for the risk assessment.
- SARA model also makes use of benchmark exposures to infer a probability that a consumer exposure to a chemical is 'low risk',

Use of consumer exposure information and clinical evidence to develop skin allergy risk benchmarks

- Traditional risk assessment approaches for skin allergy use safety factors to rescale PoDs to market-equivalent safe doses for comparison against consumer exposure estimates.
- For NGRA, publicly available benchmark exposure information can be used to establish that an exposure is low risk and can be considered safe.
- To apply this concept, we established 62 low or high risk benchmark exposures using 10 human skin allergens (e.g. MCI/MI) with an established history of use in 7 cosmetic product types.

Material	Product type	Use level (ppm)	Consumer exposure to benchmark product (ng cm^{-2})	Induction risk
MCI/MI	Deo	30	350	HIGH
		7.5	87.8	HIGH
	Face cream	30	100	HIGH
		7.5	25	HIGH
	Body lotion	30	18	HIGH
		7.5	4	HIGH
	Liquid hand soap	15	7.3	LOW
	Shampoo	15	1.1	LOW
	Shower gel	15	0.2	LOW

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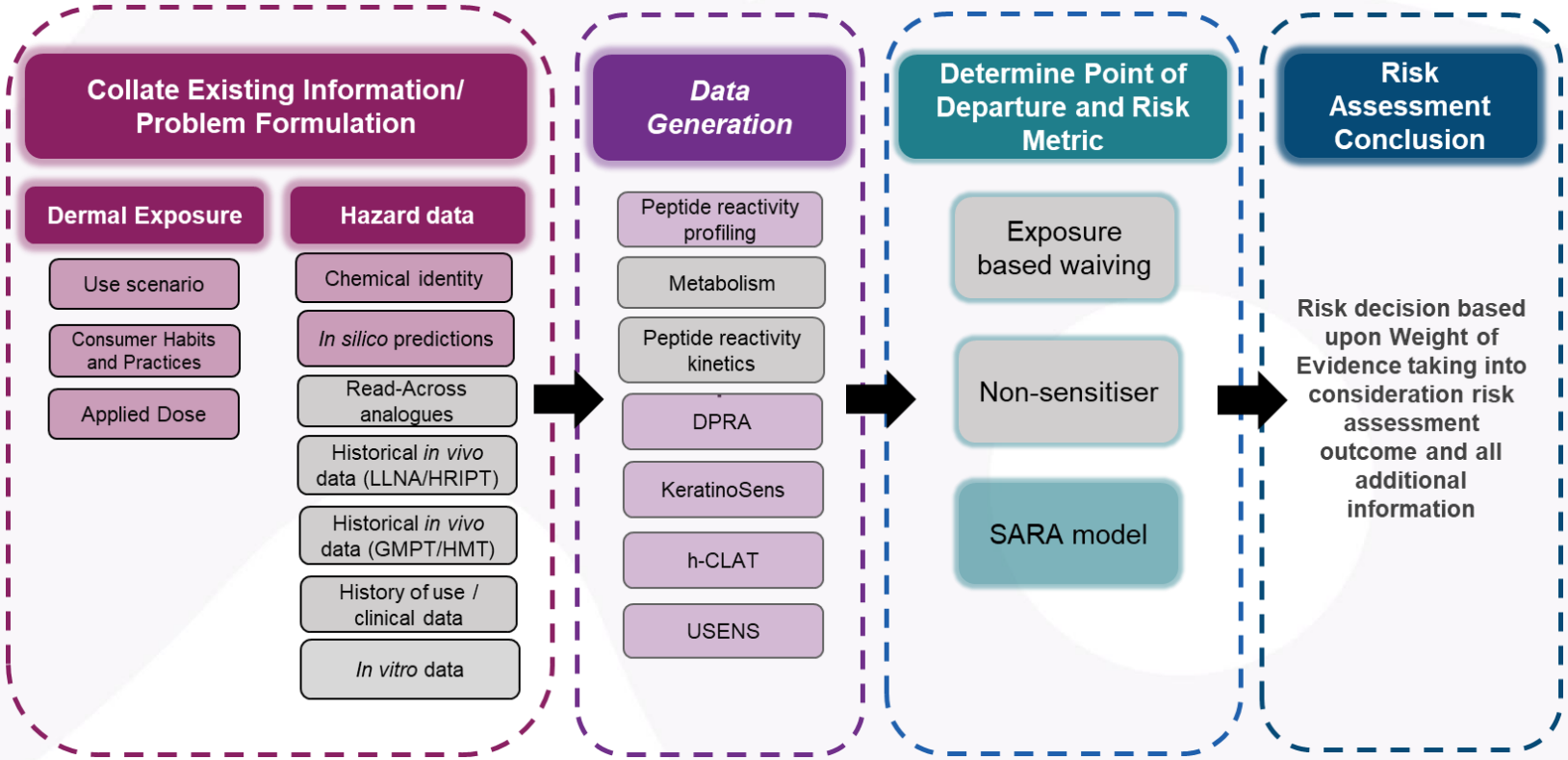
Application of NGRA framework for Skin Allergy



- Our NGRA framework is applied to a hypothetical skin allergy assessment of a consumer product: 0.02% (200ppm) geraniol in a face cream.
- For the purposes of the case study, historical *in vivo* data and read-across were not used, and the exposure was too high to apply exposure-based waiving.

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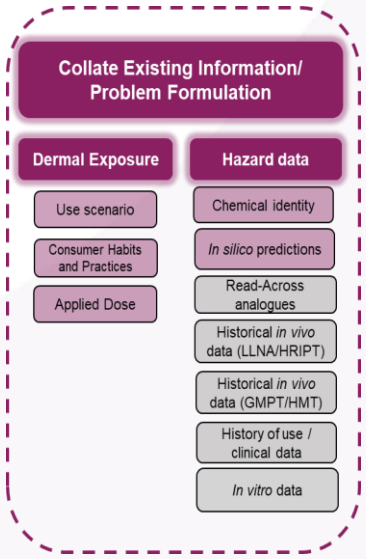
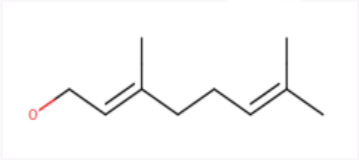
Local exposure + Collate Existing Information/ Problem Formulation



Geraniol
CAS 106-24-1



Product type	Face cream
Product used per day (90th percentile) (g/day)	1.54
Ingredient inclusion level (%)	0.02
Skin surface area face (cm^2)	565
Leave-on or Rinse-off	Leave-on
Local dermal exposure (µg/cm^2)	0.544

DEREK NEXUS v.2.4	Alert – terpenoid EC3 model – 20% (weak)
TIMES-SS v.2.30.1.11 Skin Sensitisation model with autoxidation	Parent – Non sensitiser (in domain) Metabolites – Strong sensitiser- after autoxidation to disubstituted a,b-unsaturated aldehydes, Weak sensitiser after autooxidation to hydroperoxides
ToxTree v.3.1.0	Alert for Schiff base formation
OECD QSAR Toolbox v.4.4	Protein binding by OECD Parent - No alert found Skin Metabolites (2) - Direct Acting Schiff Base Formers >> Di-substituted alpha, beta-unsaturated aldehydes

- Geraniol is activated via autooxidation to reactive molecules Schiff base adducts
- Confidence in this prediction is high based upon chemical prediction consensus from all applied *in silico* tools.
- peptide reactivity profiling data should be generated to test the hypothesis, that geraniol is activated by an abiotic activation mechanism (autoxidation)
- DPRA, KeratinoSens™, h-CLAT and U-SENS™ data should also be generated to enable a potency prediction using the SARA model

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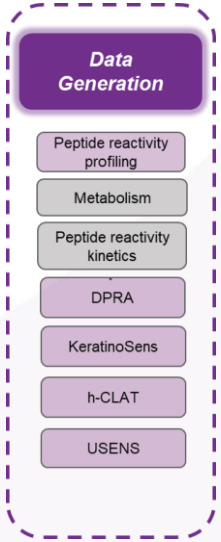
Data Generation



Reactivity Profiling	DPRA	KeratinoSens™	H-CLAT	U-SENS™
Cys (no adducts, 73.7 ± 0.8%) Lys (no adducts, 3.5 ± 0.6%) His (no adducts, -11.1 ± 8.0%) Arg (double Schiff base, 15.2 ± 0.2%) Tyr (no adducts, 8.2 ± 3.7%) N-term (acylation, Schiff base, 40.2 ± 1.1%) Ala (no adducts, -2.1 ± 17.0%)	Negative Cys depletion 0% Lys depletion 10%	Positive $EC_{1.5}$ 110 µM EC_3 >2000 µM IC_{50} 875 µM	Positive CD86 EC_{150} 123 µg ml^{-1} CD54 EC_{200} - µg ml^{-1} CV_{75} 140 µg ml^{-1}	Positive CD86 EC_{150} 53.6 µg ml^{-1} CV_{70} 113.9 µg ml^{-1}

- Geraniol was confirmed to be a reactive chemical (Schiff base formation with amines following autoxidation) by peptide profiling
- Geraniol demonstrated minimal depletion of Cys and Lys in the DPRA. Positive responses were evident in the KeratinoSens™, h-CLAT and U-SENS™.
- Thus, the weight of evidence suggests geraniol is a skin sensitiser and The human potency (ED_{01}) was estimated using the SARA model

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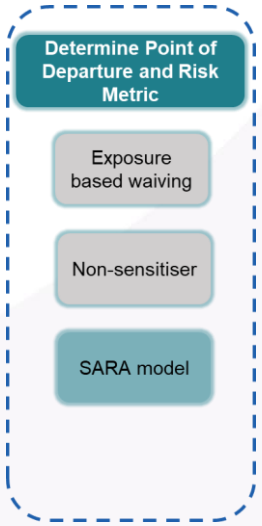
Determine Point of departure using SARA DA



- The generated DPRA, KeratinoSens™, hCLAT and USens™ data were used as inputs into the SARA model to define a human relevant PoD (ED_{01} i.e the 1% sensitising dose for a HRIPT population).

- For geraniol (NAM data only), the expected ED_{01} is 4,500 µg cm^{-2} (2.5th percentile: 180 µg cm^{-2}, 97.5th percentile: 96,000 µg cm^{-2}. Geraniol ranks with eugenol (which based upon LLNA data is reported to be of moderate potency).

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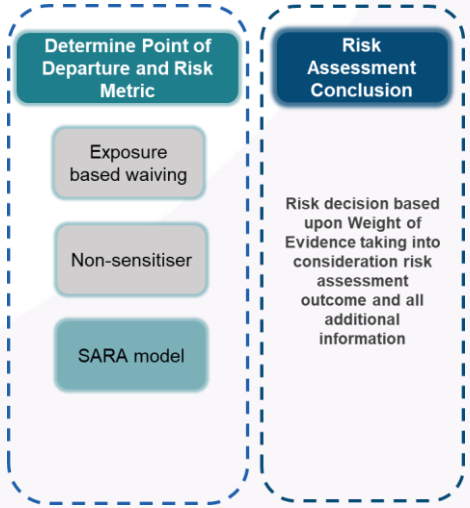
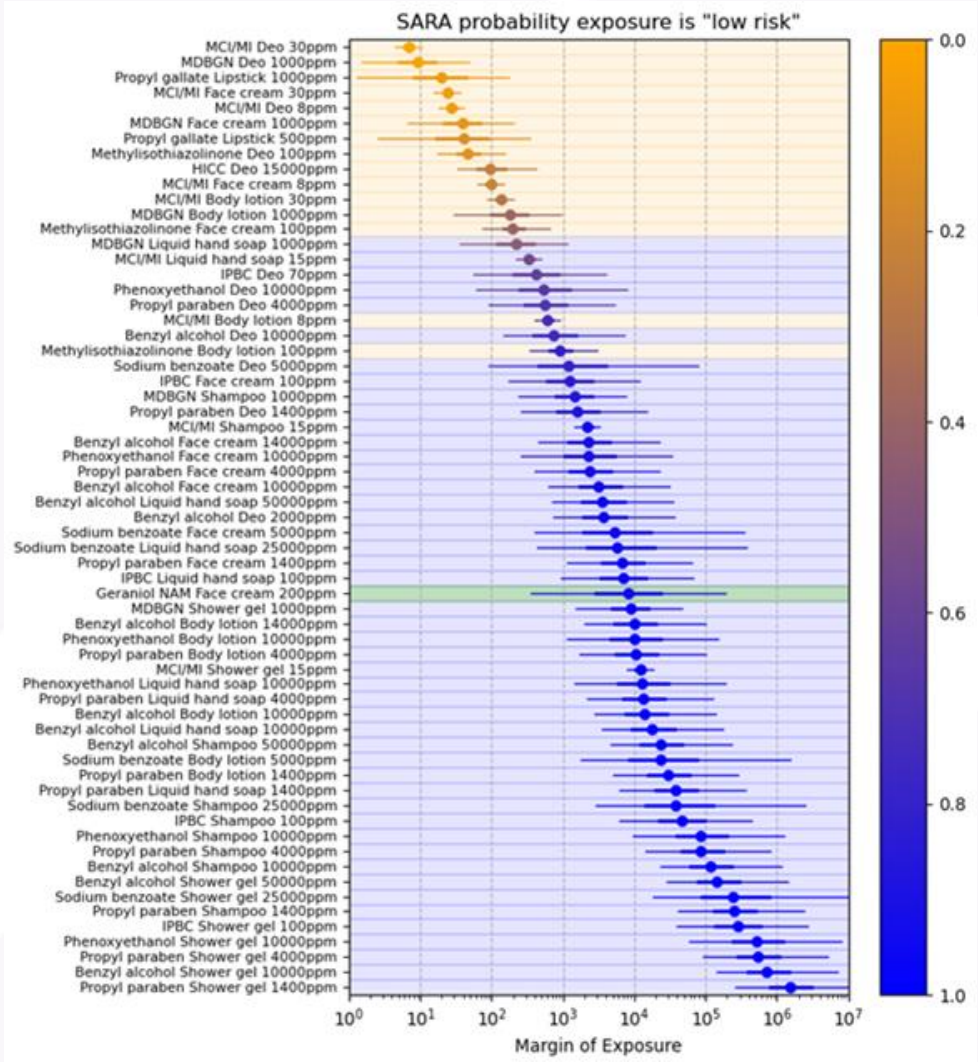
Determine MoE/Acceptable Exposure Level + NGRA conclusion





- The MoE was calculated from the ED_{01} for geraniol and the dermal exposure for 0.02% geraniol in a face cream using SARA DA
- The MoE for 0.02% face cream exposure ranks with low-risk benchmarks.
- The SARA DA probability that this exposure is low risk is calculated to be 0.95. Thus, there is a 95% probability that this exposure is low risk.
- Geraniol used at 0. 02% (200ppm) in a face cream is low risk for induction of skin sensitisation

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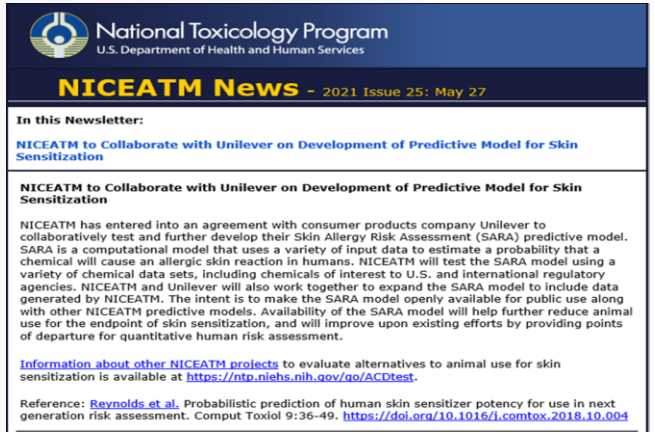
Conclusions

- This case study provides an example of how NGRA approaches can be applied to skin allergy risk assessment.

- With the adoption of new risk assessment approaches, it is essential to demonstrate that they are sufficiently protective for consumers. Here we show historical exposures can provide a means to benchmark risk assessment outcomes using clinical experience.

- However additional clinical benchmarks still need to be identified, we aim to explore further with clinical partners how we can further build upon and refine the concept of using historical exposures (both high and low risk) to define the probability that a new exposure is high or low risk.

- We have initiated a collaboration with NICEATM to further develop the SARA model and make it available for public use.



National Toxicology Program
U.S. Department of Health and Human Services

NICEATM News - 2021 Issue 25: May 27

In this Newsletter:

NICEATM to Collaborate with Unilever on Development of Predictive Model for Skin Sensitization

NICEATM to Collaborate with Unilever on Development of Predictive Model for Skin Sensitization

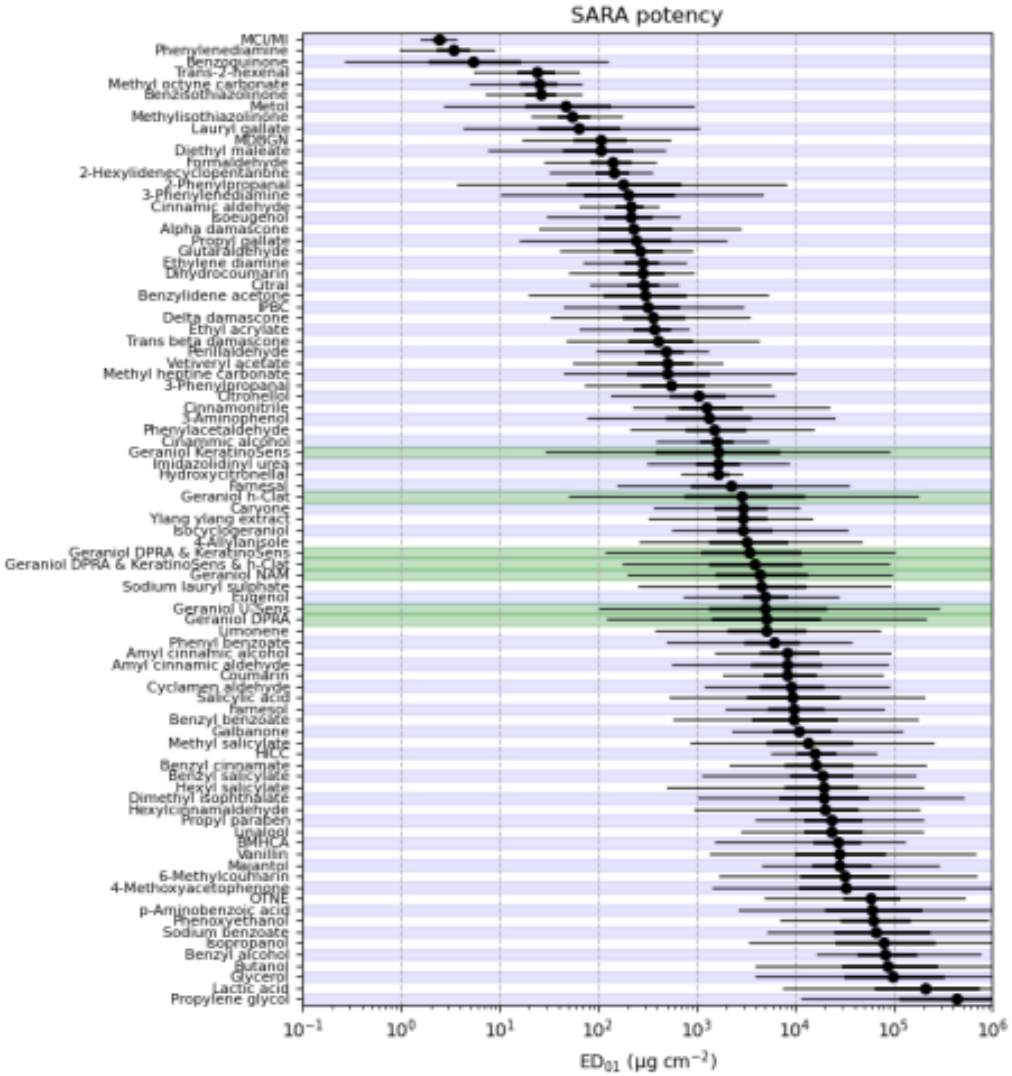
NICEATM has entered into an agreement with consumer products company Unilever to collaboratively test and further develop their Skin Allergy Risk Assessment (SARA) predictive model. SARA is a computational model that uses a variety of input data to estimate a probability that a chemical will cause an allergic skin reaction in humans. NICEATM will test the SARA model using a variety of chemical data sets, including chemicals of interest to U.S. and international regulatory agencies. NICEATM and Unilever will also work together to expand the SARA model to include data generated by NICEATM. The intent is to make the SARA model openly available for public use along with other NICEATM predictive models. Availability of the SARA model will help further reduce animal use for the endpoint of skin sensitization, and will improve upon existing efforts by providing points of departure for quantitative human risk assessment.

Information about other NICEATM projects to evaluate alternatives to animal use for skin sensitization is available at https://ntp.niehs.nih.gov/go/ACDtest.

Reference: Reynolds et al. Probabilistic prediction of human skin sensitizer potency for use in next generation risk assessment. Comput Toxiol 9:36-49. https://doi.org/10.1016/j.comtox.2018.10.004

Back up slides

SARA DA: partial datasets



- The SARA model can make predictions based upon any combination of the DPRA, KeratinoSens™, hCLAT and USens™ data.
- Predictions made using just KeratinoSens™ or hCLAT data yielded a marginally higher expected potency (lower ED_{01}) compared with the predictions made using just DPRA or USens™ data
- Combining data increases the precision in the estimate of potency (reduced uncertainty).