IDEA RCPL WORKSHOP

Towards NGRA Skin Sensitisation – Case study on DEA

22 September 2023

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on behalf of the ICCS Skin Sensitisation Working group

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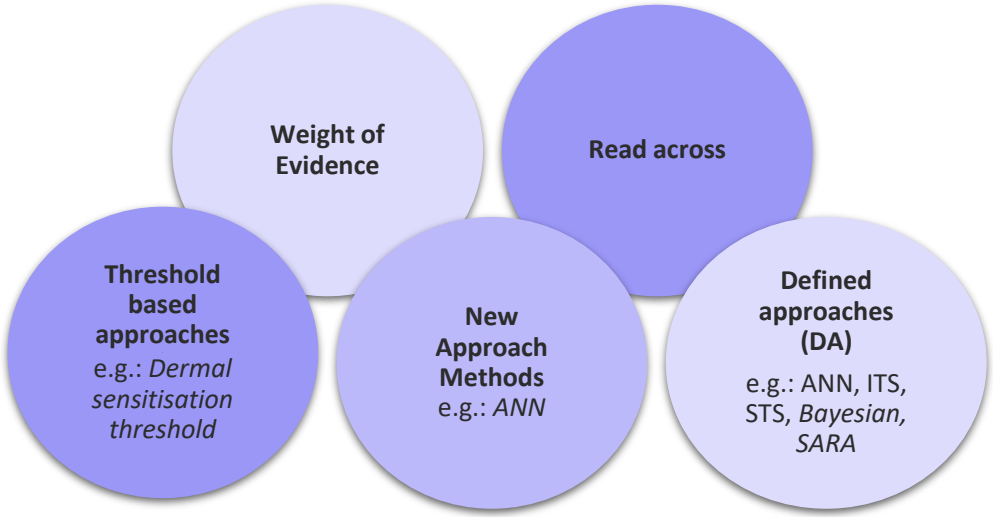
INTERNATIONAL COLLABORATION ON COSMETICS SAFETY

Objective of ICCS Skin Sensitisation WG

Provide regulatory adoption of animal-free skin sensitisation safety / risk assessments of cosmetics and their ingredients



Or combination of all of above…which utilised some or all of data provided

Determining our ability to conduct skin sensitisation safety assessment using available non-animal data in a weight of evidence approach.

Building experience in how to apply non-animal New Approach Methods (NAM) / Defined Approaches (DA) to different exposure scenarios for risk assessment decision-making (case studies)

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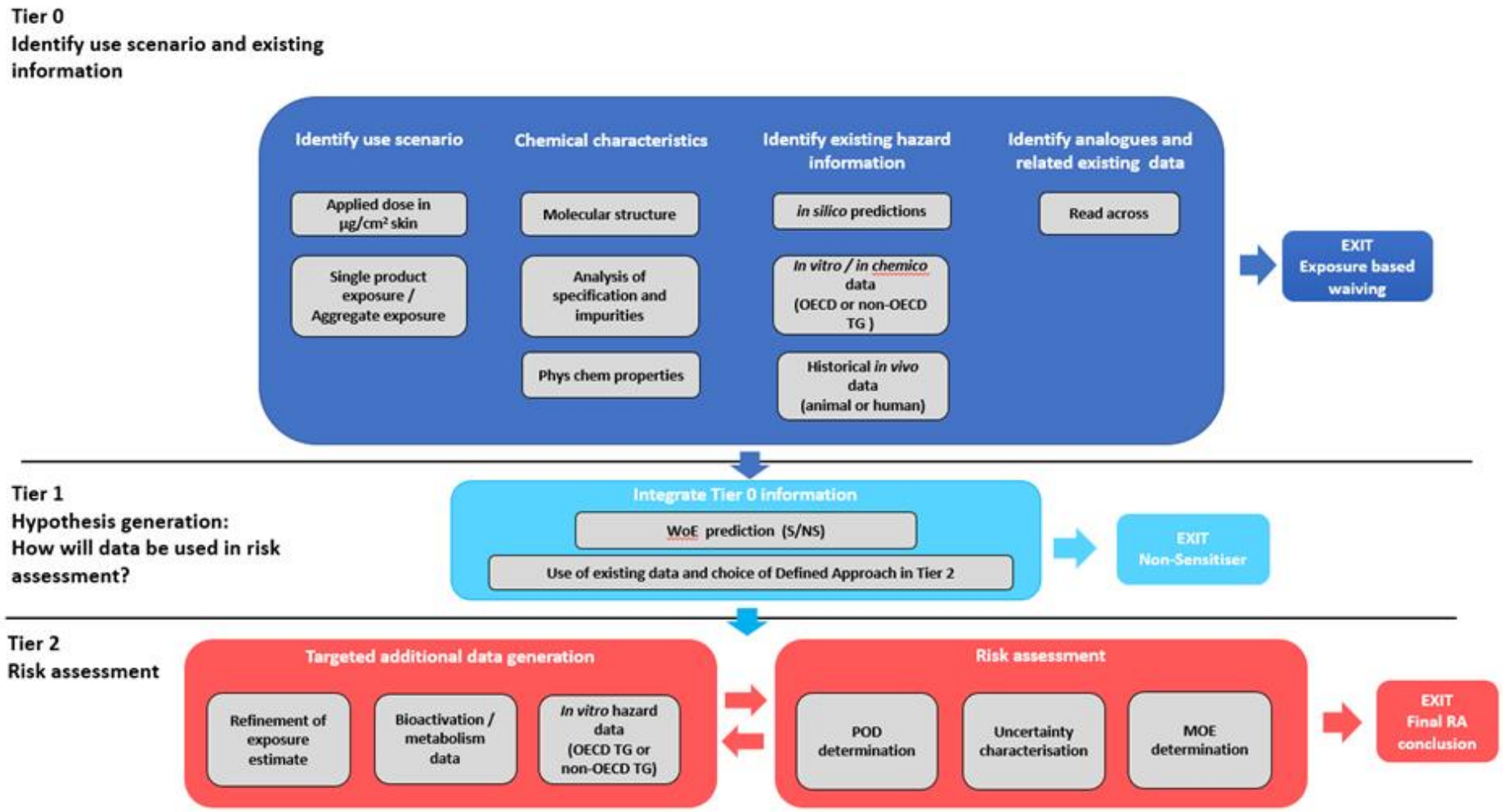
Next Generation Risk Assessment (NGRA) framework



https://health.ec.europa.eu/latest-updates/sccs-notes-guidance-testing-cosmetic-ingredients-and-their-safety-evaluation-12th-revision-2023-05-16_en

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Gilmour et al, ALTEX, 2023 doi: 10.14573/altex.2211161

Skin sensitisation NGRA framework case studies

NGRA case studies conducted and published over the last years

- eg. coumarin, geraniol, lactic acid, propyl paraben, resorcinol etc.
- Different consumer use scenarios explored
- Case study workshops (SCCS, EPAA etc.)

Case study: MDBGN

- Consistent data with clear risk decision making

- **Framework NGRA**
- **NoG SCCS**

Case study: Geraniol

- Consistent NAM info
- Slight differences in DA outcomes

- **OECD IATA case study**

What did we learn?

- NAM/DA data to be included in a weight of evidence
- Tiered approach
- Not one approach fits all
- Different from QRA approach
- New areas of uncertainty determined

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Skin sensitisation NGRA framework case studies

Increasing complexity

Case study: MDBGN
- Consistent data with clear risk decision making

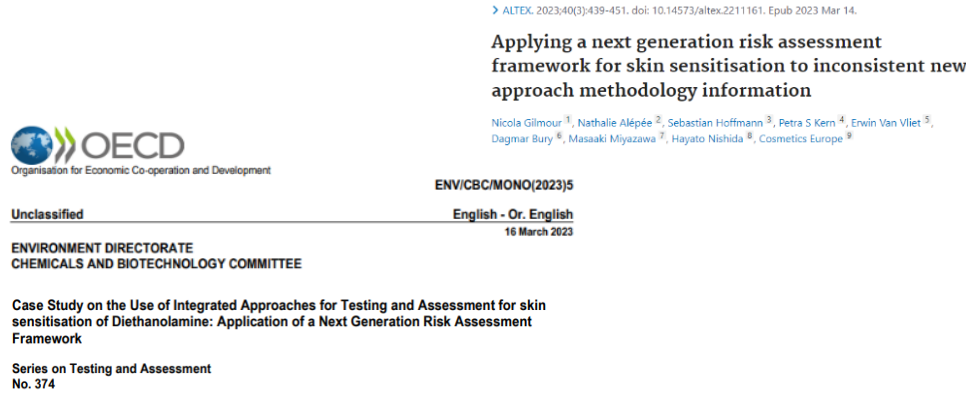
- **Framework NGRA**
- **NoG SCCS**

Case study: Geraniol
- Consistent NAM info
- Slight differences in DA outcomes

- **OECD IATA case study**

Case study: Diethanolamine
- Inconsistent NAM / DA info
- How to address uncertainty
- Refinement NGRA framework

- **NGRA refinement**
- **OECD IATA case study**
- **Publication in 2023**



ALTEX. 2023;40(3):439-451. doi: 10.14573/altex.2211161. Epub 2023 Mar 14.

Applying a next generation risk assessment framework for skin sensitisation to inconsistent new approach methodology information

Nicola Gilmour [1], Nathalie Alépée [2], Sebastian Hoffmann [3], Petra S Kern [4], Erwin Van Vliet [5], Dagmar Bury [6], Masaaki Miyazawa [7], Hayato Nishida [8], Cosmetics Europe [9]

OECD
Organisation for Economic Co-operation and Development

ENV/CBC/MONO(2023)5

Unclassified — English - Or. English

16 March 2023

ENVIRONMENT DIRECTORATE
CHEMICALS AND BIOTECHNOLOGY COMMITTEE

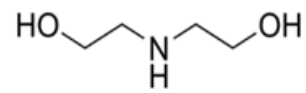
Case Study on the Use of Integrated Approaches for Testing and Assessment for skin sensitisation of Diethanolamine: Application of a Next Generation Risk Assessment Framework

Series on Testing and Assessment
No. 374

Potential risk induction of skin sensitisation of Diethanolamine (DEA)

NGRA Tier 0 : Scenarios -Existing information

CASRN 111-42-2



- Hypothetical exposure scenarios
  - Rinse-off product: 0.8% in a shampoo (exposure of 0.6 µg/cm^2)
  - Leave-on: 0.8% DEA in a deodorant (60 µg/cm^2)
- Derivation a Point of Departure (POD) from selected DAs
- Aggregate exposure & read across not considered in this case study
- Aim: How to address uncertainty in the risk assessment process?

TIER 0 : NO EXIT

Exposure based waiving not applicable to the exposure scenario

Name	Diethanolamine	AOP KE addressed
Mechanistic domain based on expert review	Pro-Schiff base	KE-1
TIMES-SS (v2.30.1.11)	Parent: Non-sensitiser Metabolite: Non-sensitiser	KE-1
TOXTREE (v2.6.13) Skin sensitisation reactivity domains Protein binding alerts	 No alert Schiff base formation	KE-1
OECD Toolbox (TB) (v4.4): https://qsartoolbox.org OASIS protein binding alerts for skin sensitisation Skin sensitisation automated workflow for DASS	 No alert Negative (no analogues identified)	KE-1
DEREK 6.01 (Nexus 2.2.2)	Positive (Equivocal) [2]	KE-1
DPRA	Negative/minimal (Cys depl: 5.9% and Lys depl: 2.2%)	KE-1
KeratinoSens™	Negative (EC1.5: >2000 µM, EC3: >2000 µM, Imax: 1, IC50%: >2000 µM)	KE-2
U-SENS™	Positive (CD86 EC150: 26.9 µg/mL, CV70: >200 µg/ml)	KE-3
h-CLAT	Positive (CD86 EC150: 1242.5 µg/mL, CD54 EC200: 1280.9 µg/mL, CV75: 2277 µg/mL)	KE-3
Dermal penetration rate (from Brain et al. 2005; Kraeling et al. 2004)	Minimal <3%	

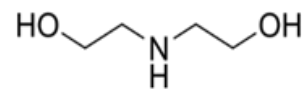
NOT an exhaustive list (what was collected for this case study)

No indication of applicability domain issues for *in vitro* / *in silico* NAMs based upon phys chem information

Potential risk induction of skin sensitisation of Diethanolamine (DEA)

NGRA Tier 1 : Hypothesis generation

CASRN 111-42-2



The available NAM information demonstrate inconsistent outcomes with respect to sensitisation potential of DEA.

- *In silico tools*
  - TIMES-SS/OECD TB: no reactivity or sensitisation potential
  - Derek Nexus: DEA being a skin sensitiser
  - ToxTree reported: DEA could form a Schiff base after activation
- NAM in the respective OECD TG
  - DPRA and KeratinoSens™ gave negative results
  - U-SENS™ and h-CLAT were positive
- Due to the possibility that DEA could be a pro-hapten, the DPRA and KeratinoSens™ data need to be considered with caution.

Name	Diethanolamine	AOP KE addressed
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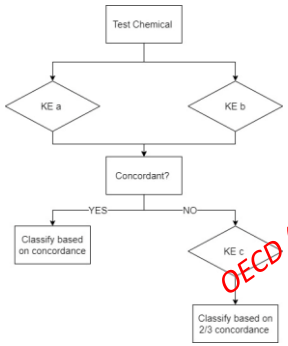
TIER 1 : NO EXIT

A weight of evidence assessment demonstrated that it is not possible to reach the conclusion with high certainty that DEA is a non-sensitiser

7 Defined Approaches applied in Case Study for DEA

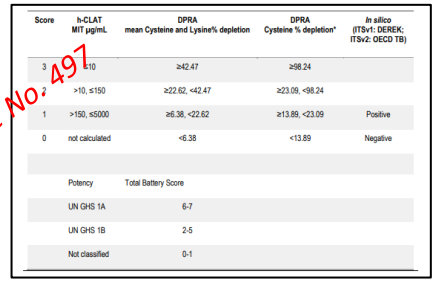
- DA were considered individually (no need to use more than one DA for NGRA)
- DA potency predictions and risk outcomes were compared.

Hazard	Potency (GHS 1A/ 1B)	Potency grouping	Continuous PoD values



2 out of 3

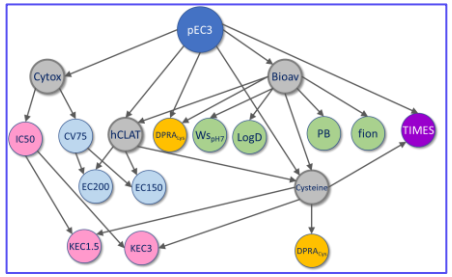
OECD (2021), Guideline No. 497



Score	h-CLAT MIT µg/mL	DPRA mean Cysteine and Lysine% depletion	DPRA Cysteine % depletion*	In silico (ITSv1: DEREK; ITSv2: OECD TB)
3	≤10	≥42.47	≥98.24	
	>10, ≤150	≥22.62, <42.47	≥23.09, <98.24	
1	>150, ≤5000	≥6.38, <22.62	≥13.89, <23.09	Positive
0	not calculated	<6.38	<13.89	Negative

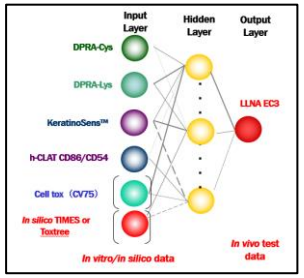
Potency	Total Battery Score
UN GHS 1A	6-7
UN GHS 1B	2-5
Not classified	0-1

ITSv1/v2



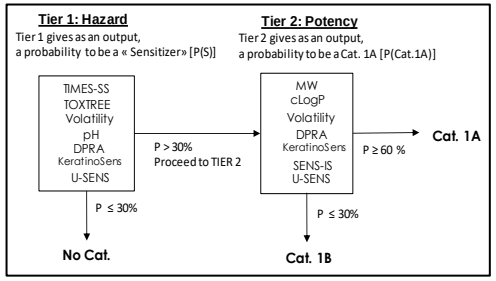
BN-ITS

(Jaworska et al. 2015)



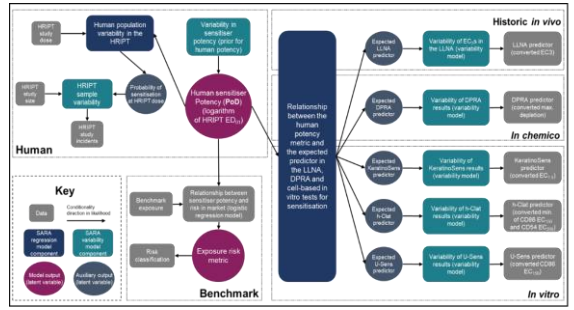
2x ANN EC3

(Hirota et al 2015, 2018)



Sequential Testing Strategy

(Tourneix et al. 2020)



(Gilmour et al 2022)

SARA

Tier 2: Risk assessment based on 7 Defined Approaches (DA)

Defined Approach	DA prediction for DEA
ITSv1 DA	GHS Cat. 1B **skin sensitiser** (ITS score of 2).
ITSv2 DA	**Inconclusive**
ANN (TIMES-SS)	**Weak sensitiser** (EC3 value: 81.5%).
ANN (Toxtree)	**Weak sensitiser** (EC3 value: 59.1%).
Sequential Testing Strategy (STS)	Tier 1: **Non-sensitiser** (13% probability to be a sensitiser) Due to NS in Tier 1 potency prediction: Tier 2 not applicable.
BN ITS	High probability (> 99%) to be a **non-sensitiser** (Bayes Factor: >30, strong evidence).
SARA	**Human sensitiser** potency ED_{01} = 13000 µg/cm^2 (95th % confidence interval 530 – 370000 µg/cm^2) SARA risk metric Probability exposure is low risk : 0.5 (Deo) / 0.98 (Shamp)

TIER 2 :

- Convert to PoD for risk assessment
- Different NAM outcomes introduced uncertainty
- Therefore, a DA prediction of non-sensitiser was also converted into a PoD with the aim to further increase confidence in the risk assessment.

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NGRA Tier 2: Risk assessment – uncertainty assessment

0.8% in SHAMPOO	ITSv1	ITSv2	ANN (TIMES)	ANN (Toxtree)	STS	BN-ITS	SARA
	DA output						
DA output	Cat. 1B	Inconclusive	EC3=81.5 %	EC3=59.1 %	NS P(S)= 13%	NS P(NS)=99% BF (>30%)	ED_{01}=13000 µg/cm^2 (530–370000) µg/cm^2
PoD (µg/cm^2)	> 500	> 500	14 775	20 375	25 000	25 000	13 000

EC3 (%) is converted to µg/cm2 Using a standardised approach (Robinson *et al*. 2000, Griem *et al*. 2003)

NGRA Tier 2: Risk assessment – uncertainty assessment

0.8% in DEODORANT	ITSv1	ITSv2	ANN (TIMES)	ANN (Toxtree)	STS	BN-ITS	SARA
DA output							
DA ouput	Cat. 1B	Inconclusive	EC3=81.5 %	EC3=59.1 %	NS P(S)= 13%	NS P(NS)=99% BF (>30%)	ED_{01}=13000 µg/cm^2 (530–370000) µg/cm^2
PoD (µg/cm^2)	> 500	> 500	14 775	20 375	25 000	25 000	13 000
Calculate MoE for 0.8% in NON-SPRAY DEODORANT							
Consumer exposure level (µg/cm^2)	60	60	60	60	60	60	60
MoE (PoD/CEL)	>8	>8	246	340	416	416	217 (8.8-617)
Weight of evidence assessment / Characterise uncertainty							
WoE : confidence in NAM	Moderate						
WoE : Conservatism in transformation of DA outcome to PoD	Unknown		Low		High	High	Low
WoE: MoE certainty P(low risk)*SARA ONLY	Low	Low	High	High	High	High	Low P (low risk) = 0.5
Risk assessment outcome	UNSAFE	UNSAFE	SAFE	SAFE	SAFE	SAFE	UNSAFE

Deodorant (0,8%)

SAFE/UNSAFE use, dependent upon PoD determination based on individual DA

Case Study Conclusions

- DEA suitable case study chemical due to inconsistencies in the existing NAM information.
- Information from NAMs can be applied within a WoE IATA (following the NGRA framework) to reach a conclusion on consumer risk.
- DEA was predicted to be a pro-hapten which introduced uncertainty in the use of some NAM information within DA and decision making.
- In order to reach a decision on safety using NAM we have calculated a MoE and then evaluated possible areas of uncertainty
  - Chemistry reaction is a critical element to understand the applicability domain of the NAM.
  - Impact of the applicability domain of NAM on DA outcome is a prerequisite
- Whilst the inconsistencies in the NAM information led to differences in the DA outputs, there was less impact on the risk assessment outcomes:
  - 4 of the 7 applied DA resulted in a conclusion of safe (STS, BN-ITS and the two ANN versions)
  - 3 resulted in a conclusion of un-safe (ITSv1, ITSv2, SARA)
  - Relative conservatism in deriving a PoD from the DA outcome is observed.

Learnings

- A standardised way of the Next Generation Risk Assessment (NGRA)
- Pave the way for other endpoints
- Confidence in risk assessment outcome was greatest for materials with concordant data
- Where non-concordant data are generated, greater uncertainty is introduced.
- In order to reach a decision on safety using NAM, MoE and possible areas of uncertainty have been evaluated

To be continued…

- More case studies & stakeholder exchanges (e.g. read-across to be addressed)
- More research on
  - Mixtures and lipophilic compounds with 3D models
  - NAM portfolio expansion in NGRA
  - Sources of uncertainty assessment

Acknowledgements

Nathalie Alépée
Dagmar Bury
Nicola Gilmour
Sebastian Hoffmann
Petra Kern
Masaaki Miyazawa
Kanako Nakayama
Hayato Nishida
Erwin van Vliet

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