Applying a Next Generation Risk Assessment (NGRA) framework for Skin Sensitisation to inconsistent New Approach Methodology (NAM) information

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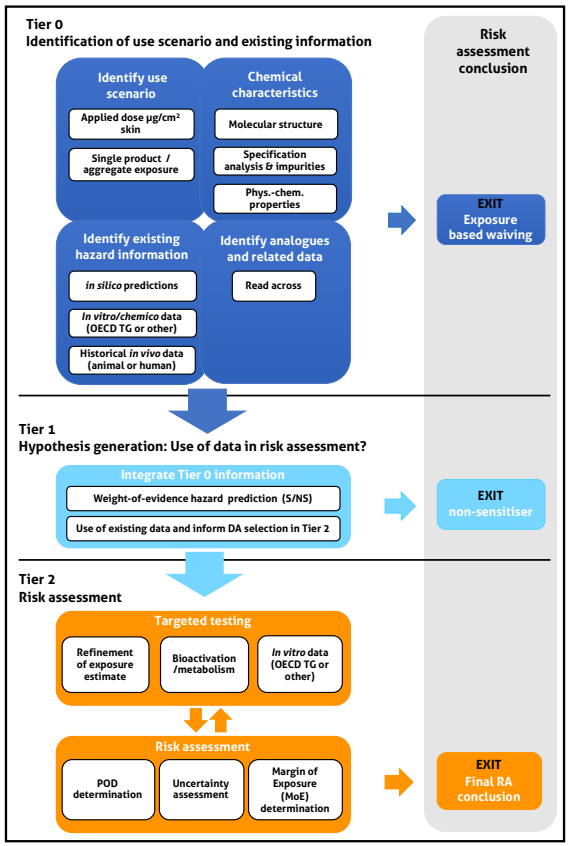
NGRA case study scope

The aim of this case study was to explore the impact of inconsistent NAM information on the final risk assessment outcome for hypothetical (not representing real consumer exposures) exposure scenarios. The use of read across, including the use of analogue data, was considered out of scope to allow focus on how to deal with the inconsistent data in absence of analogues. The case study will become publicly available[1].

NGRA framework



Case study conclusions

- NGRA framework was successfully applied to a complex case
- inconsistency in NAM results can be compensated for in a risk assessment context
- selection of the individual DA to be used in NGRA is critical and a main reason for inconsistent risk assessment conclusions
- sources of uncertainty have been identified, e.g. NAM applicability, in silico tool selection and model versions, conservatism in DA outcome transformation to PoD → to be continued
- MoE-approach to uncertainty assessment was introduced → to be continued

Tier 0
Identification of use scenario and existing information

Use scenarios: consumer cosmetic use

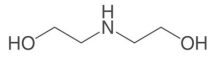
- rinse-off: exposure from use of 0.8% DEA in a shampoo was calculated to be 0.6 µg/cm²
- leave-on: exposure from use of 0.8% DEA in a deodorant was calculated to be 60 µg/cm²
- exposure-based waiving not applicable
- aggregate exposure not considered

Existing hazard information (NAM)	
TIMES-SS	Parent and metabolites: non-sensitiser
ToxTree	Protein binding alert: Schiff Base
OECD Toolbox	Protein binding alerts for skin sensitisation: no alerts Skin sensitisation automated workflow for DASS: negative/non-sensitser
DEREK Nexus	Positive/sensitiser (equivocal)
Mechanistic domain expert review	Pro-Schiff base
DPRA (KE1)	Cys depl: 5.9%; Lys depl: 2.2% → negative/minimal
KeratinoSens™ (KE2)	EC 1.5, EC3 & IC50 >2000 µM; Imax: 1.0 → negative
U-SENS™ (KE3)	CD86 EC150: 26.9 µg/ml; CV70: >200 µg/ml → positive
h-CLAT (KE3)	CD86 EC150: 1242.5 µg/ml; CD54 EC200: 1280.9 µg/ml; CV75: 2277 µg/ml → positive

Chemical characteristics

Diethanolamine (DEA) (CAS-no. 111-42-2) was selected as inconsistent NAM information was available[2]:

- MW: 105.14 Da
- LogP: -1.46
- Fraction ionised: 0
- LogD @ pH 7: -3.38
- Volatility: semi-volatile
- pH: 10.3
- H2O solubility @ pH 7: 3.0 g/L
- Plasma protein binding (% bound): 11.3



Risk assessment conclusion

NO EXIT
Exposure based waiving not applicable to both exposure scenarios

Tier 1 - Hypothesis generation: Use of data in risk assessment?

Weight of Evidence

- DEA acts potentially as a pro-Schiff base (TOXTREE protein binding alert & expert review)
- KE1 and KE2 NAMs: negative, but lack of enzymatic metabolic capability vs. KE3 NAMs: positive (enzymatically active)

→ DEA may be a skin sensitiser

Defined Approach (DA) selection

Comparison of risk assessment conclusions based on individual DA (all inputs available): ITS (v1 & v2), ANN (TIMES-SS & ToxTree), STS, BN-ITS, SARA)

NO EXIT
non-sensitiser cannot be concluded with sufficient certainty

Tier 2 - Risk assessment

Exposure scenario	Shampoo (0.8%, CEL=0.6 µg/cm²)							Deodorant (0.8%, CEL=60 µg/cm²)						
DA name	ITS v1	ITS v2	ANN (TIMES-SS)	ANN (ToxTree)	STS	BN-ITS	SARA	ITS v1	ITS v2	ANN (TIMES-SS)	ANN (ToxTree)	STS	BN-ITS	SARA
DA output	Cat. 1B	inc.	EC3 = 81.5%	EC3 = 59.1 %	NS P(NS)= 87%	NS P(NS)=99%	ED01=13000 µg/cm² (5%-tile: 530 µg/cm²)	Cat. 1B	inc.	EC3 = 81.5%	EC3 = 59.1 %	NS P(NS)= 87%	NS P(NS)=99%	ED01=13000 µg/cm² (5%-tile: 530 µg/cm²)
PoD (µg/cm²)	>500	>500	20375	14775	25000	25000	13000	>500	>500	20375	14775	25000	25000	13000
MoE (PoD/CEL)	>833	>833	33958	24625	41667	41667	24000	>8	>8	340	246	416	416	217
WoE: Confidence in NAMs	moderate							moderate						
WoE: Conservatism in transformation of DA outcome to PoD	unknown		low	low	high	high	low	unknown		low	low	high	high	low
WoE: MoE certainty	high	high	high	high	high	high	high	low	low	high	high	high	high	low
P(low risk)SARA ONLY							P(low risk) = 0.98							P(low risk) = 0.5
Risk assessment conclusion	SAFE							UNSAFE	UNSAFE	SAFE	SAFE	SAFE	SAFE	UNSAFE

Shampoo
EXIT
SAVE use, regardless of PoD determination based on individual DA

Deodorant
EXIT
SAVE/UNSAVE use, depending on PoD determination based on individual DA

Conflict of interest
The authors NG, NA, PK, DB, MM, HN are employed by cosmetic companies.
The authors SH and EvV are consultants paid for their services by Cosmetics Europe.

1 Gilmour N, Alépée N, Hoffmann S et al., (2023). Applying a Next Generation Risk Assessment (NGRA) framework for Skin Sensitisation to inconsistent New Approach Methodology (NAM) information. ALTEX, accepted.
2 Hoffmann S, Alépée N, Gilmour N, et al. (2022). Expansion of the Cosmetics Europe skin sensitisation database with new substances and PPRA data. Regul Toxicol Pharmacol, doi:10.1016/j.yrtph.2022.105124