Decision making in Next Generation Risk Assessment (NGRA) for Skin Sensitisation: How useful Read-Across Analogue Data can be

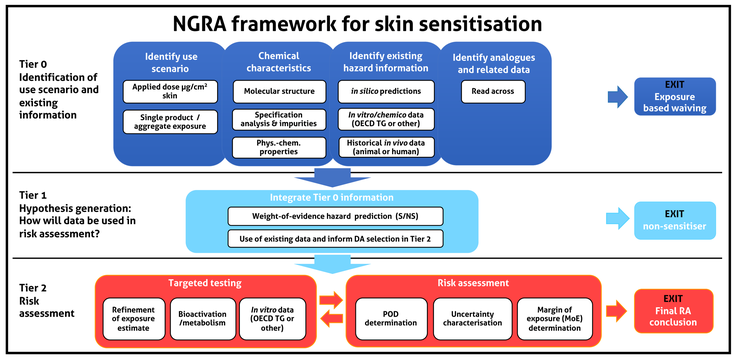
P 321
ID: 3208

P. Kern[1], N. Alépée[2], A. Aptula[3], D. Bury[4], E. DeConinck[1], J. Ebmeyer[5], F. Gautier[4], N. Gilmour[3], S. Hoffmann[6], J. Kühnl[5], C. Lester[7], M.Miyazawa[8], K. Nakayama[8], H. Nishida[9], E. van Vliet[10], and G. Yan[7]

[1]Procter & Gamble Services NV/SA, Strombeek-Bever, Belgium; [2]L'Oréal, Aulnaysous-Bois, France; [3]Unilever, Bedford, United Kingdom; [4]L'Oréal, Clichy, France; [5]Beiersdorf AG, Hamburg, Germany; [6]seh consulting + services, Paderborn, Germany; [7]The Procter & Gamble Company, Mason, OH; [8]Kao, Tochigi, Japan; [9]Shiseido Global Innovation Center, Takashima, Japan; and [10]Innovitox Consulting & Services, Houten, Netherlands

NGRA case study scope

Advancements have been made in the evaluation of skin sensitisation hazard and potency by using new approach methodologies (NAM) and Defined Approaches (DA) for decision-making within a Next Generation Risk Assessment (NGRA). However, the derivation of a point of departure (PoD) remains a challenge for chemicals for which NAM data and/or DA outputs are associated with limitations and excessive uncertainty. This case study demonstrates how information from read across analogues can be applied, separately or in combination with NAM data to support PoD setting. Anisyl alcohol (AA) was selected as case study ingredient, due to its data richness and its suitability for investigating and identifying read-across analogue(s).



Case study Results

- Suitable analogues were identified using a variety of approaches considering structural similarity, biological and toxicological features, reactivity, metabolism and expert knowledge.
- Three analogues with historical human, in vivo data or NAM information were selected, all.
- PoD were derived using a) analogues, b) NAM/DA and c) analogues in combination with NAM/ DA (where needed)
- Analogues alone did not provide sufficient confidence to conclude on risk.
- DA outputs varied considerably, leading to differences in PoD and resulting in inconsistent risk assessment conclusions.
- Analogue information was added to refine risk assessments, where needed. For the DA ITSv1, a PoD was derived from in vivo data of an analogue. For others, DA outputs were consistent with PoDs based on analogues, which allowed to refine the PoD and to increase the confidence in the NGRA, with one exception.

Conclusions

This case study illustrated how data from read-across analogues either as stand alone or in combination with NAM/ DA information can support PoD derivation. Read-across information can be critical in an NGRA for decision making, in particular when NAM data and DA outputs are associated with limitations and high uncertainty.

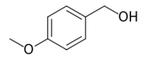
Tier 0 - Identification of use scenario and existing information

Use scenario (cosmetic leave-on)

Consumer exposure level (CEL) using 0.8% AA in a deodorant: 60 µg/cm²

Anisyl alcohol (AA) CAS# 105-13-5: characteristics

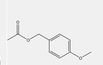
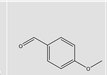
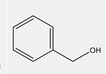
- MW: 138.17 Da
- LogP: 1.1
- Fraction ionised: 0
- LogD @ pH 7: -3.38
- Volatility: semi-volatile
- pH: 7.8
- log H2O solubility (pH 7): -1.03 g/L
- Plasma protein binding (% bound): 26.7



Existing hazard information (NAM)		
TIMES-SS	Parent: non-sensitiser; Metabolite: weak sensitiser (e.g. hydroxy benzaldehyde, anisaldehyde)	
ToxTree	No reactivity domains, MA and SN2 binding alerts	
OECD Toolbox	Protein binding alerts for skin sensitisation: no alerts	
DEREK Nexus	Positive ; Expert review: Pro-Schiff base	
DPRA (KE1)	Cys depl: 7.1%; Lys depl: 3.2%	→ minimal
KeratinoSens™ (KE2)	EC 1.5, EC3 & IC50 >2000 µM; Imax: 1.23	→ negative
U-SENS™ (KE3)	CD86 EC150: >200 µg/ml; CV70: >200 µg/ml	→ negative
h-CLAT (KE3)	CD86 EC150: 822.2 µg/ml; CD54 EC200 and CV75: > 1000 µg/ml	→ positive

NO EXIT
Exposure based waiving not applicable

Suitable analogues identified (using automated tools and expert judgement)

Chemical (CAS#)	Structure	Rating	In vivo sensitisation data
Anisyl acetate (104-21-2)		Suitable with precondition (hydrolysis/ metabolite)	LLNA EC3 9-20.4%, HMT 10% no effects
Anis-aldehyde (123-11-5)		Suitable with precondition (hydrolysis/ metabolite)	LLNA EC3 > 25%, negative OET GP, HRIPT negative at 3.5 g/cm², HRIPT positive at 4.7 g/cm²
Benzyl alcohol (100-51-6)		Suitable with interpretation	LLNA EC3 > 50%, HRIPT negative at 5.9 g/cm², HRIPT positive at > 8.0 g/cm², HMT and GP negative

Summary of Risk Assessment using analogues

Analogues selected	3 analogues explored
Reason for analogue selection for PoD derivation	Worst case (also considering similarity scores, structural alerts, metabolism information)
PoD (µg/cm²)	2300 (LLNA EC3 conversion)
MoE (PoD/CEL)	38
Conclusion	UNSAFE

NO EXIT

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

Weight of Evidence

- Reactivity & DEREK alerts
- KE1 and KE2 NAMs: negative, but lack of enzymatic metabolic capability
- KE3 NAMs: negative/ positive
- Analogues: weak sensitiser

Hypothesis and DA selection

- Discordant data
- Sensitisation potential unclear
- Select DA
- Comparison of risk assessment conclusions based on individual DA (ITS v1, ANN, STS, BN-ITS, SARA)

NO EXIT
non-sensitiser cannot be concluded with sufficient certainty

Tier 2 - Targeted Testing and Risk assessment

PoD setting and Risk assessment based on NAM/DA data alone					
	ITS V1	ANN	STS	BN-ITS	SARA
DA output	Cat 1B	EC3= 77.7%	NS P(Cat 1) = 19%	Weak Sensitizer P(W) = 90%	ED_{01}=23000 µg/cm² (2.5%, 97.5%: 1100 -580000 µg/cm²)
PoD (µg/cm²)	>500	19425	25000	1000-4700	23000
MoE (PoD/CEL)	>8.3	324	420	16-50	
Confidence in NAMs	High (in applicability domain, no technical issues)				
Conservatism in transforming DA outcome to PoD	unknown	low	high	high	low
MoE certainty	low	high	high	low	
P(low risk)^{SARA}					P (low risk) = 0.57
Risk assessment conclusion	UNSAFE	SAFE	SAFE	UNSAFE	UNSAFE
Refined PoD setting and Risk assessment by adding analogues					
Add Analogue information	Yes	Yes	No (high certainty & MoE)	Yes	Yes
Analogs used	All three used and evaluated by all				
Reason for picking analogues for PoD setting	Similar scores for Benzyl alcohol and AA	Similarity scores and structural alerts of Benzyl alcohol		WoE of all analogs, including BN-ITS results	ED_{01} is within, but at lower potency end, of the range of ED_{01} derived for analogues
PoD (µg/cm²)	5900	5900		3000-35000	2300-30000 µg/cm²
MoE (PoD/CEL)	>99	>99		50-580	
MoE certainty	high	high	high	high	
Risk assessment conclusion	Borderline SAFE	Borderline SAFE	SAFE	Borderline SAFE	UNSAFE

EXIT
SAFE/UNSAFE, depends on PoD and DA-specific confidence

EXIT
SAFE or Borderline SAFE or UNSAFE

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, 2023. DOI: 10.14573/altex.2211161
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.2022.105169

Conflict of interest
The authors PK, NA, AA, DB, ED, JE, FG, NG, JK, CL, MM, KN, HN, and GY are employed by cosmetic companies.
The authors SH and EvV are consultants paid for their services by ICCS..