Skin Sensitization Risk Assessment and Confidence in New Approach Methodologies

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Expert Panel for Cosmetic Ingredient Safety
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Outline

- Part 1: Interpretation of Human Repeat Insult Patch Test* (HRIPT) data
  - Importance of the dose metric for risk assessments

- Part 2: Confidence in skin sensitization New Approach Methodologies (NAMs)

*Note that RIFM is changing terminology of HRIPT to “Confirmation of No Induction in Humans” (CNIH).

The role of HRIPTs in skin sensitization risk assessment

- A Quantitative Risk Assessment (QRA) for skin sensitization uses multiple data sources to establish a No Expected Sensitization Induction Level (NESIL)
  - Analytical and structural characterization
  - Literature review
  - Previous animal testing (murine local lymph node assay or guinea pig tests)
  - New approach methodologies
  - HRIPT
- HRIPTs are done to confirm a No Effect Level as one of the data sources in establishing a NESIL or to demonstrate that humans will not respond adversely to a particular formulation (NOT FOR HAZARD ID)
- The methodology has evolved over the past 79 years since first proposed in 1944 by Schwartz and Peck.

Api et al., Regulatory Toxicology and Pharmacology 118: 104805, 2020

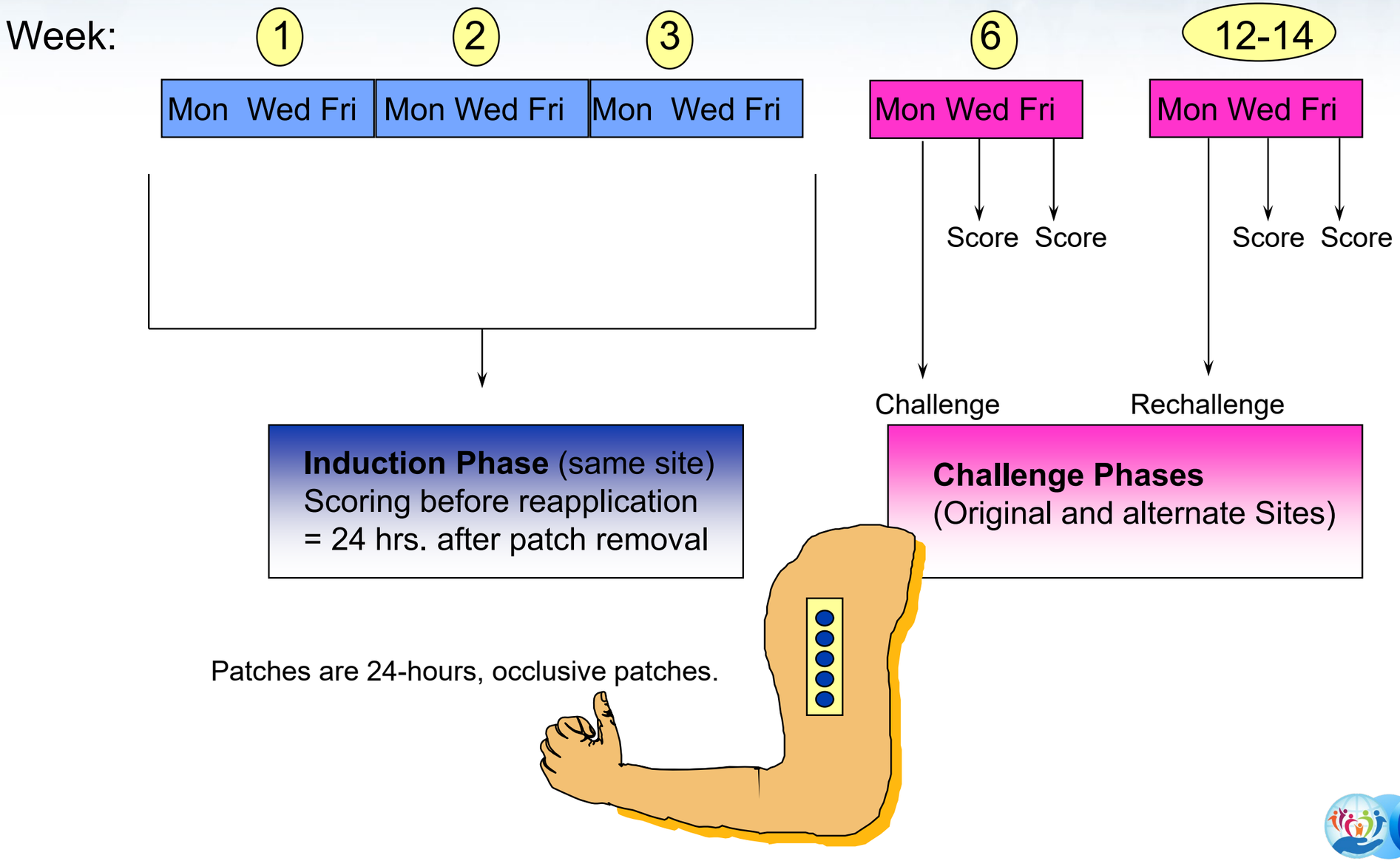
McNamee et al., Regulatory Toxicology and Pharmacology 52: 24-34, 2008

A comment on ethical consideration of HRIPTs

- Ethical concerns have been raised about the potential risk of induction of contact allergy to those who participate in any HRIPT
  - An independent ethical review committee approves or rejects the study prior to testing
  - Subject Informed Consent is provided and Good Clinical Practices are followed
  - RIFM has undertaken an extensive review of this issue from over 30 years
  - The level of risk of induction in an HRIPT is very low
  - Outcomes from 154 studies on 134 substances using 16,512 volunteers, demonstrated induction of allergy in 20 subjects (0.12%). However in the last 11 years, only 3 of 9,854 subjects (0.03%) were sensitized, perhaps due to improved methods (e.g., LLNA) and a more standardized HRIPT protocol.

Na et al., Dermatitis 32(5): 339-352, 2021

Human Repeat Insult Patch Test (HRIPT)



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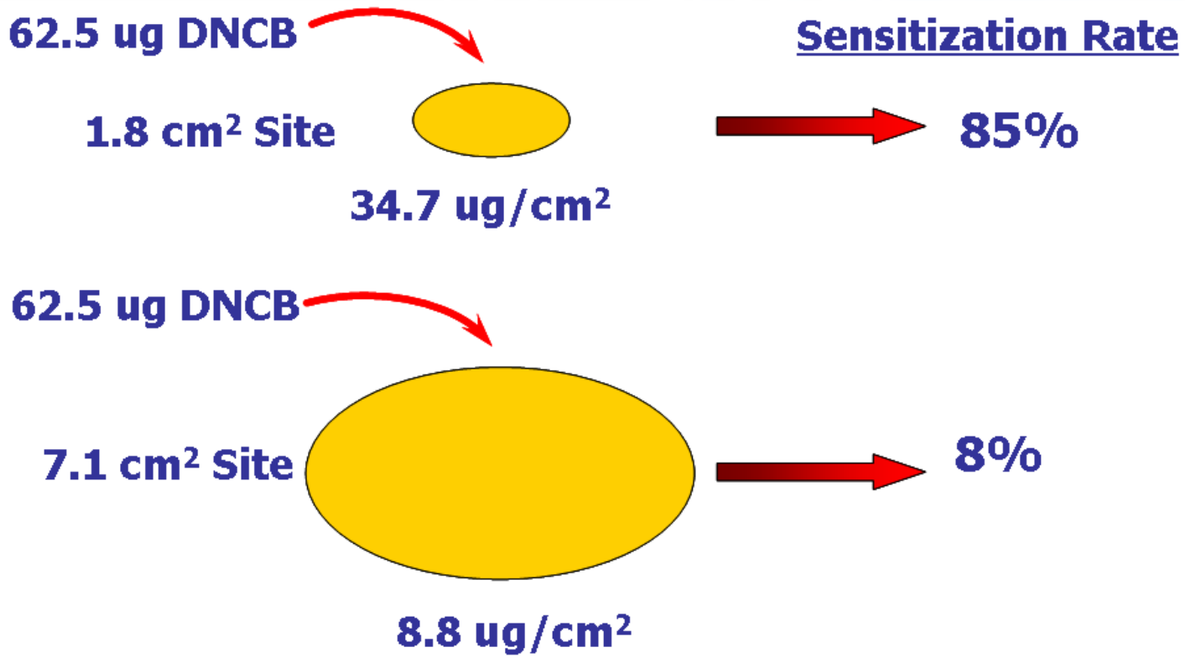
Critical factors for HRIPT design and interpretation

- Vehicle/matrix effects
- Test material concentration (dose/unit area)
- Amount of test material applied
- Occlusion
- Chemistry
- Target population
- Allergen potency

Dose Per Unit Area versus Total Dose

The Influence of Area of Application of Allergen on Sensitization Testing



Valid for all sensitizers of different potency, except when area of application drops below a certain critical level (~0.1 to 0.4 cm^2)

Upadhye and Maibach Cont Derm 1992, 27:281-286

Kimber I. et al. 2008, RTP 52(1): 39-45.

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Phytosteryl/Behenyl/Octyldodecyl Lauroyl Glutamate Human Sensitization Studies

Study type	Volume, patch size	% phytosteryl glutamate	Dose phytosteryl glutamate/area	Result (sensitized/total)
HRIPT	0.2 mL, 4 cm^2 occlusive	5%	2.5 mg/cm^2	0/102
HRIPT	0.2 mL, 4 cm^2 occlusive	5.99%	2.995 mg/cm^2	0/219

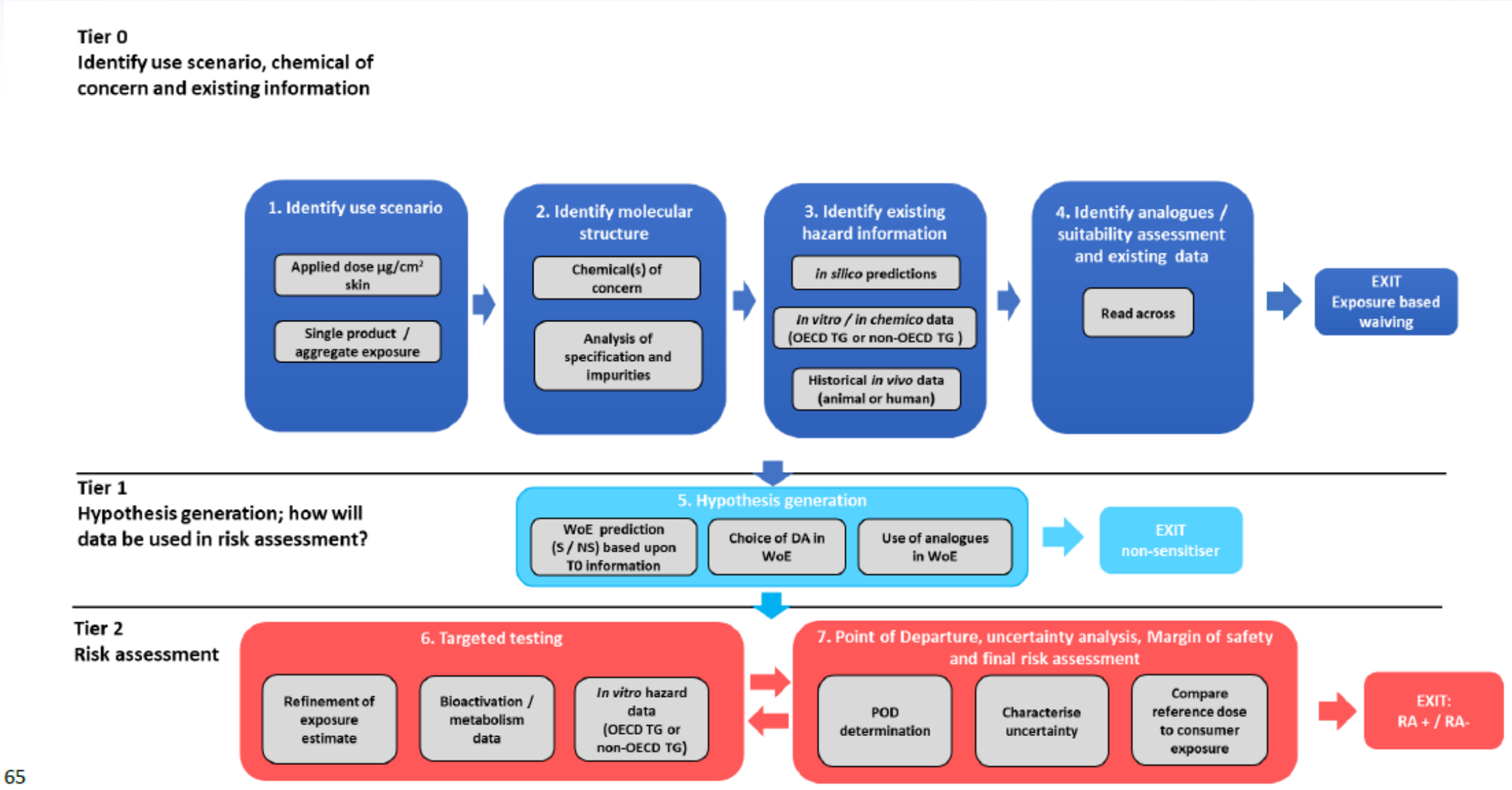
Cosmetic Product Maximum Reported Exposures

Product type	Exposure to product (reference)	Maximum % of phytosteryl glutamate in product	Exposure to phytosteryl glutamate from product	Margin of exposure
Lipstick	11.46 mg/cm^2 (Api et al., 2008)	25%	2.865 mg/cm^2	1.04
Rouges	1.00 mg/cm^2 (IFRA RIFM QRA 2011[1])	25%	0.25 mg/cm^2	12.0
Eye shadows	2.17 mg/cm^2 (Api et al., 2008)	9%	0.189 mg/cm^2	15.8
Face and neck products	2.70 mg/cm^2 (Api et al., 2008)	8%	0.216 mg/cm^2	13.9
Hand and body lotions	1.12 mg/cm^2 (Api et al., 2008)	1%	0.0112 mg/cm^2	267

Building confidence in New Approach Methodologies

- Adds to the continuum of understanding from all the previous research
- Next generation risk assessment approach, exposure led and fit for purpose
- Focuses on adverse outcome pathway using non-animal methods
- Utilization of weight of evidence from many sources of information and tools
  - NAMs = In silico, in chemico, in vitro
  - In vivo (previous animal studies and human studies)
  - Structure activity read-across
  - Dermal sensitization threshold
- Validation of assays and defined approaches
- Case studies
- Regulatory acceptance

Next Generation Risk Assessment (NGRA) Framework for Skin Sensitisation



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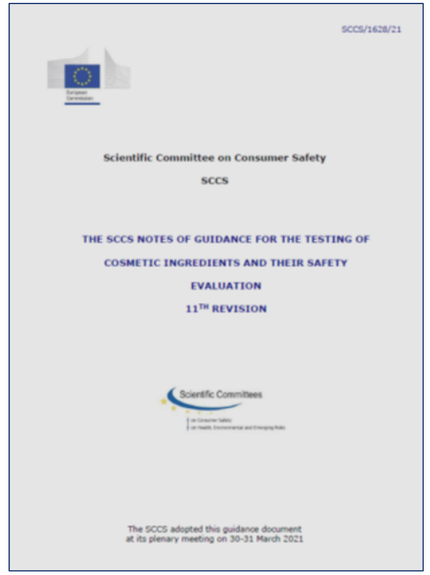
SCCS/1628/21

Scientific Committee on Consumer Safety

SCCS

THE SCCS NOTES OF GUIDANCE FOR THE TESTING OF COSMETIC INGREDIENTS AND THEIR SAFETY EVALUATION

11TH REVISION

Scientific Committees

The SCCS adopted this guidance document at its plenary meeting on 30-31 March 2021

SCCS 11th NoG 2021
(SCCS/1628/21)

Gilmour & Kern et al, RTP, 116, 2020 https://doi.org/10.1016/j.yrtph.2020.104721

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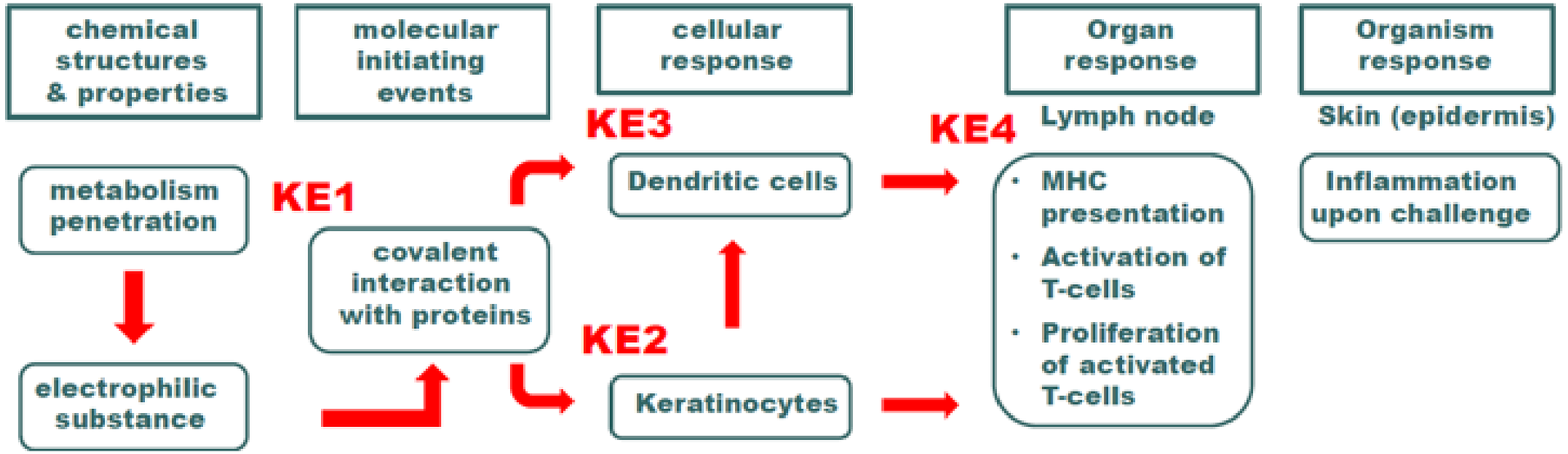
Adverse Outcome Pathway and Predictive Testing



DPRA Direct Peptide Reactivity Assay
ADRA *Amino acid Derivative Reactivity Assay*

Are-Nrf2 Luciferase test methods: **Keratinosens™** **LuSens**

h-CLAT Human Cell line Activation Test
U-SENS™ U937 Cell line activation test
IL-8-Luc Interleukin-8 Reporter Gene Assay

OECD 442C
In chemico (KE1)

OECD 442D
In vitro (KE2)

OECD 442E
In vitro (KE3)

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Validated NAMs Skin Sensitization Risk Assessment

Test Method or Defined Approach	OECD Test Guideline [31–34]	AOP Key Event [30]	Prediction Model Outcome
DPRA	442C, 2021	Key Event 1, peptide/protein binding	Positive/Negative on KE1
ADPRA	442C, 2021	Key Event 1, peptide/protein binding	Positive/Negative on KE1
kDPRA	442C, 2021	Key Event 1, peptide/protein binding	Positive/Negative on KE1 and quantitative information for Cat 1A or Cat 1B/NS
KeratinoSens™	442D, 2018	Key Event 2, keratinocyte response	Positive/Negative on KE2
LuSens	442D, 2018	Key Event 2, keratinocyte response	Positive/Negative on KE2
h-CLAT	442E, 2018	Key Event 3, Monocyte/dendritic cell response	Positive/Negative on KE3
U-SENS™	442E, 2018	Key Event 3, Monocyte/dendritic cell response	Positive/Negative on KE3
IL-8 Luc	442E, 2018	Key Event 3, Monocyte/dendritic cell response	Positive/Negative on KE3
2 out of 3 DA	497, 2021	Combining Key Events 1, 2 and 3	Positive/Negative for sensitizer
ITS v1 and v2 DA	497, 2021	Combining Key Events 1 and 3	Positive/Negative for sensitizer and information for Cat 1A or Cat 1B/NS

Basketter and Gerberick, Cosmetics 2022, 9, 38. https://doi.org/10.3390/cosmetics9020038

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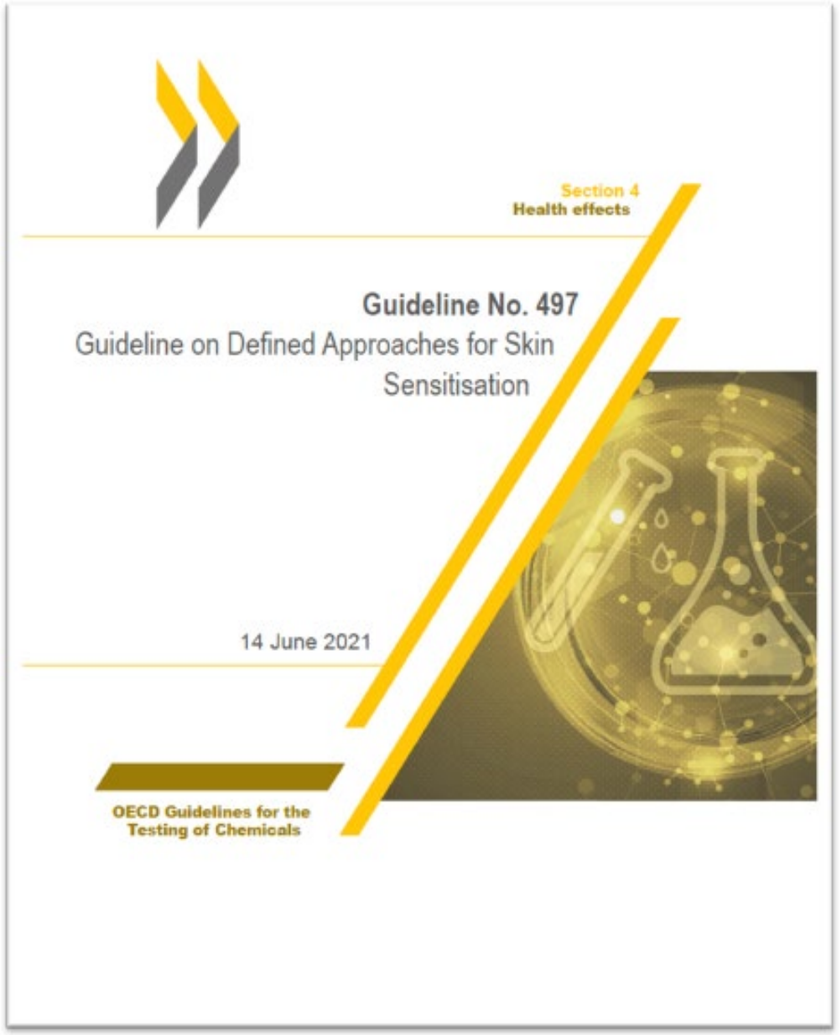
OECD GL 497 Guideline on Defined Approaches to Skin Sensitisation



Defined Approaches …

- are designed to address pre-defined endpoint/prediction
- are from defined information sources
- the sequence is defined and next steps are rule-based
- are fixed data interpretation procedures
- provide clear regulatory conclusions

Defined approaches remove expert judgement and are not flexible, which makes them suitable for harmonization.

Defined Approaches – under OECD evaluation

					MIE	KE2	KE3				
	Case Study	Bioavailability	Phys-chem properties	*In silico*	Protein binding /reactivity	Events in Keratinocytes	Events in DC	Events in T cells	Adverse effect	Others
1	Sensitiser potency prediction Key event 1+2 (**Givaudan**)		X	TIMES SS	Cor1C420-assay	TG 442D				
2	The artificial neural network model for predicting LLNA EC3 (**Shiseido**)		X		SH Test	AREc32 assay	TG 442E			
3	ITS/DS for hazard and potency identification of skin sensitisers (**P&G**)	penetration (PBPK model)	X	TIMES SS	TG 442C	TG 442D	TG 442E U937 test	TG 429		
4	Tiered system for predicting sensitising potential and potency of a substance (STS) (**Kao Corporation**)				TG 442C		TG 442E			
5	Score-based battery system for predicting sensitising potential and potency of a substance (ITS) (**Kao Corporation**)			DEREK Nexus	TG 442C		TG 442E			
6	IATA for skin sensitisation risk assessment (**Unilever**)	penetration modified OECD TG428			modified OECD TG428					
7	Weight of evidence in vitro ITS for skin hazard identification (**BASF**)				TG 442C	TG 442D LuSens	TG 442E m-MUSST			
8	STS for hazard identification of skin sensitisers (**RIVM**)			Various	TG 442C	TG 442D HaCaT gene signature	TG 442E			
9	IATA (**Dupont**)		X	Various	TG 442C glutathione depletion assay	TG 442D	TG 442E U937	TG 429	TG 406	E.g. Skin Irr/Corr, Ames
10	Decision strategy (**L'Oréal**)		X	Various	TG 442C	TG 442D ARE-Nrf2 Assay	U-SENS™ PGE2 Assay			
11	Integrated decision strategy for skin sensitisation hazard (**ICCVAM**)		X	OECD Toolbox			TG 442E			
12	Consensus decision tree model for skin sensitisation hazard prediction (**EC JRC**)			TIMES SS Dragon						

- Some based fully on *in vitro* methods, some on *in silico*, or both
- *in vitro* methods are mainly OECD TG
- Algorithms used to combine data vary in complexity

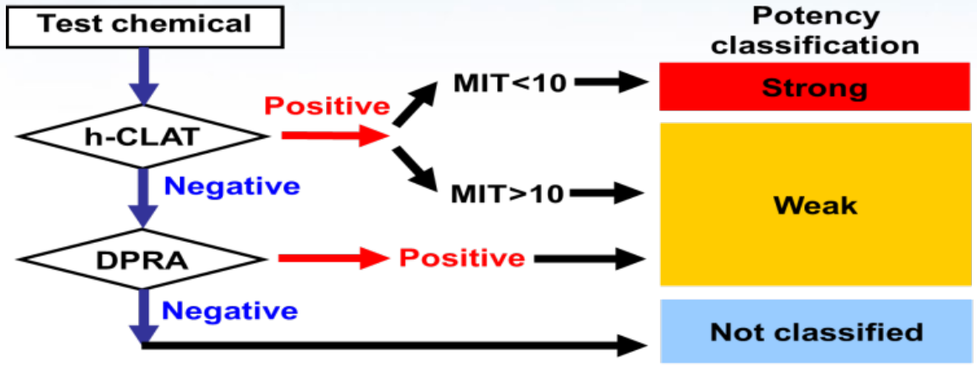
Annex 1 to Guidance Document No. 256

Summary of the DAs Included in OECD GL 497

DA/Method	Information Sources	Capability (Hazard and/or Potency)	Hazard Performance vs. LLNA N~168	Hazard Performance vs. Human N~63	GHS Potency Performance vs. LLNA (Accuracy)	GHS Potency Performance vs. Human (Accuracy)
2o3 DA	DPRA, KeratinoSens™, h-CLAT	Hazard	84% BA, 82% Sens, 85% Spec	88% BA, 89% Sens, 88% Spec	-	-
ITSv1 DA	DPRA, h-CLAT, DEREK Nexus v6.1.0	Hazard, Potency (GHS)	81% BA, 92% Sens, 70% Spec	69% BA, 93% Sens, 44% Spec	70% NC, 71% 1B, 74% 1A	44% NC, 77% 1B, 65% 1A
ITSv2 DA	DPRA, h-CLAT, OECD QSAR Toolbox v4.5	Hazard, Potency (GHS)	80% BA, 93% Sens, 67% Spec	69% BA, 94% Sens, 44% Spec	67% NC, 72% 1B, 72% 1A	44% NC, 80% 1B, 67% 1A
LLNA (provided for comparison)	*in vivo*	Hazard, Potency	-	58% BA, 94% Sens, 22% Spec	-	25% NC, 74% 1B, 56% 1A

*BA = Balanced Accuracy, average of Sensitivity and Specificity

Examples Defined Approaches

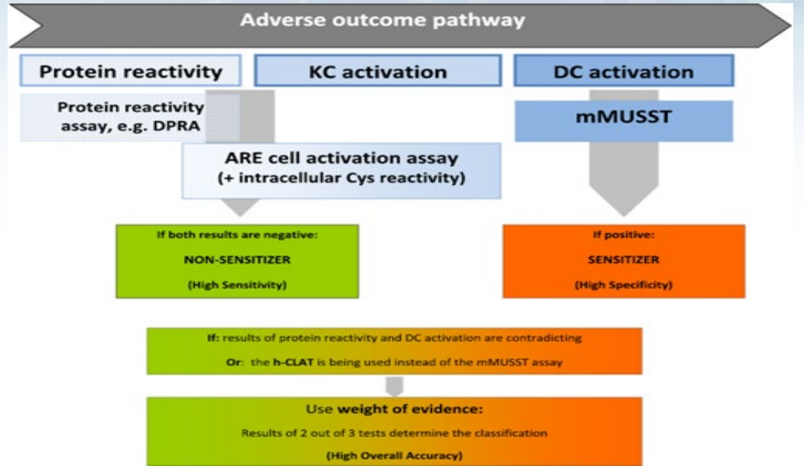


Takenouchi et al. (2015) J. Appl. Toxicol.: STS & ITS

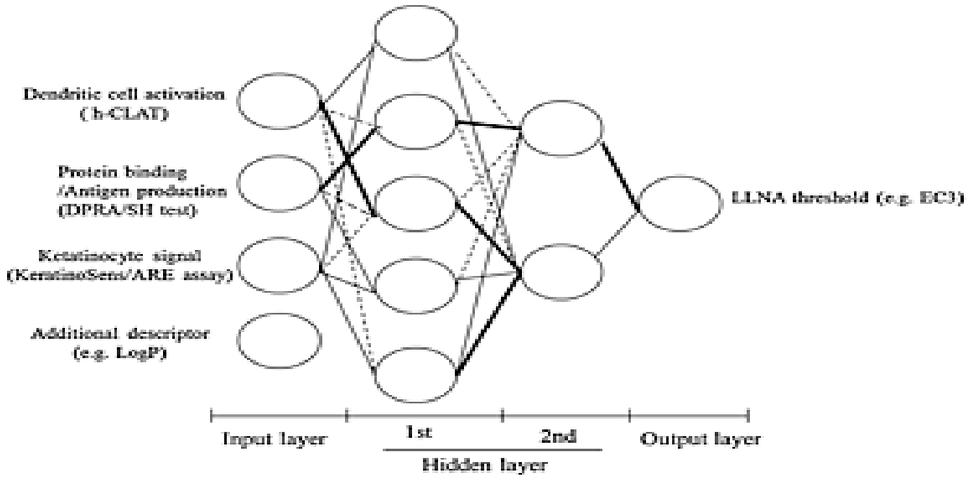
Score	h-CLAT MIT	DPRA depletion	DEREK
3	≤10 µg/mL	≥42.47%	-
2	>10, ≤150 µg/mL	≥22.62, <42.47%	-
1	>150, ≤5000 µg/mL	≥6.376, <22.62%	Alert
0	not calculated	<6.376%	No alert

Potency: Total battery score

Strong :	7
Weak :	2-6
Not classified :	0-1



Bauch et al. (2012) Regul. Toxicol. and Pharmacol.: 2 out of 3



Hirota et al. (2015) J. Appl. Toxicol.: Artificial Neural Network

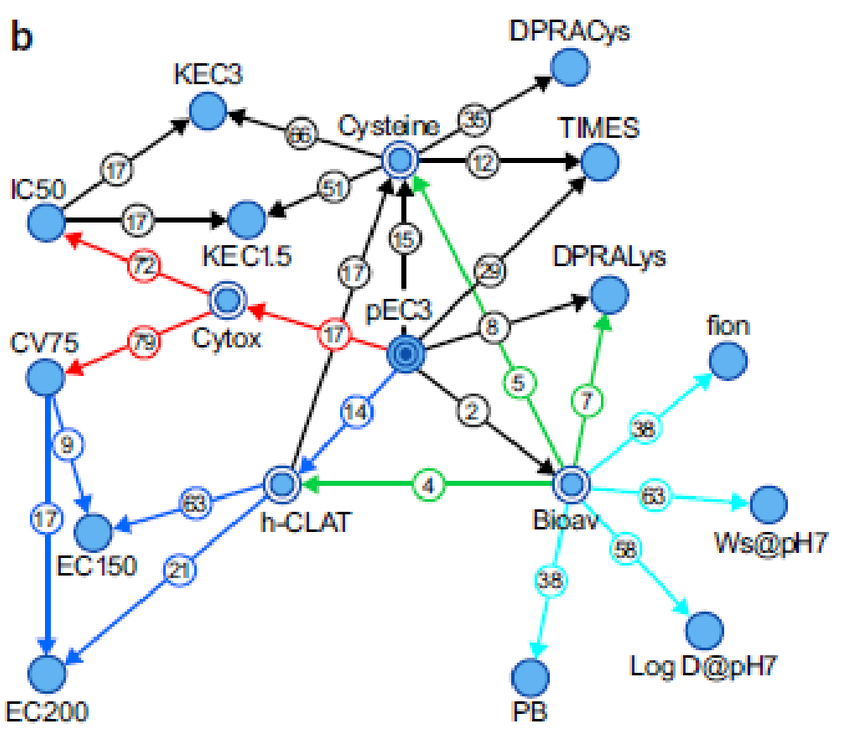
P&G DA: Bayesian Net (BN) ITS-3

Input:

- Phys Chem properties
- Prediction considering metabolism and auto-oxidation (TIMES-SS)
- **KE1:** DPRA
- **KE2:** KeratinoSens™
- **KE3:** h-CLAT

Output:

- Predicts probability to be within a LLNA pEC3 skin sensitization potency class
- 4 potency classes: nonsensitizers (NS), weak (W), moderate (M), and combined strong and extreme (S) sensitizers.
- Uncertainty of the prediction is considered.



Jaworska et al. Arch. Toxicol. 2015
Or : www.its.douglasconnect.com

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QRA Special Considerations

- RIFM approach to evaluating Natural Complex Substances (NCS)
  - Api et al., Food and Chemical Toxicology 159: 112715. https://doi.org/10.1016/j.fct.2021.112715
- A series of decision trees are utilized and a tiered approach for each endpoint uses a 4-step process with testing only as a last resort
  1. Evaluate available data on NCS
  2. Verify whether a TTC can be applied
  3. Verify whether the NCS risk assessment can be achieved on a component basis
  4. Determine whether data must be generated
- Dermal Sensitization Thresholds (DST) are utilized on the whole NCS or individual components.
  - A reactive DST of 64 µg/cm^2
  - A non-reactive DST of 900 µg/cm^2

Ongoing NAMs research for botanical extracts and complex mixtures

- Kolle et al., 2023 utilized DPRA, h-CLAT and KeratinoSens/LuSens and the 2 out of 3 DA for 8 plant extracts with a balanced accuracy of 50% (overall, not recommended)
- Also, for 11 plant extracts using the SENS-IS the balanced accuracy was 88%
  - SENS-IS is a 3D human skin model using multiple gene activation endpoints to identify skin sensitizing materials
- Careful analysis is needed before positive or negative results can be accepted
- Strickland et al., 2022 tested 27 agrochemical formulations in the DPRA, KeratinoSens and h-CLAT and input into 3 DAs
- 2 of 3 was the best performing DA with balanced accuracy of 78%
- Testing strategies such as DA anchored to human biology and mechanistic information provide a promising approach for agrochemicals

Kolle et al., Regulatory Toxicology and Pharmacology 138: 105330. https://doi.org/10.1016/j.yrtph.2022.105330
Strickland et al., Frontiers in Toxicology 4: 852856. https://doi.org/10.3389/ftox.2022.852856

Case study – Acetyl glucosamine (160th CIR March 7, 2022) Weight of Evidence and Conclusions

In vivo animal data:

- none

In silico data:

- DEREK alert for skin sensitization (aldehyde precursor), however sugars are excluded.
- ToxTree = no alerts.
- TIMES prediction out of domain.

In chemico and in vitro data:

- DPRA average depletion rate 1% = Non-Sensitizer
- KeratinoSens IC50 > 2000 uM = Negative
- h-CLAT viability >50% = Negative

Defined Approaches:

- **Bayesian Net ITS = strong evidence (BF>40) non-sensitizer**
- *OECD 497 2 out of 3 = non-sensitizer*
- *OECD 497 ITS1 (DEREK) = non-sensitizer*
- *OECD 497 ITS2 (OECD Toolbox) = non-sensitizer*

Acetyl glucosamine is concluded with strong evidence to be a non-sensitizer.

Skin Sensitization Risk Assessment – Acetyl glucosamine
Supportive Clinical Data

- Repeated insult patch test performed in 108 subjects using a mask containing 0.005% Acetyl Glucosamine; non sensitizing; Anonymous 2018; submitted February 19, 2021 (data1_Glucosamine_122021) Estimated exposure under patch = 2.5 ug/cm^2.
- Maximization assay performed in 25 subjects using a leave-on product containing 0.25% Glucosamine HCl; non sensitizing; Anonymous 2007; submitted February 19, 2021 (data1_Glucosamine_122021) Estimated exposure under patch = 55.6 ug/cm^2.
- Maximization assay performed in 25 subjects using a product containing 0.01% Glucosamine; non-sensitizing; Anonymous 2005; submitted February 19, 2021 (data1_Glucosamine_122021) Estimated exposure under patch = 1.25 ug/cm^2.
- Repeated insult patch test performed in 51 subjects using a leave-on product containing 0.005% Glucosamine HCl; Anonymous 2012; submitted February 29, 2021 (data2_Glucosamine_122021) Estimated exposure under patch = 1.25 – 1.90 ug/cm^2.
- Repeated insult patch test performed in 105 subjects using a liquid foundation containing 2% Acetyl Glucosamine; non-sensitizing; Anonymous 2011; submitted February 11, 2022 (*data_Glucosamine_032022*; TKL Research 2011). Estimated exposure under patch = 1,000 ug/cm^2.

- HRIPT and HMT glucosamine testing concentrations of 1.25 – 1,000 ug/cm^2 exceed the maximum estimated usage concentration of 136 ug/cm^2 by 7-fold, confirming the lack of sensitization at the maximum consumer exposure level. Therefore, this data confirms the conclusion of the Next Generation Risk Assessment for Acetyl glucosamine.

Clinical data confirms that Acetyl glucosamine is a non-sensitizer.

Published case study with NAMs and DAs

- Gilmour et al., 2023 provide a hypothetical case study with diethanolamine that demonstrates the challenge of how DAs can be used to derive a quantitative point of departure for NGRA
- Existing NAM information differed between in silico predictions and in chemico / in vitro data
  - DPRA (-), KeratinoSens (-), U-SENS (+) h-CLAT (+)
  - DEREK in silico (S) Cat 1B, OECD Toolbox (NS) Not Categorized
- Seven DAs were applied to the hypothetical exposure scenarios (rinse-off shampoo and leave-on deodorant product)
- OECD IATA Case Studies Project evaluated the leave-on application to demonstrate the impact of inconsistent NAM information on a hypothetical risk assessment (a more complex scenario than previous case study with geraniol)

Gilmour et al., 2023 ALTEX 40(3): 439-451. doi: 10.14573/altex.2211161
OECD Series on Testing and Assessment No. 385. ENV/CBC/MONO(2023)31

Tab. 1: Summary of which NAM information are used within the individual DA applied within this case study

NAM	NAM information	ITSv1	ITSv2	ANN (TIMES-SS)	ANN (ToxTree)	STS		BN-ITS	SARA
						Tier 1	Tier 2		
PC properties	MW: 105.14 Da						√		
	LogP: -1.46						√		
	Fraction ionized: 0							√	
	LogD @ pH 7: -3.38							√	
	LogKoW							√	
	Volatility: semi-volatile					√	√		
	pH: 10.3					√			
	H_2O solubility @ pH 7: 3.0 g/L							√	
	Plasma protein binding (% bound): 11.3							√	
TIMES-SS	Parent: non-sensitizer; Metabolite: non-sensitizer			√		√		√	
TOXTREE	Protein binding alert: Schiff base				√	√			
OECD Toolbox	OASIS protein binding alerts for skin sensitization: negative/no alerts; Skin sensitization automated workflow for DASS: negative/non-sensitizer		√						
DEREK Nexus	Positive/sensitizer (equivocal)	√							
Mechanistic domain: expert review	Pro-Schiff base								
DPRA	Negative/minimal					√			
	Cys depl.: 5.9%	√	√	√	√		√	√	√
	Lys depl.: 2.2%	√	√	√	√		√	√	√
KeratinoSens™	Negative					√			
	EC1.5: > 2000 µM			√	√		√	√	√
	EC3: > 2000 µM							√	
	Imax: 1.0								
	IC50%: > 2000 µM							√	
U-SENS™	Positive					√			
	CD86 EC150: 26.9 µg/mL						√		√
	CV70: > 200 µg/mL								
h-CLAT	Positive								
	CD86 EC150: 1242.5 µg/mL	√	√	√	√			√	√
	CD54 EC200: 1260.9 µg/mL	√	√	√	√			√	√
	CV75: 2277 µg/mL			√	√			√	

Tab. 2: Summary of NAM risk assessment outcomes based on the 7 DA for the use of 0.8% DEA in a shampoo

DA	ITSv1	ITSv2	ANN (TIMES-SS)	ANN (ToxTree)	STS	BN-ITS	SARA
DA output							
	Cat. 1B	inconclusive	EC3 = 81.5%	EC3 = 59.1%	NS P(NS) = 87%	NS P(NS) = 99% Bayes factor (> 30%)	ED_{01} = 13,000 $\mu g/cm^2$ (5^{th}-95^{th} percentile 530-370,000 $\mu g/cm^2$)
PoD ($\mu g/cm^2$)							
	> 500	> 500	20,375	14,775	25,000	25,000	13,000
Calculate MoE for 0.8% shampoo							
Consumer exposure level ($\mu g/cm^2$)	0.6	0.6	0.6	0.6	0.6	0.6	0.6
MoE (PoD/CEL) **p(low risk)*SARA ONLY**	> 833	> 833	33,958	24,625	41,667	41,667	24,000 p(low risk) = 0.98
Weight of evidence assessment / characterize uncertainty							
Confidence in NAM input	moderate[a]	moderate[a]	moderate[b]	moderate[b]	moderate[b]	moderate[b]	moderate[b]
Conservatism in transformation of DA outcome to PoD	unknown[c]	unknown[c]	low[d]	low[d]	high[e]	high[e]	low[f]
MoE **p(low risk)*SARA ONLY**	high[g]	high[g]	high[g]	high[g]	high[g]	high[g]	p(low risk) = 0.98 high[h]
Risk assessment							
Risk assessment outcome	**SAFE**	**SAFE**	**SAFE**	**SAFE**	**SAFE**	**SAFE**	**SAFE**

Tab. 3: Summary of NAM risk assessment outcomes based on the 7 DA for the use of 0.8% DEA in an underarm deodorant product

DA	ITSv1	ITSv2	ANN (TIMES-SS)	ANN (ToxTree)	STS	BN-ITS	SARA
DA output							
	Cat. 1B	inconclusive	EC3 = 81.5%	EC3 = 59.1%	NS P(NS) = 87%	NS P(NS) = 99% Bayes factor (> 30%)	ED_{01} = 13,000 µg/cm² (5^{th}-95^{th} percentile 530-370,000 µg/cm²)
PoD (µg/cm²)							
	> 500	> 500	20,375	14,775	25,000	25,000	13,000
Calculate MoE for 0.8% deodorant							
Consumer exposure level (µg/cm²)	60	60	60	60	60	60	60
MoE (PoD/CEL) **p(low risk)*** SARA ONLY	> 8	> 8	340	246	416	416	217 (8.8-617) p(low risk) = 0.5
Weight of evidence assessment / characterize uncertainty							
Confidence in NAM input	moderate[a]	moderate[a]	moderate[b]	moderate[b]	moderate[b]	moderate[b]	moderate[b]
Conservatism in trans-formation of DA outcome to PoD	unknown[c]	unknown[c]	low[d]	low[d]	high[e]	high[e]	low[f]
MoE **p(low risk)*** SARA ONLY	low[g]	low[g]	high[h]	high[h]	high[h]	high[h]	p(low risk) = 0.5 low[j]
Risk assessment							
Risk assessment outcome	**UNSAFE**	**UNSAFE**	**SAFE**	**SAFE**	**SAFE**	**SAFE**	**UNSAFE**

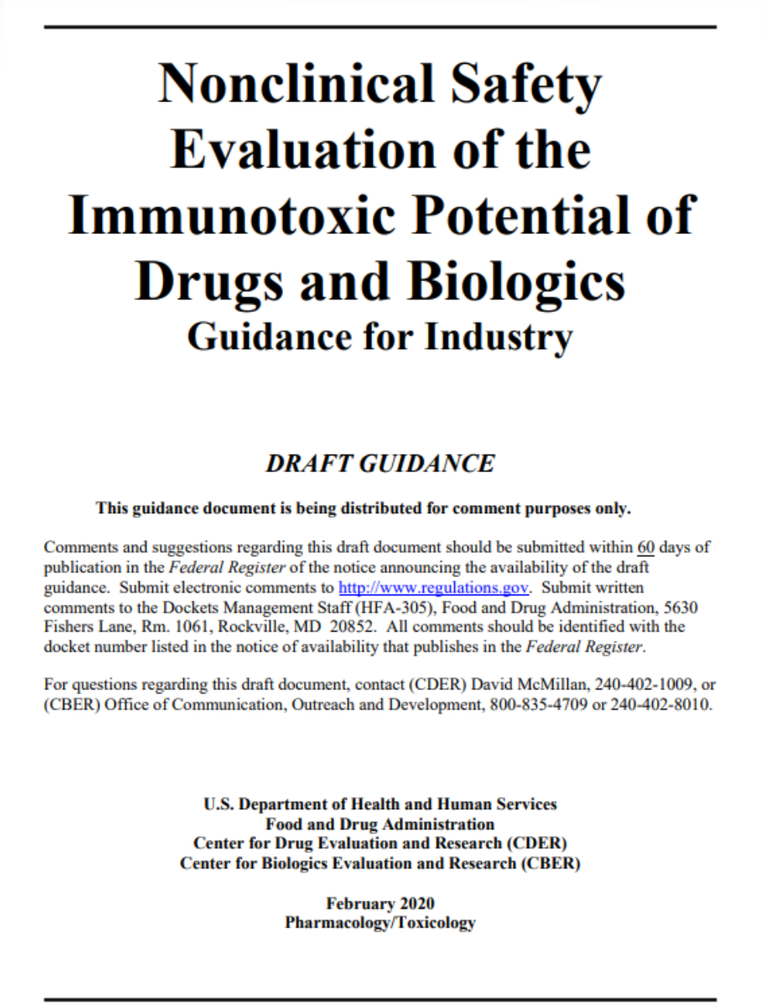
OECD IATA Case Study Project Outcome

- Areas identified for future Guidance Documents
  - Guidance on what to do with inconsistent results
  - Guidance on how to deal with substances that may be outside the domain of applicability for some data sources
- Additional perspective
  - Steps to calculate POD requires further scientific scrutiny
  - The NGRA framework can be applied to this complex case study

EU REACH acceptance of Alternatives

AOP Key event measured[59]	Test method	Validation status, regulatory acceptance	EU Test Methods/ OECD test guideline	Outcome according to the test method/guideline	EURL ECVAM DB-ALM protocol Nr.
Skin sensitisation					
Key Event 1 Peptide/protein binding	DPRA	Validated and regulatory acceptance	B.59/TG 442C	SS or NS with complementary information	154
Key Event 2 Keratinocyte response	KeratinoSens™	Validated and regulatory acceptance	B.60/TG 442D	SS or NS with complementary information	155
	LuSens[60]	Under validation assessment	N.A/N.A	SS or NS with complementary information	184
	SENS-IS[61]	Under validation assessment	N.A/N.A	SS or NS with complementary information	N.A
Key Event 3 Monocytic /Dendritic cell response	h-CLAT	Validated and regulatory acceptance	N.A/TG 442E	SS or NS with complementary information	158
	U-SENS™[60]	Validated and under regulatory adoption	N.A/draft TG available	SS or NS with complementary information	183
	IL-8 Luc Assay[62]	Validated and under regulatory adoption	N.A/draft TG available	SS or NS with complementary information	N.A.
Key Event 4[63] T-cell response	N.A	N.A	N.A/N.A	N.A.	N.A.

US FDA Guidance on Nonclinical Safety Evaluation of Immunotoxic Potential of Drugs and Biologics



Nonclinical Safety Evaluation of the Immunotoxic Potential of Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) David McMillan, 240-402-1009, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2020
Pharmacology/Toxicology

New approaches …

FDA no longer recommends LLNA to assess sensitization potential of topical drug products.

As an alternative to accepted guinea pig tests, FDA will consider a battery of in silico, in chemico, and in vitro studies that have been shown to adequately predict human skin sensitization with an accuracy similar to existing in vivo methods.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/nonclinical-safety-evaluationimmunotoxic-potential-drugs-and-biologics-guidance-industry

US EPA Draft Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing

Interim Science Policy: Use of Alternative Approaches for Skin Sensitization as a Replacement for Laboratory Animal Testing

DRAFT FOR PUBLIC COMMENT
April 4, 2018

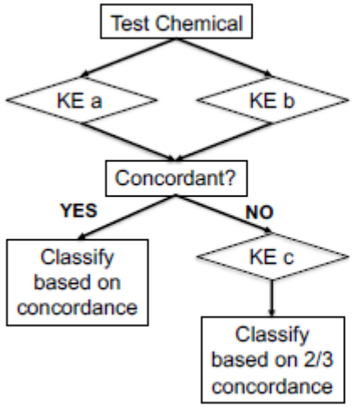
EPA's Office of Chemical Safety and Pollution Prevention:

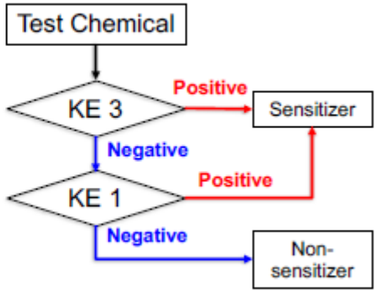
Office of Pesticide Programs
Office of Pollution Prevention and Toxics

New approaches …

Applies to pesticide active ingredients, inerts, and single chemicals regulated under amended TSCA.

Two DAs currently accepted: AOP 2 out of 3 and KE3/1 STS.





https://www.epa.gov/pesticides/epa-releases-draft-policy-reduce-animal-testing-skin-sensitization

Human Safety
Ensuring Safe Products

Take aways

- Confidence in decision making using NAM data is growing
- No one DA fits all
- Read-across analogues can be used to reduce uncertainty in decision making
- NGRA framework is useful to structure the risk assessment
- The AOP defines the key elements of skin sensitization by which methods can be developed and applied
- As with any risk assessment tool, understanding the domains of applicability and limitations for each of the assays is important
- Additional case studies will challenge the current approaches to make them better
- Each risk assessment should be done on a case-by-case basis using the weight of evidence and expert judgement to determine the confidence in the outcome

Scientific Committee on Consumer Safety (SCCS/1647/22)

- “The SCCS needs to build up experience with the NGRA, as well as with DASS (3-4.7 B), and will evaluate and accept the approach on a case-by-case basis”
- Confidence in reliability of Dermal Sensitization Threshold (DST) is still lacking

Additional Resources and Case Studies

- Reynolds, G, Reynolds, J, Gilmour, N, Cubberley, R, Spriggs, S, Aptula, A, Przybylak, K, Windebank, S, Maxwell, G and Baltazar, MT (2021). A hypothetical skin sensitization next generation risk assessment for coumarin in cosmetic products. Regulatory Toxicology and Pharmacology 127: 105075. https://doi.org/10.1016/j.yrtph.2021.105075
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