The Skin Sensitization Best Guidance in Practice

Case study: Thioglycerol

ICCS BPG Skin Sensitization: Safety Assessment Using NAMs for Substances in Cosmetics and Personal Care Products Webinar

Nathalie Alépée, PhD
Senior Scientific Officer
L'Oréal Research & Innovation

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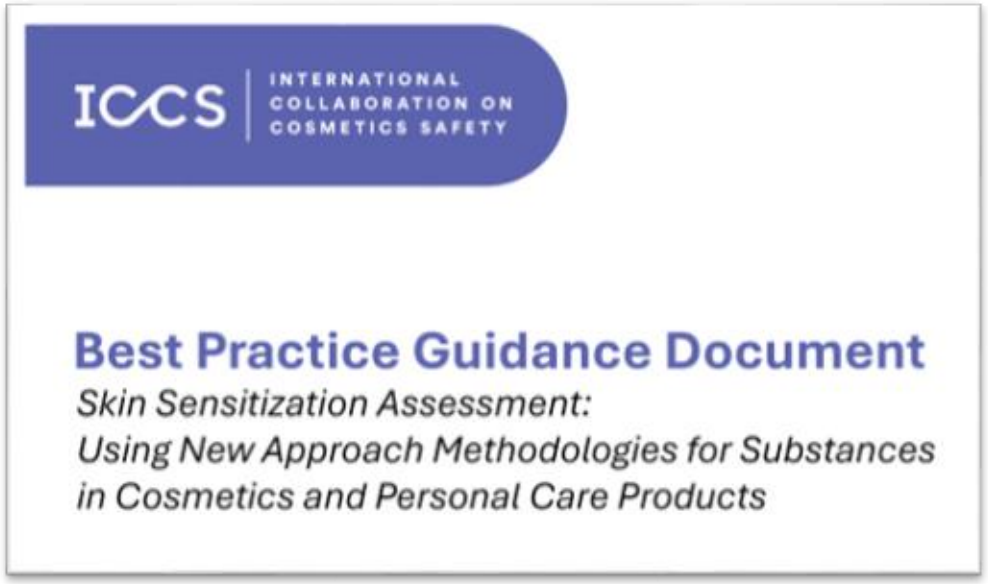
Overview

- Practical application of the ICCS Best Practice Guidance (BPG) workflow to a specific cosmetic ingredient
- Going through the workflow
  - Problem formulation
  - Data integration
  - Data evaluation
  - Weight of Evidence (WoE)
  - Decision criteria
  - Uncertainty characterization



The Case Study: Thioglycerol

1. Product Scenario

- Company: Lily & Lavender
- Product Type: Leave-on anti-aging face cream
- Ingredient under evaluation: Thioglycerol (CASRN 96-27-5)
- Proposed Concentration: 1% in the final formulation

INCI name	Thioglycerol
Preferred IUPAC name	3-Sulfanylpropane-1,2-diol
CASRN	96-27-5

2. The Challenge & Objective

- Primary Goal: Assess skin sensitization risk for the intended use
- Methodological Constraint: Conduct the assessment using only NAMs
- Compliance: Ensure the evaluation meets the requirements for a non-animal safety dossier

3. Methodological Framework

- Guidance followed: ICCS Skin Sensitization Best Practice Guidance (BPG)
- Strategic Approach: Utilizing the structured 6-step NGRA workflow
- Focus: Data organization and evidence-based scientific decision-making

Step 1. Problem Formulation & Scoping

Step 1. Provide a clear statement scope and the hypothesis to be evaluated

Why?

Specific concerns?

Regulatory considerations

Timing/resource considerations

Problem statement:

Ensure consumer safety before product launch

1. Is the **ingredient a sensitizer?**
2. If so, which **UN GHS hazard classification** is assigned?
3. Is there an **adequate margin of exposure** for using Thioglycerol at 1% in a face cream when **using the semi-quantitative approach?**
4. Is there an adequate **margin of exposure when using the quantitative approach?**

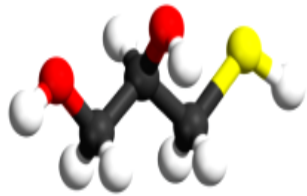
to support Go/No-Go decisions

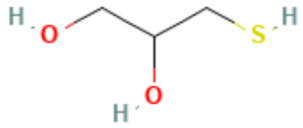
Step 2. Substance Characterization & Gather Existing Data

Step 2. Collect data on Thioglycerol

Element	Description
INCI name	**Thioglycerol**
Synonyms[a]	**3-sulfanylpropane-1,2-diol**
CASRN[a,b]	**96-27-5**
Molecular formula[a]	**$C_3H_8O_2S$**
Molecular weight[a,b]	**108.16 g/mol**
Particulate size or size range (if applicable)	**Not applicable**
Purity	**100% for case study**
Known impurities	None identified for case study
Potential impurities	None identified for case study
Physical form[a]	**Liquid**
Water solubility[b]	**6.46 mol/L**
Partition coefficient	**Not available**
Vapor pressure[b]	**0.00000933 mmHg**
Additional physico-chemical properties that impact skin sensitization	None identified for case study
Non-cosmetic uses or exposures[a]	**Cleaning agent, preservative**

[a] source: PubChem (https://pubchem.ncbi.nlm.nih.gov/compound/7291)
[b] source: EPA ComptoxDashboard (https://comptox.epa.gov/dashboard/chemical/properties/DTXSID5046512)





Step 3. Identify Use Scenario

- Use scenario and exposure amount is an initial step in conducting a safety assessment
  - Not needed for a hazard assessment
- Consumer exposure level (CEL) is calculated for skin sensitization
- Problem formulation considered before evaluating the exposure

Table 4. Data to Collect to Support Derivation of a Consumer Exposure Level (CEL)

Element	Description
Product types of interest	[Insert product types to be assessed for the substance] Example: Body lotion and shower gel
Concentration of substance in each product	[Insert the substance amount that will be in each product of interest] Example: 1% in all products (provide data source)
Method and location of application for each product type	[Insert description of application method and intention for leave on/rinse off] Example: Rubbed on body lotion, applied to full body, and then rinsed off
Population, including targeted or special consumer groups (if applicable)	[Insert description of targeted or special consumer group considerations] Examples: substance or product known to be used by children or people with sensitive skin

Step 3. Identify Use Scenario

Step 3. Define the exposure scenario to estimate Quantitative Exposure Level of Thioglycerol to the consumer

Element	Description
Product types of interest	Face Cream
Concentration of substance in each product	1%
Method and location of application for each product type	Leave on
Population, including targeted or special consumer groups (if applicable)	General adult (male and female) population

Assumption: A deterministic, single product exposure approach is assumed

Step 3. Identify Use Scenario

Step 3. Derivation of a Consumer Exposure Level (CEL)

- Calculating dermal exposure using data on previous slide
- Referring to SCCS Notes of Guidance Table 3A

Product and inclusion	Daily amount (q) (g/day)	f_{ret}
Face cream, 1%	1.54	1.00

$$E_{product} = q \times f_{ret} \qquad \text{(Equation 2)}$$

Where:

- $E_{product}$ (µg/day) = the daily amount of the cosmetic product to which a user is externally exposed
- q (µg/day) = total amount of product that is applied per day
- f_{ret} = Product-specific retention factor (ranges from 0.01 to 1).

$E_{product}$ = 1.54 x 1.00

1.54 (g/d)

Table 3A: Daily exposure levels for different cosmetic product categories in Europe, calculated by multiplying daily amounts (Hall *et al.*, 2007, 2011) and f_{ret}.

Product type	Estimated daily amount applied q_x (g/d)	Relative daily amount applied[1] q_x /bw (mg/kg bw/d)	Retention factor[2] f_{ret}	Calculated daily exposure $E_{product}$ (g/d)	Calculated relative daily exposure[1] $E_{product}$ /bw (mg/kg bw/d)
Bathing, showering					
Shower gel	18.67	279.20	0.01	**0.19**	**2.79**
Hair care					
Shampoo	10.46	150.49	0.01	**0.11**	**1.51**
Hair styling products	4.00	57.4	0.10	**0.40**	**5.74**
Skin care					
Face cream	1.54	24.14	1.00	**1.54**	**24.14**
Make-up					
Liquid foundation	0.51	7.90	1.00	**0.51**	**7.90**
Lipstick, lip salve	0.057	0.90	1.00	**0.057**	**0.90**
Deodorant					
Deodorant non-spray	1.50	22.08	1.00	**1.50**	**22.08**
Deodorant spray[3]	6.54	93.7	1.00	**6.54**	**93.7**
Oral hygiene					
Toothpaste (adult)	2.75	43.29	0.05	**0.138**	**2.16**
Mouthwash	21.62	325.40	0.10	**2.16**	**32.54**

Step 3. Identify Use Scenario

Step 3. Derivation of a Consumer Exposure Level (CEL)

Scientific Committees
on Consumer Safety
on Health, Environmental and Emerging Risks

$$E_{dermal} = \left(\frac{C}{100}\right) \times E_{product} \qquad \text{(Equation 3)}$$

Where:

- E_{dermal} (µg/day) = the daily amount of the substance to which the skin is exposed
- C (%) = concentration of the substance in the cosmetic product
- $E_{product}$ (µg/day) = the daily amount of the cosmetic product to which a user is externally exposed.

E_{dermal} = (1/100) x 1.54

0.0154 (g/d)

15.4 (mg/d)

15,400 (µg/d)

Table 3A: Daily exposure levels for different cosmetic product categories in Europe, calculated by multiplying daily amounts (Hall *et al.*, 2007, 2011) and f_{ret}.

Product type	Estimated daily amount applied q_x (g/d)	Relative daily amount applied[1] q_x /bw (mg/kg bw/d)	Retention factor[2] f_{ret}	Calculated daily exposure $E_{product}$ (g/d)	Calculated relative daily exposure[1] $E_{product}$ /bw (mg/kg bw/d)
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Shower gel	18.67	279.20	0.01	**0.19**	**2.79**
Hair care					
Shampoo	10.46	150.49	0.01	**0.11**	**1.51**
Hair styling products	4.00	57.4	0.10	**0.40**	**5.74**
Skin care					
Face cream	1.54	24.14	1.00	**1.54**	**24.14**
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Liquid foundation	0.51	7.90	1.00	**0.51**	**7.90**
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Mouthwash	21.62	325.40	0.10	**2.16**	**32.54**

Step 3. Identify Use Scenario

Step 3. Derivation of a Consumer Exposure Level (CEL)

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For a skin sensitization assessment, the E_{dermal} value in the unit of µg/day needs to be normalized by the area of the skin applied. That is, the local dose should be divided by the skin surface area (SSA) to derive a CEL. Equation 4 below presents the method to calculate the CEL:

$$CEL = \frac{E_{dermal}}{SSA} \qquad \text{(Equation 4)}$$

Where:

- CEL (µg/cm²) = consumer exposure level
- E_{dermal} (µg/day) = the daily substance amount to which the skin is exposed
- SSA (cm²) = Skin surface area expected to be exposed to the cosmetic product, based on product use information available in the literature. If the data allow, the 90th percentile from a distribution for this parameter should be used.

Table 4: Mean exposed skin surface area per product category (Bremmer *et al.*, 2006a; Bremmer *et al.*, 2006b) and frequency of application per product category

Product type	Surface area for application SSA (cm²)	Body areas	Frequency of application
Bathing, showering			
Shower gel	17500	total body area	1.43/day
Hand wash soap	860	area hands	10/day[3]
Bath oil, salts, etc.	16340	area body- area hands	1/day
Hair care			
Shampoo	1440	area hands+ ½ area head	1/day
Hair conditioner	1440	area hands+ ½ area head	0.28/day
Hair styling products	1010	½ area hands+ ½ area head	1.14/day
Semi-permanent hair dyes (and lotions)	580	½ area head	1/week (20min.)
Oxidative/ permanent hair dyes	580	½ area head	1/month (30min.)
Skin care			
Body lotion	15670	area body-area head (female)	2.28/day
Face cream	565	½ area head (female)	2.14/day
(+ applied on back of neck)	80[2]		
Hand cream	860	area hands	2/day
Make-up			
Liquid foundation	565	½ area head (female)	1/day
Make-up remover	565	½ area head (female)	1/day

$CEL = E_{dermal} / SSA$

15,400 / 565

27.26 µg/cm²

Step 3. Identify Use Scenario

Step 3. Dermal Exposure Values for a Face Cream of Thioglycerol to the consumer

Element	Description
Product types of interest	Face Cream
Concentration of substance in each product	1%
Method and location of application for each product type	Leave on
Population, including targeted or special consumer groups	General adult population

Product and Inclusion %	Product Use (g/day)	Skin Surface Area (cm^2)	Product Exposure ($\mu g/cm^2$)	Substance Exposure ($\mu g/cm^2$)
Face cream, 1%	**1.54**	**565**	**2726**	**27.26**

Scientific Committees on Consumer Safety on Health, Environmental and Emerging Risks

from SCCS (Scientific Committee on Consumer Safety), SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation 12th revision, 15 May 2023, corrigendum 1 on 26 October 2023, corrigendum 2 on 21 December 2023, SCCS/1647/22.

Step 3. Exposure-Based Waiving

- At this phase in a safety assessment, in the absence of substance-specific information or as part of the WoE, the assessor could evaluate if the exposure estimated is such that exposure-based waiving could be implemented
- Exposure-based waiving is when a full quantitative safety assessment is determined unnecessary because the estimated exposure to a chemical is anticipated to be negligible or below a pre-defined safety threshold
- If existing data is available and/or exposure-based waiving is not feasible, the safety assessor should continue through the workflow process

=>

Thioglycerol Exposure (µg/cm^2)
27.26

Waiving threshold - Existing Data
-> Proceed to **Step 4**

Step 4. Evaluate Existing data

Organize and evaluate existing data regarding reliability, relevancy, and adequacy

Evidence Stream	KE	Data Available?	Result	Outcome P/N/Border
Physico-chemical properties	NA	Yes	MW = 108.02	
ANIMAL				
Buehler	AO	No	N/A	
GPMT	AO	No	N/A	
LLNA	AO	No	N/A	
HUMAN/CLINICAL				
HRIPT	AO	No	N/A	
HMT	AO	No	N/A	
Diagnostic Patch Testing	AO	No	N/A	
IN CHEMICO				
DPRA	MIE/KE1	Yes	% Cysteine (Cys) depletion = 27.3% % Lysine (Lys) depletion = 28.4% Mean of % cys and lys depletion =27.85%	**Positive**
ADRA	MIE/KE1	No	N/A	
kDPRA	MIE/KE1	No	N/A	
IN VITRO				
KeratinoSens™	KE2	Yes	EC1.5 = 4000 µM EC3 = 4000 µM IC50 = 4000 µM	**Negative**
LuSens	KE2	No	N/A	
EpiSensA	KE2	Yes	Imax ATF3 = 0 Imax GCLM = 0 Imax DNAJB4 = 0 Imax IL-8 = 0	**Negative**

Evidence Stream	KE	Data Available?	Result	Outcome P/N/Border
IN VITRO				
hCLAT	KE3	Yes	CD86 EC150 = 813.6 µg/mL CD54 EC200 = NA MIT = 813.6 µg/mL CV75 = 2860.4 µg/mL	**Positive**
U-SENS	KE3	YYes	CD86 EC150 = 88.2 µg/mL CV70 >200 µg/mL	**Positive**
IL-8 Luc	KE3	No	Sensitizer	**Positive**
GARD®skin	KE3	Yes	Mean Decision Value = 0.09831	**Borderline** -0.450 DV +0.450
Metabolism	No	N/A	NA	
IN SILICO				
Derek Nexus	NA	Yes	Positive, in domain/Thiol or thiol exchange agent	**Positive**
OECD QSAR Toolbox	NA	Yes	Positive, read-across, in domain (mechanistic)	**Positive**
ANALOG DATA				
Read-across data	NA	NA		

Assumption: We have no animal, human/clinical data, no analogs, and will generate NAM data as needed

Curated data from OECD (Annex 2; https://one.oecd.org/document/ENV/CBC/MONO(2025)2/en/pdf) and NICETAM ICE (https://ice.ntp.niehs.nih.gov/)

Step 5. Define the approach

Identify data gaps in the existing data

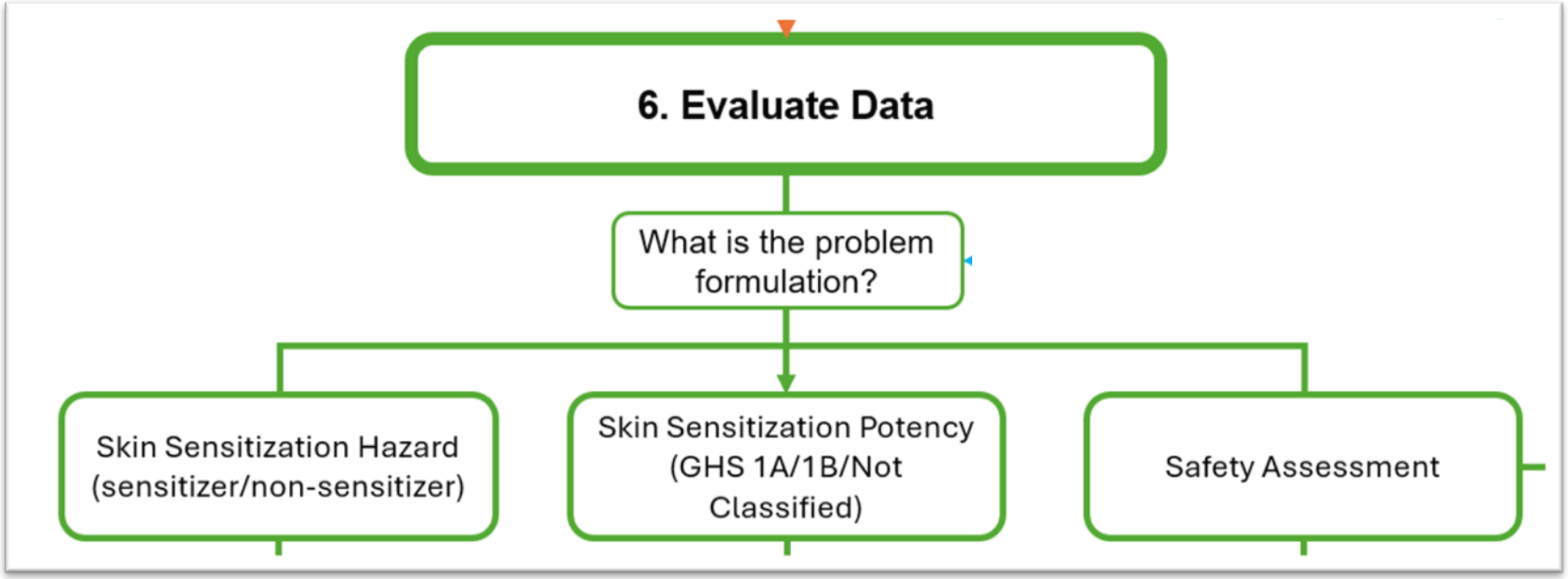
Defined Approach	Problem Formulation Addressed	Input			
		KE1: ADRA or DPRA	KE2: KeratinoSens™ EpiSensA or LuSens	KE3: h-CLAT, U-SENS™ GARD™Skin or IL-8 Luc	*In Silico*: Derek Nexus, OECD QSAR Toolbox
2o3	Hazard (GHS 1 vs GHS NC)	X	X	X	--
ITS	Hazard (GHS 1 vs GHS NC) Potency Category (GHS 1A vs. GHS 1B)	X	--	X	X
SARA-ICE	Inputs	KE1: DPRA, kDPRA	KE2: KeratinoSens™	KE3: h-CLAT, U-SENS™	--
	Point of Departure (ED_{01})	X	X	X	--

X = inputs permitted in DA

- Available KE1–3 and *in silico* data support the use of Defined Approaches (DA)
- DAs will be used to determine hazard, potency, and the Point of Departure (PoD)

Step 6. What is the Problem Formulation?

Hazard, Potency or Safety Assessment

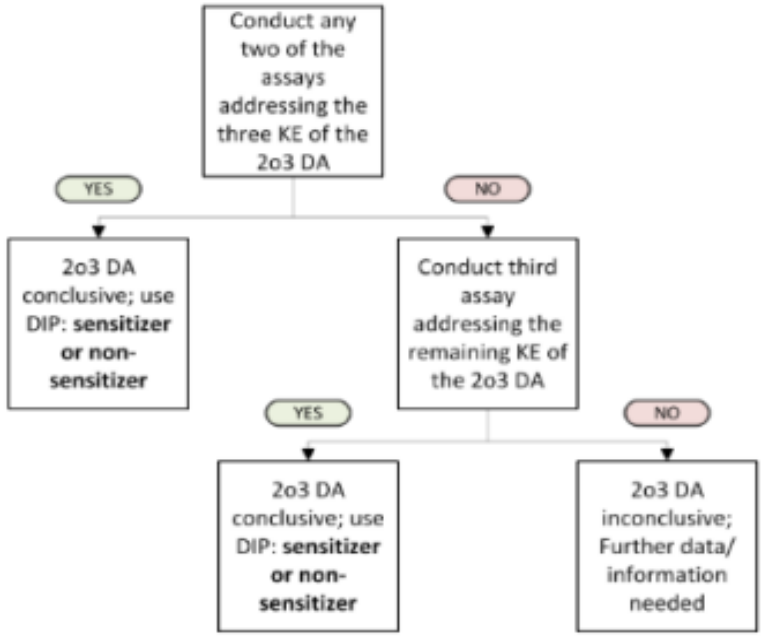


Identify and apply the most appropriate assessment approach based on the problem formulation

Step 6. Is Thioglycerol a sensitizer?

Hazard Assessment

Defined Approach	Problem Formulation Addressed	KE1: ADRA or DPRA	KE2: KeratinoSens™ EpiSensA or LuSens	KE3: h-CLAT, U-SENS™ GARD®Skin or IL-8 Luc
2o3	Hazard (UN GHS 1 vs NC)	X	X	X
	Existing Data	DPRA : Positive	KeratinoSens™: Negative EpiSensA: Negative	h-CLAT: Positive U-SENS™: Positive



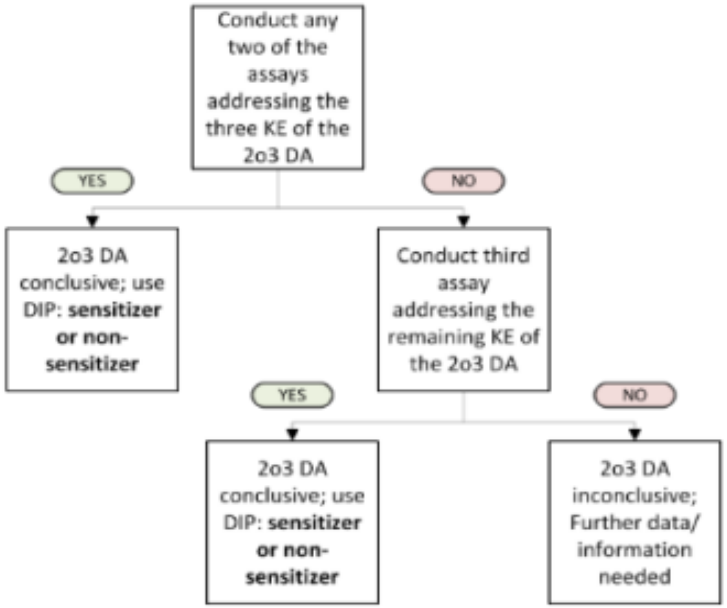
- Test 2 assays: If they match, the conclusion is final
- If they differ: Conduct a 3rd assay as a tie-breaker
- Majority rule: The final result is the 2-out-of-3 consensus

2 out of 3 Conclusion	KE1 Positive KE2 Negative KE3 Positive	**SENSITIZER**

Step 6. Is Thioglycerol a sensitizer?

Borderline - Hazard Assessment

Defined Approach	Problem Formulation Addressed	KE1: ADRA or DPRA	KE2: KeratinoSens™ EpiSensA or LuSens	KE3: h-CLAT, U-SENS™ GARD®Skin or IL-8 Luc
2o3	Hazard (UN GHS 1 vs NC)	X	X	X
	Existing Data	DPRA : Positive	KeratinoSens™: Negative EpiSensA: Negative	GARD®Skin : Borderline



- KE1 & KE2 : Non concordant
- KE 3: GARD®skin
  - **Result**: Mean Decision Value (DV) of **0.09831**
  - Check Borderline Range: **-0.450 to +0.450**
  - Status: The value **0.09831** falls directly **within the Borderline Range**
- KE1 – KE3 : Majority rule not met

2 out of 3 Conclusion	KE1 Positive KE2 Negative KE3 Borderline	**INCONCLUSIVE**

Step 6. Potency of Thioglycerol?

Determine the Potency using the OECD ITS approach

Information Source Type	KE1 (TG 442C)	KE3 (TG 442E)		*In silico*
Score	**DPRA** Mean Cys & Lys % depletion	**h-CLAT** MIT (µg/mL)	**U-SENS™** CD86 EC150 (µg/mL)	Derek Nexus/ OECD QSAR Toolbox
3	≥42.47	≤10	≤3	
2	≥22.62, <42.47	>10, ≤150	>3; ≤35	
1	≥6.38, <22.62	>150, ≤5000	>35; <200	Positive
0	<6.38	Not calculated	not calculated (≥200)	Negative

Hazard	Potency	Total Score from ITS DA
Sensitizer	UN GHS 1A	6-7
Sensitizer	UN GHS 1B	2-5
Non Sensitizer	NC	0-1

DPRA	Mean of % cys and lys depletion = **27.85%**
h-CLAT	MIT = **813.6 µg/mL**
U-SENS	CD86 EC150 = **88.2 µg/mL**

- **Three Sources:** Combines KE1, KE3 & *in silico* data
- **Threshold:** Requires at least two applicable sources for a conclusion
- **Scenario 1:** All three information sources are valid and in domain

ITS Conclusion	KE1 Score **2** KE3 Score **1** *In silico* Score **1** **Total Score 4**	**SENSITIZER UN GHS 1B**

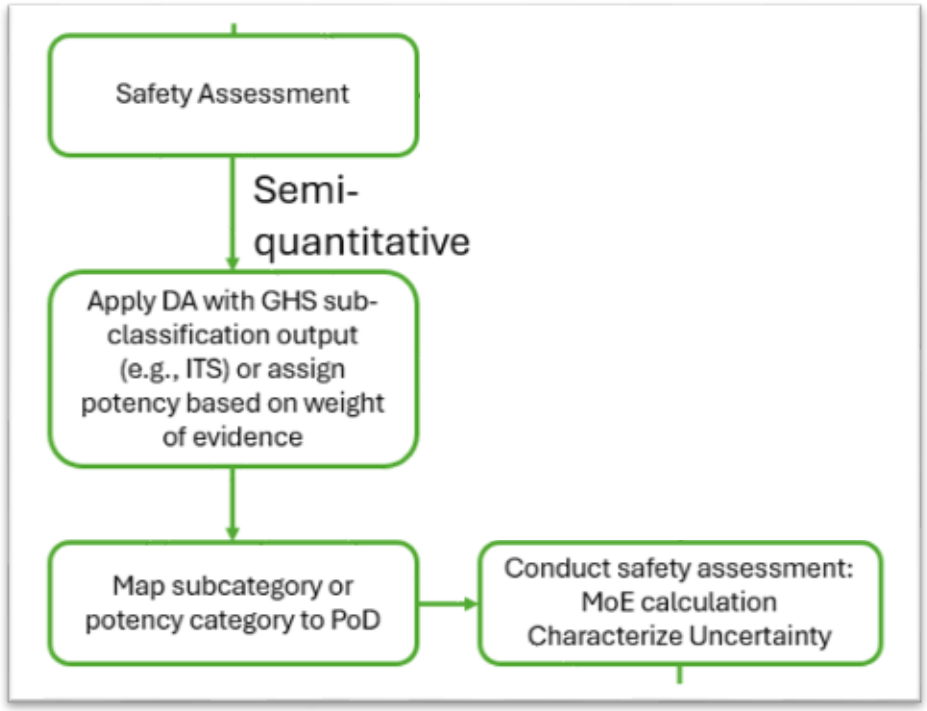
Data interchangeability & Consistency

- ***In silico* ITS v1 (**Derek Nexus) **vs ITS v2 (**OECD QSAR Toolbox)
- ***In vitro* KE3** (h-CLAT or U-SENS™)
- **Outcome :** Identical conclusions reached

Conclusion: The high level of agreement between different models and assays reinforces the confidence in the overall hazard and potency assessment

Step 6. Semi Quantitative Assessment

Determine the Potency using the OECD ITS approach



- **Challenge:** Some DAs provide qualitative results instead of quantitative values
- **Solution:** Convert UN GHS subcategories (1A/1B) into a quantitative PoD_{NAM}
- **Method:** Use conservative MoE (e.g., Gilmour et al., 2023)
- **UN GHS 1B** implies an **LLNA EC3 > 2% or HRIPT > 500 µg/cm²**
- **Conservative NESIL value :** at the lower bound of 500 µg/cm² to ensure safety

Margin of Exposure (MoE) Calculation:

- Consumer Exposure Level (CEL): 27.26 µg/cm² (from Slide 10)
- Formula: MoE = NESIL Value / CEL = 500 / 27.26 = 18.34

Historically applied Safety Assessment Factors (SAFs)

- Products applied to face 100 (Api et al. (2020)

PoD Source	POD Value (µg/cm²)	Consumer Exposure (µg/cm²)	MoE	Acceptable MoE	Outcome
Semi-quantitative	500	27.26	18.34	100	Inadequate MoE

Using the semi-quantitative approach, an inadequate MoE is predicted if thioglycerol is included at 1% in an anti-aging face cream

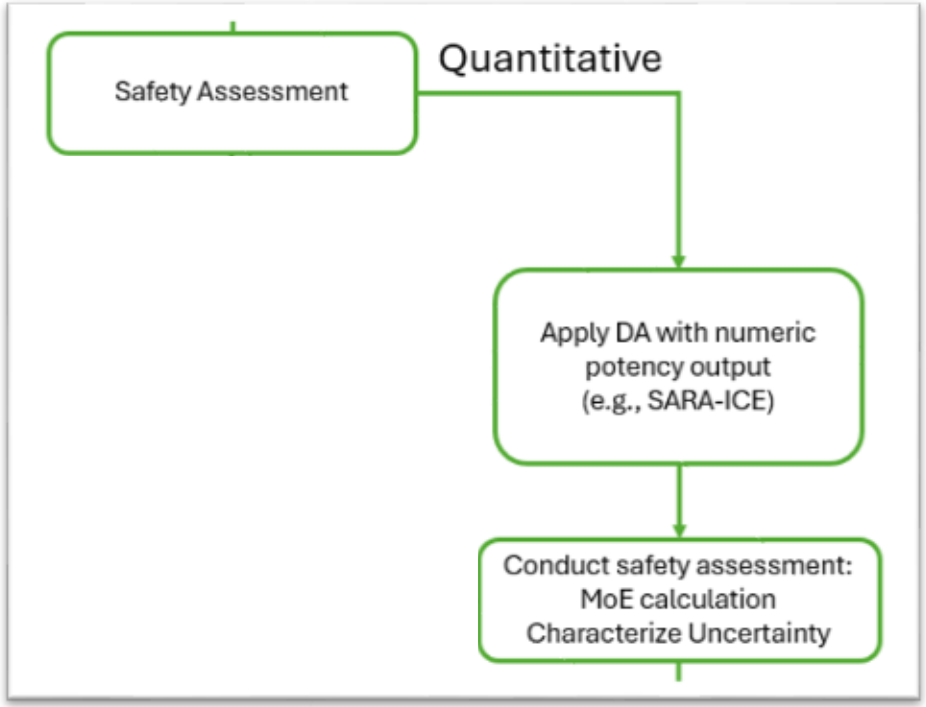
Gilmour N, Alépée N, Hoffmann S, Kern PS, ..et al. 2023. ALTEX 40(3):439-451; https://doi.org/10.14573/altex.2211161

Api AM, Basketter D, et al. 2020. Regul Toxicol Pharmacol 118:104805. https://doi.org/10.1016/j.yrtph.2020.104805

Step 6. Quantitative Assessment

Determine a precise numerical safety limit for an ingredient

- **Key Metric (PoD):** Identifies a Point of Departure (PoD), which is the specific dose below which no significant risk of sensitization is expected
  - NESIL : No Expected Sensitization Induction Level, or
  - ED01 : Effective Dose for 1% risk
- **Data Integration:** Combines results from multiple NAMs (*in chemico*, *in vitro*, *in silico*) into a single numerical value using a quantitative DA
- **Risk Characterization (MoE):** Compares the PoD to the Consumer Exposure Level (CEL) to calculate the Margin of Exposure (MoE)
  - MOE = PoD / CEL
- **Source**: Calculated by statistical models like **SARA-ICE** DA (OECD TG 497) using *in chemico*, *in vitro* and *in silico* inputs



Step 6. Quantitative Assessment

Step 6. SARA-ICE OECD TG 497 DA (version 1.0)

Evidence Stream	KE	Result	Inputs
Physico-chemical properties	NA	**MW = 108.02**	**Y**
IN CHEMICO			
DPRA	MIE/KE1	**% Cysteine depletion = 27.3%** **% Lysine depletion = 28.4%** Mean of % cys and lys depletion =27.85%	**Y**
IN VITRO			
KeratinoSens™	KE2	**EC1.5 = 4000 µM** EC3 = 4000 µM **IC50 = 4000 µM**	**Y**
EpiSensA	KE2	Imax ATF3 = 0 Imax GCLM = 0 Imax DNAJB4 = 0 Imax IL-8 = 0	**Non eligible**
hCLAT	KE3	**CD86 EC150 = 813.6 µg/mL** **CD54 EC200** = NA MIT = 813.6 µg/mL **CV75 = 2860.4 µg/mL**	**Incomplete data**
U-SENS	KE3	**CD86 EC150 = 88.2 µg/mL** **CV70 >200 µg/mL**	**Y**
GARD®skin	KE3	Mean Decision Value = 0.09831	**Non eligible**

Data Source included : MW, DPRA (KE1), KeratinoSens™ (KE2), U-SENS™ (KE3)

- h-CLAT data was excluded due to the missing CD54 EC200 endpoint
- GARD®skin & EpiSensA excluded by design, not a parameter in the algorithm

Results

- Model Output: **Point of Departure** (PoD / ED01) = 7,000 µg/cm^2
- Represents the dose associated with a **1%** chance of skin sensitization

Substance	CASRN	POD	ED_{01} 5th	ED_{01} 50th	ED_{01} 95th
thioglyc	96-27-5	7,000	290	9,900	50,000

Margin of Exposure (MoE) Calculation:

- MoE = PoD Value / CEL = 7,000 / 27.26 = 257

PoD Source	POD Value (µg/cm^2)	CEL (µg/cm^2)	MoE	Acceptable MoE	Outcome
Quantitative	7,000	27.26	257	100	Adequate MoE

- **ED_{01} 5th** — 5th Percentile of the ED_{01} distribution (µg/cm^2)
- **ED_{01} 50th** — 50th Percentile of the ED_{01} distribution (µg/cm^2)
- **ED_{01} 95th** — 95th Percentile of the ED_{01} distribution (µg/cm^2)

https://ntp.niehs.nih.gov/sites/default/files/sara-ice/analysis

Using the quantitative approach, adequate MoE is predicted if thioglycerol is included at 1% in an anti-aging face cream.

Step 6. Quantitative Assessment

Step 6. SARA-ICE DA - Impact of the Data Source e.g. for KE2

Evidence Stream	KE	Result
Physico-chemical properties	NA	**MW = 108.02**
IN CHEMICO		
DPRA	MIE/KE1	**% Cysteine depletion = 27.3%** **% Lysine depletion = 28.4%** Mean of % cys and lys depletion =27.85%
IN VITRO		
KeratinoSens™	KE2	**EC1.5 = 4000 µM** EC3 = 4000 µM **IC50 = 4000 µM**
		EC1.5 > 2000 µM **IC50 = 2000 µM**
U-SENS®™	KE3	**CD86 EC150 = 88.2 µg/mL** **CV70 >200 µg/mL**

KeratinoSens™ Logic:

- Result: EC1.5 **> 2000 µM** (No induction)
- Viability: IC50 = **2000 µM** (Cytotoxicity at top dose only)
- Non-sensitizing for Key Event 2

Quantitative Outcome:

- **Input Strategy:** Combined DPRA, U-SENS™, and revised KeratinoSens™ input
- **With EC1.5 > 2000 µM:** Derived **PoD of 6,700 µg/cm²** results in an **MoE of 245**
- **With EC1.5 = 4000 µM:** The MoE would slightly increase (approaching **257**)

Substance	CASRN	POD	ED_{01} 5th	ED_{01} 50th	ED_{01} 95th
thioglyc	96-27-5	6,700	270	9,400	50,000

Final Safety Verdict: Both scenarios yield an **MoE >> 100**

Outcome: The safety conclusion remains **identical and stable**.

The ingredient is safe at 1%, and the high MoE provides a comfortable safety buffer regardless of the upper concentration limit used in the model

Step 7. Uncertainty characterization

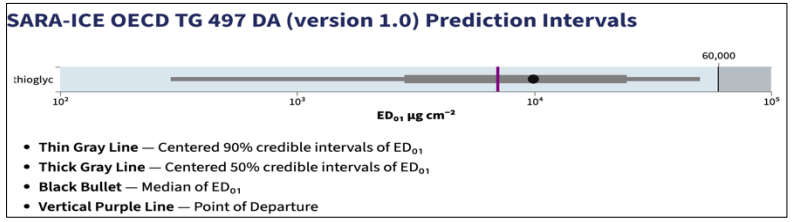
Ensuring Confidence in Safety

- **Objective:** Identify uncertainty sources and assess their impact on the final safety conclusion
- **Exposure Assessment (Conservative Bias):**
    - Estimates rely on SCCS default assumptions (product amount, frequency, use patterns)
    - **Impact**: Likely overestimates actual consumer exposure, providing an inherent safety buffer
- **Methodological Robustness:**
    - **Assay Scope**: While individual NAMs target specific Key Events (KEs) rather than the full biology, they are applied within a validated Integrated Testing Strategy (ITS)
    - **Assay variability**: All test methods, whether in vivo or in vitro, will have implicit variability. Note, this is explicitly modelled in the SARA-ICE DA.
    - **Regulatory Alignment:** Methods are standardized (OECD) with well-characterized performance
- **Overall Confidence:**
    - Residual uncertainties are well-understood and transparently documented
    - **Conclusion:** Collective uncertainty does not compromise the safety conclusion

THE ASSESSMENT REMAINS PROTECTIVE OF HUMAN HEALTH

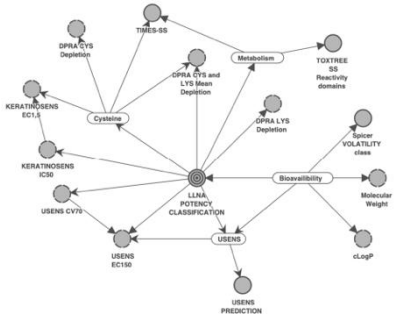
Step 7. Uncertainty

SARA-ICE Predictions Intervals & Other Prediction Tools Analyses



- **Prediction Range (ED01):** Credible interval for Thioglycerol is **290 to 50,000 µg/cm^2** (5th–95th percentile)
- **Uncertainty Width:** A variance of several orders of magnitude is typical for SARA-ICE DA outputs, capturing e.g. inherent variability in assay input data and human variability
- **Driving Factors:** Uncertainty reduction depends on the **number, type, and concordance** of the input data.
- **Methodological Compliance:**
  - Meets OECD TG 497 requirements (minimum of **2 KEs**)
  - **Uncertainty Reduction:** Achieved by integrating three high-quality inputs: **DPRA**, **KeratinoSens™**, and **U-SENS™**

Non-OECD approaches were evaluated



SkinSens-BN probability profile

p(NS) 0.16 - p(weak) 0.63

p(moderate) 0.19 - p(strong/extreme) 0.02

PoD_{BN} = 22.33 % (weak)

PoD_{BN} = 5582 µg/cm^2

MoE = PoD_{BN} / CEL = 5582 / 27.26 = **204 >> 100**

Tourneix et al. Toxics. 2024 doi: 10.3390/toxics12080536

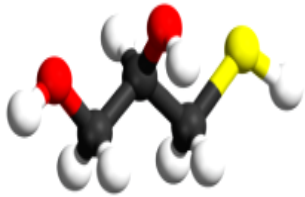
Model Alignment: Other models yielded similar PoDs and adequate MoEs

Concordance: High agreement across diverse tools significantly reduces uncertainty

Problem Formulation & Conclusion

Ensure consumer safety before Thioglycerol product launch at 1% in a face cream

INCI name	Thioglycerol
Preferred IUPAC name	3-Sulfanylpropane-1,2-diol
CASRN	96-27-5



1. **Hazard Identification**
   - Sensitizer? **YES**
   - UN GHS hazard classification? **UN GHS 1B**

2. **Risk Characterization**
   - **Semi-Quantitative Approach:** ❌ **Inadequate** (MoE = 18)
     - *GHS class-specific PoD more likely to be conservative*
   - **Quantitative Approach** (SARA-ICE DA V1.0): ✅ **Adequate** (MoE = 245)
     - *Chemical-specific PoD evidence confirms safety with an accepted MOE > 100*

🚀 **GO for Product Launch**

The 1% concentration is safe for use in anti-aging face cream

THANK YOU!

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