ICCS | INTERNATIONAL COLLABORATION ON COSMETICS SAFETY

ICCS Best Practice Guidance on Skin Sensitization Case Study: Cinnamaldehyde

12 March 2026

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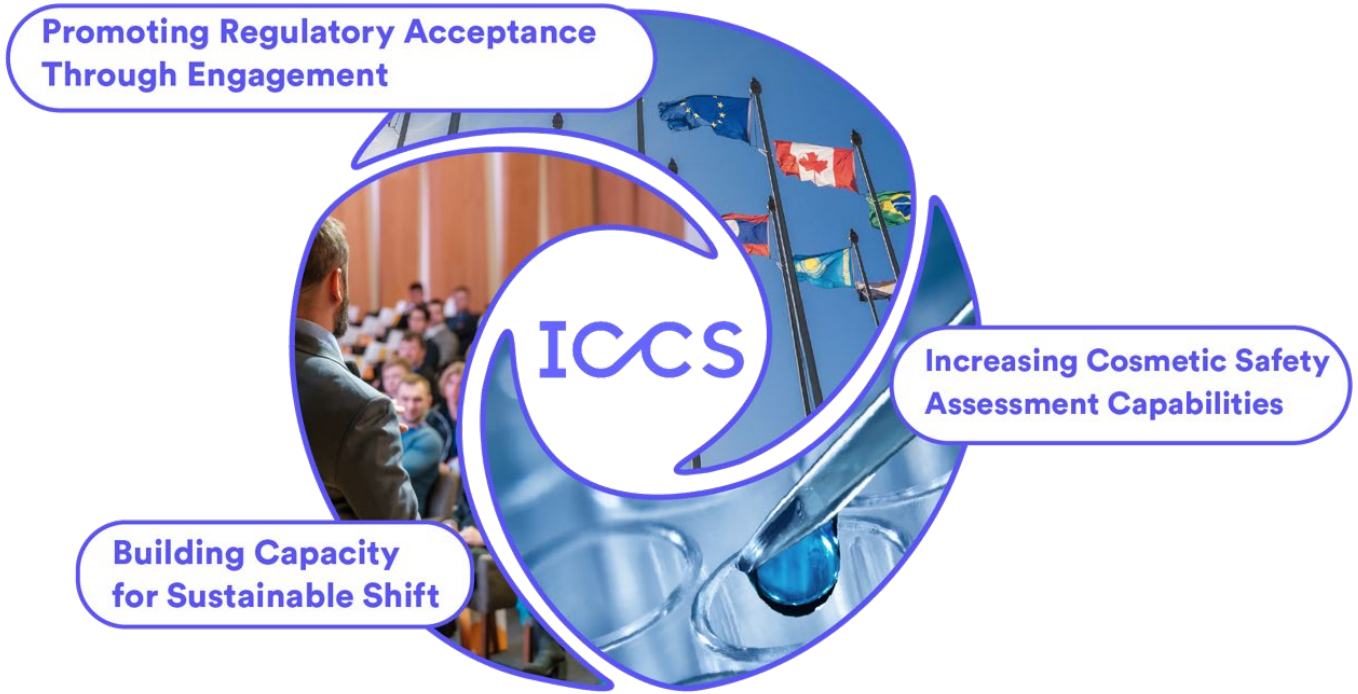
CIR Expert Panel for Cosmetic Ingredient Safety

The International Collaboration on Cosmetics Safety

- Global, **multi-stakeholder** organization headquartered in U.S.
- Advancing **animal-free** safety assessments
- For **cosmetic products** and their **ingredients**
- Covering **human health** and **environmental safety**



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BASF — We create chemistry

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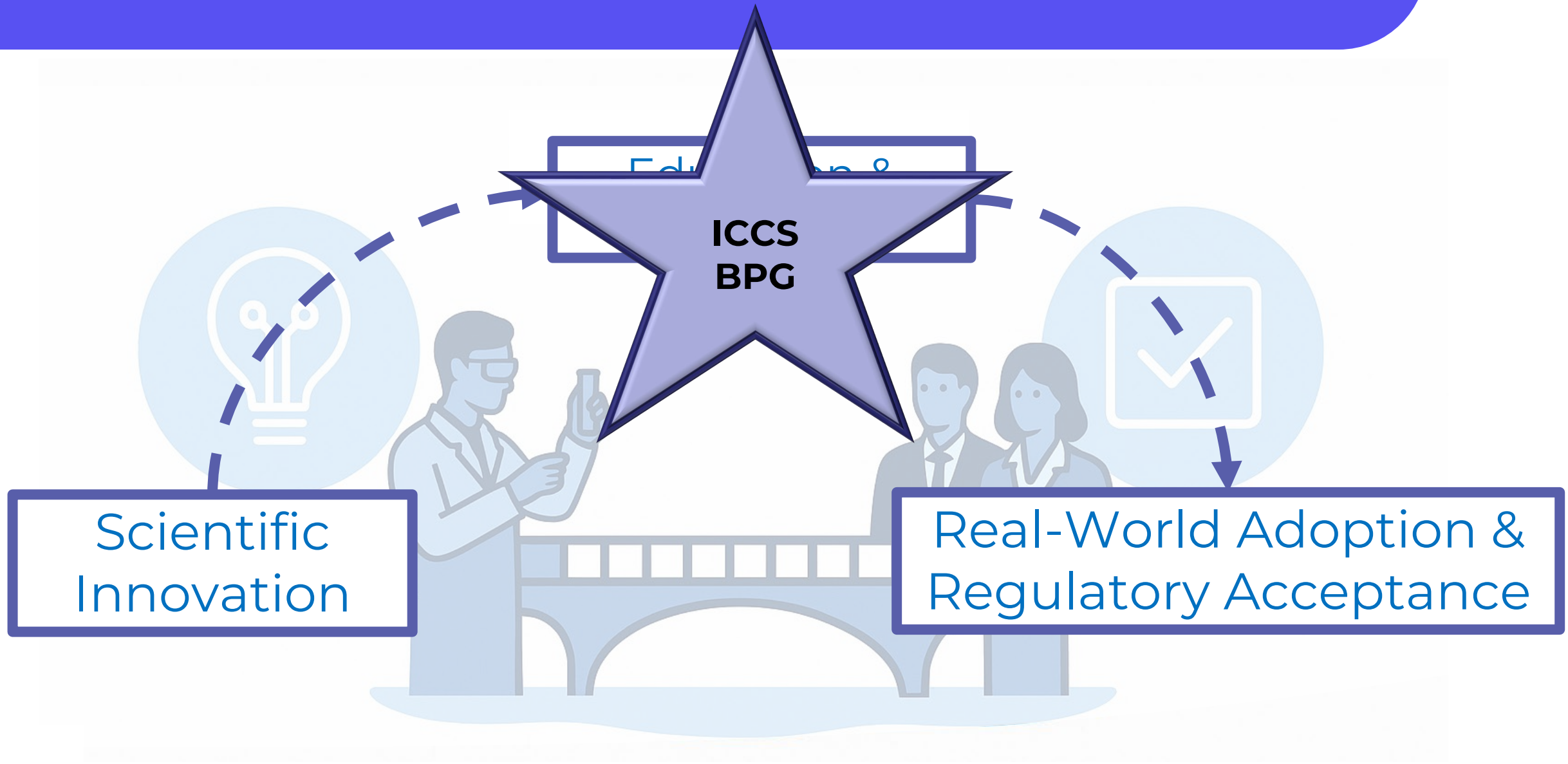
Edgewell PERSONAL CARE

L'ORÉAL

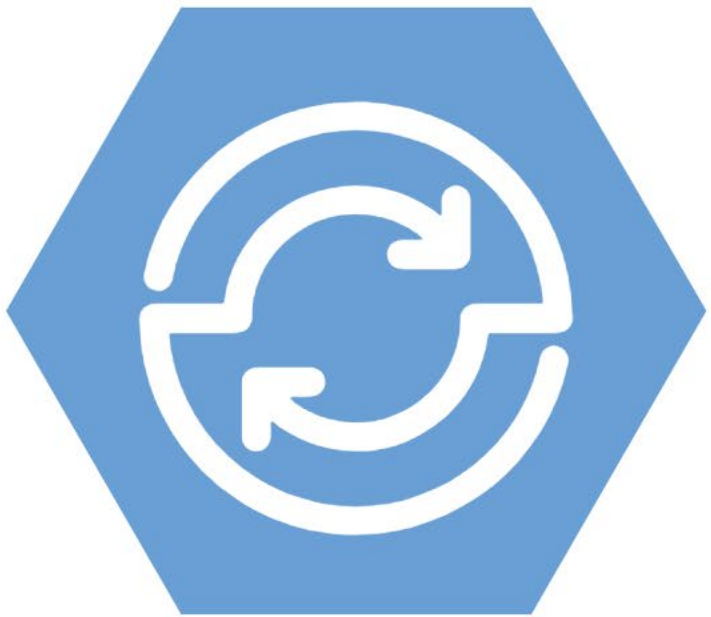
EVONIK — Leading Beyond Chemistry

LVMH

Confidence building in animal-free assessments



Goals of ICCS Best Practice Guidance Documents



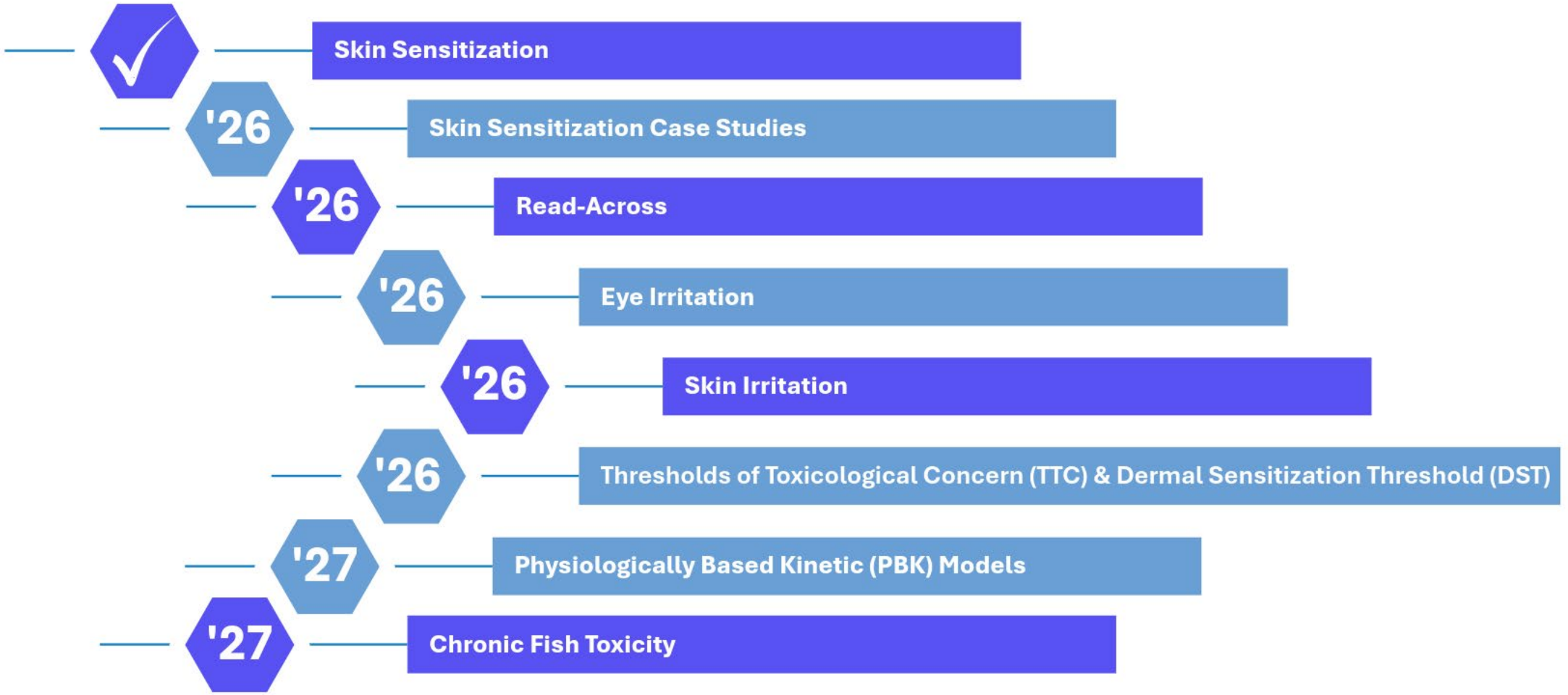
ENABLE BROADER ADOPTION OF NAMs
by providing practical, science-based guidance

IMPROVE THE QUALITY AND ROBUSTNESS
of safety assessments

FACILITATE REGULATORY HARMONIZATION
by consensus-based approaches, aligned terminology, often leading to standard setting

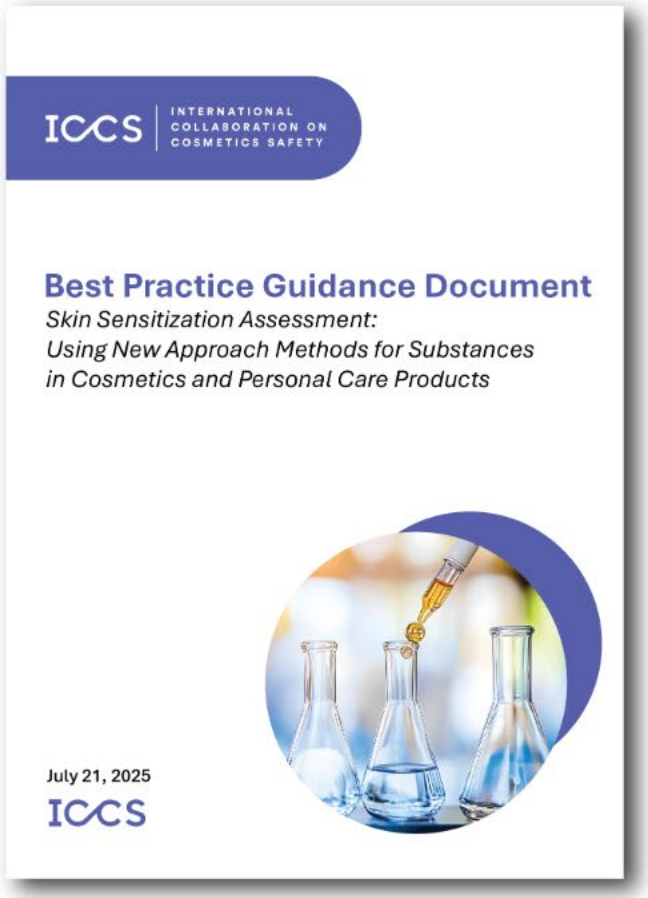
SUPPORT NGRA PRINCIPLES
through integrated evidence-based frameworks

ICCS Best Practice Guidance Document Portfolio



’26 Expected publication date = 2026
‘27 Expected publication date = 2027

ICCS Best Practice Guidance Document
Skin Sensitization Assessment



WHAT IS IT

- Step-by-step workflow to guide through skin sensitization hazard and safety assessments without new animal tests
- Designed for regulatory use

HOW DOES IT HELP

- Bridges the gap between advancing science and regulatory requirements
- Streamlines decision-making
- Supports consistency, transparency, and reproducibility enhancing global harmonization

HOW WAS IT DEVELOPED

- Widely accepted based on current knowledge
- Incorporates insights from global subject matter experts

WHO IT'S FOR

- Safety assessors and regulatory scientists integrating NAMs into safety assessments
- NGOs and government agencies engaged in risk assessment and policy development

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

Webinar | April 9, 2026 | 1:00 – 4:30 PM CET

ICCS Best Practice Guidance Document – Skin Sensitization Assessment: Using New Approach Methods for Substances in Cosmetics and Personal Care Products, released July 2025, welcomed by regulators and safety assessors, sets a global foundation for NAM-based skin sensitization assessment. This webinar will highlight practical regulatory application of OECD GL 497 defined approaches (2o3, ITS, SARA-ICE) and an in-practice case study, supporting robust, animal-free safety decisions.

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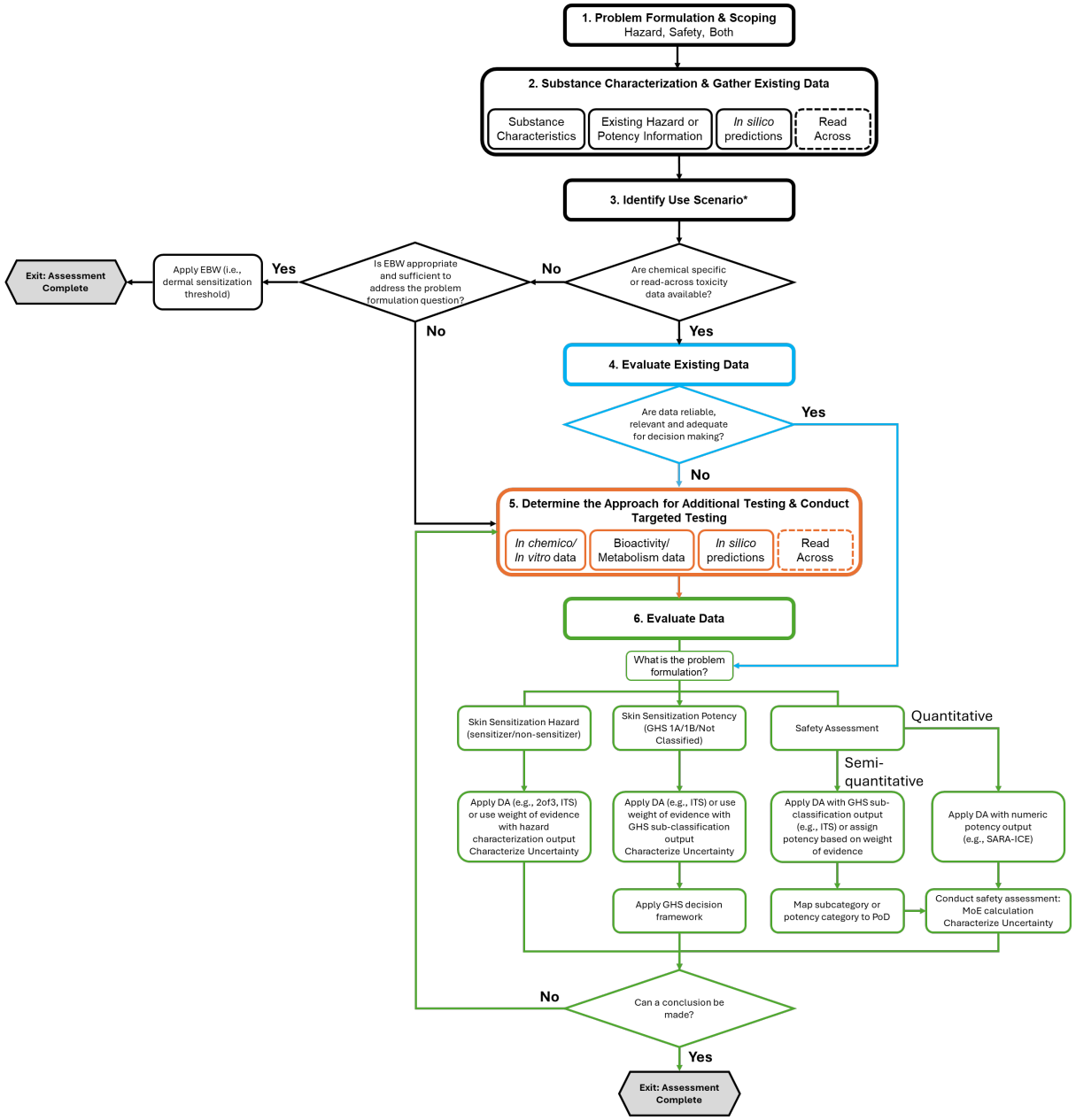
ICCS BPG Skin Sensitization Workflow



ICCS

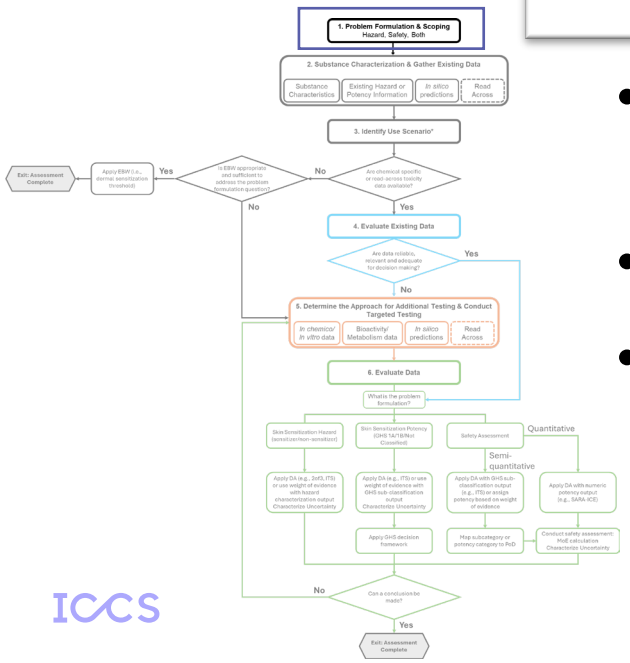
Skin Sensitization Case Study

Cinnamaldehyde

ICCS

Step 1 – Problem Formulation & Scoping

1. Problem Formulation & Scoping
Hazard, Safety, Both



- A **problem formulation** defines the purpose and scope of the assessment
- Establishes the key question to be answered
- Ensures the assessment is hypothesis-driven and exposure-led from the outset and aligns all subsequent steps to a fit-for-purpose decision context

Step 1 – Problem Formulation & Scoping

Hazard, safety, both?

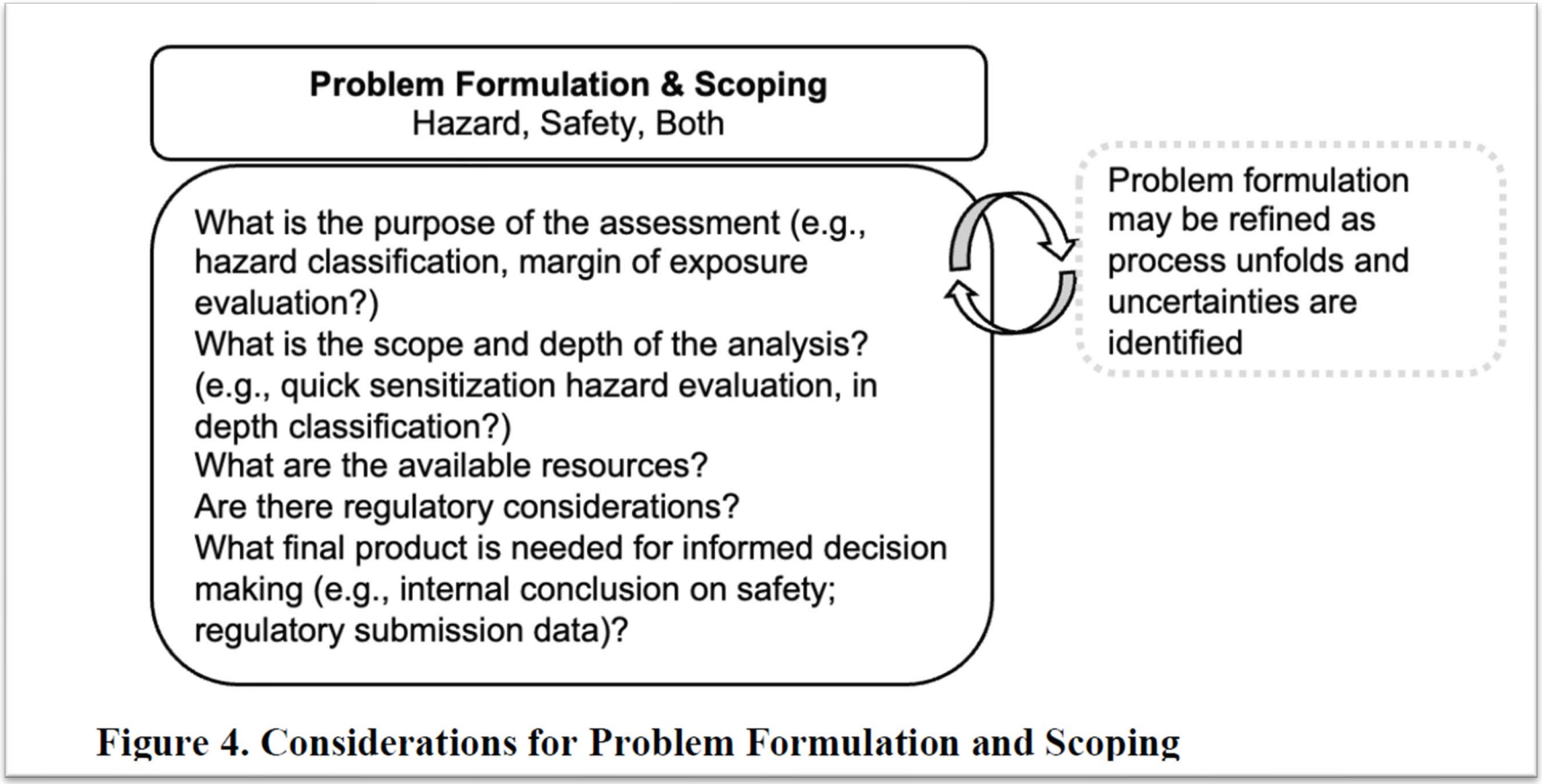
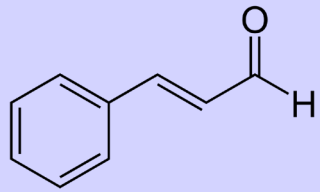


Figure 4. Considerations for Problem Formulation and Scoping

Step 1. Problem Formulation & Scoping

Cinnamaldehyde



Problem statement:

Why?

Cinnamaldehyde has been identified as a substance of interest for inclusion in cosmetic products. A skin sensitisation assessmer Specific concerns? ne if cinnamaldehyde poses a significant risk at the intended use levels. This evaluation is needed to ensure consumer safety before product launch and to meet regulatory and internal standards. Stakeh Regulatory considerations due to reports of adverse skin reactions to similar fragrance ingredients.

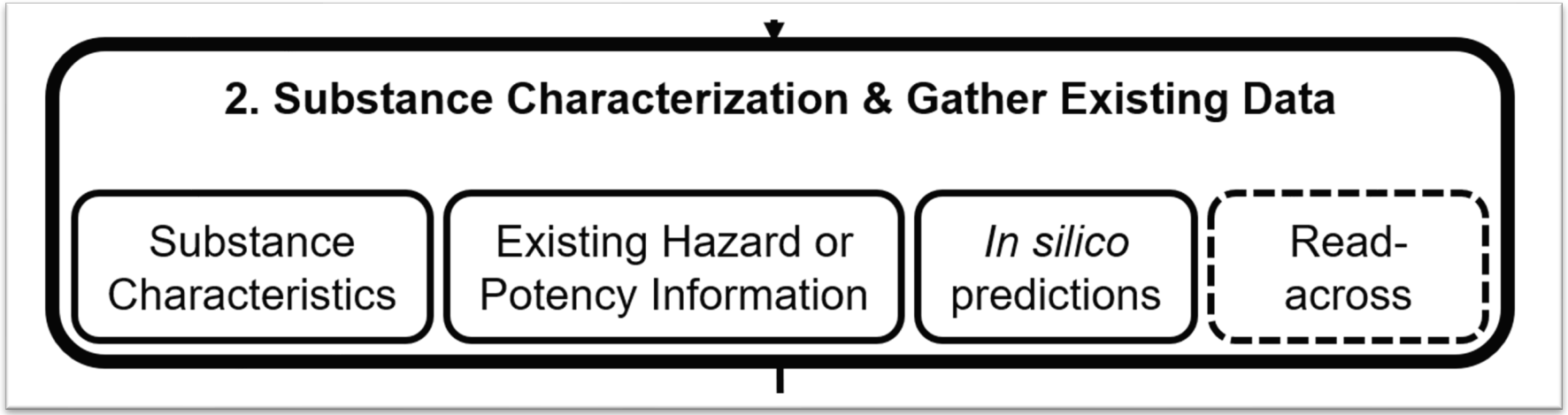
The assessment must address: The UN GHS classification of cinnamaldehyde and the risk of adverse effects at the proposed use levels (2% in a face cream).

This evaluation is being conducted under a tight timeline to inform go/no-go decisions for product formulation and to address stakeholder queries regarding ingredient safety so a rapid review is necessary.

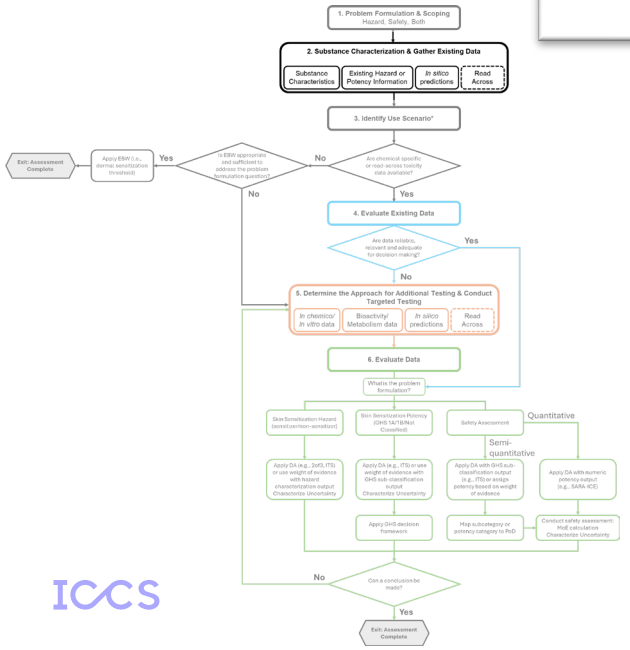
Timing/resource considerations

Step 1 Objective: Provide a clear statement of the assessment scope and the hypothesis to be evaluated.

Step 2 – Substance Characterization & Gather Existing Data



Read-across in dashed box to indicate optional use at Step 2



Step 2 – Substance Characterization & Gather Existing Data

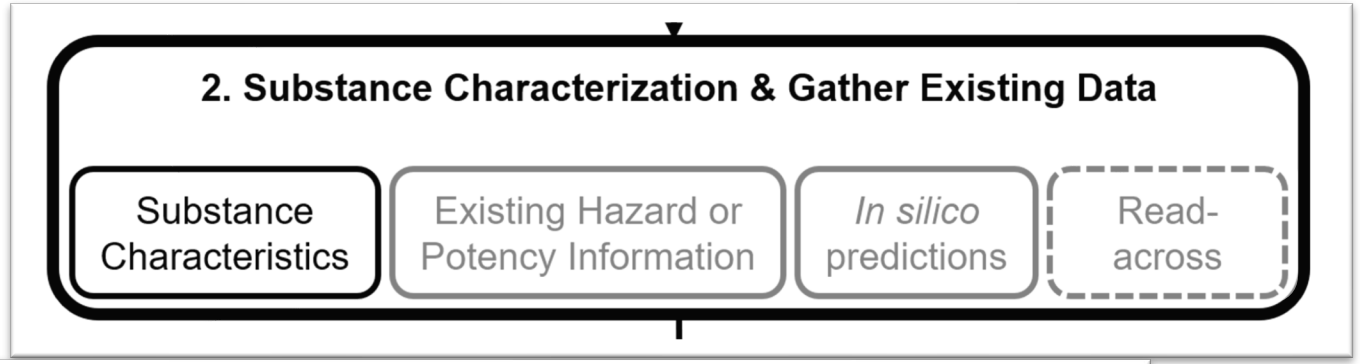
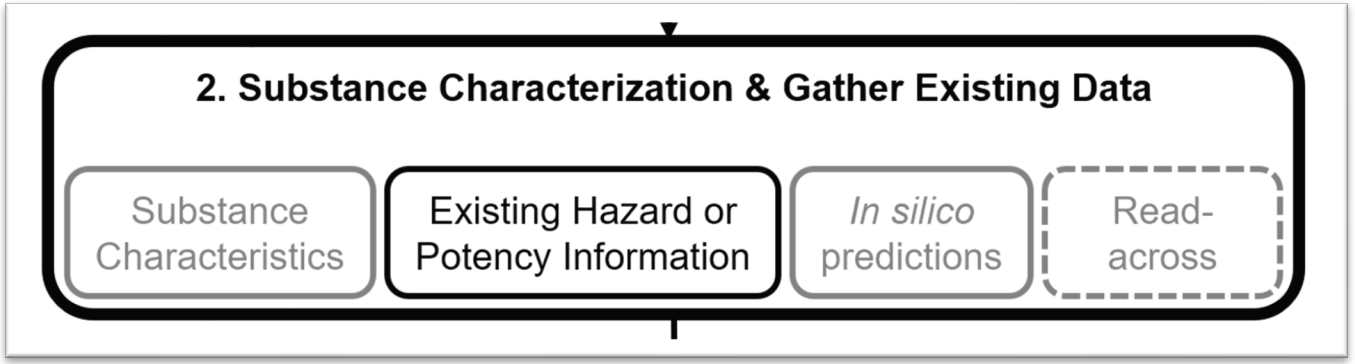


Table 3. Summary of D
Assessment

Element
Common name
INCI name
Synonyms
CASRN
Structure
Molecular formula
Molecular weight (or MW distribution, if applicable)

Element	Description*
Particulate size or size range (if applicable)	[If relevant, identify the size of substance particulates. If range of size, enter the total range of particulate sizes encompassing the minimum and maximum sizes]
Purity	[Identify the substance purity]
Known impurities	[Identify known impurities within the substance. If concentrations are available, include information]
Potential impurities	[Identify potential impurities within the substance]
Physical form	[Identify the physical form of the pure substance (e.g., solid)]
Water solubility	[Identify the predicted or experimental water solubility of the substance]
Partition coefficient	[Identify the partition coefficient between two immiscible solvents]
Vapor pressure	[Identify the predicted or experimental vapor pressure]
Additional physico-chemical properties that impact skin sensitization	(e.g., presence of electrophilic functional groups, pH; density)
Non-cosmetic uses or exposures	[Insert any known uses of the substance that are non-cosmetic] Examples: antiseptic; solvent; food additive

Step 2 – Substance Characterization & Gather Existing Data



- Are there assessments of skin sensitization potential in existing SCCS or CIR reviews? If yes, how does the scope compare? What is the year of assessment? How can these be used pragmatically for the current assessments?
- In relevant assessments, was a NESIL identified? Are there hazard conclusions by endpoint that could be considered?
- How can the current assessment be made more efficient and pragmatic based on existing knowledge?
- Do the existing data demonstrate a particularly sensitive subpopulation that needs to be considered in the assessment (e.g., genetically susceptible groups; children)?
- Are there any key issues identified across the available assessments that this assessment needs to specifically address?

Step 2 – Substance Characterization & Gather Existing Data

Box 4. Examples of *in silico* Platforms and Models for Skin Sensitization Hazard and Potency Evaluations

Hazard assessments

- Leadscope Model Profiler (https://www.instem.com/solutions/discovery/leadscope-model-applier/)
- Toxtree: Skin Sensitization Reactivity Domains (https://toxtree.sourceforge.net/)
- OECD QSAR Toolbox: Protein Binding Alerts for Skin sensitization by OASIS (https://qsartoolbox.org/)
- Derek Nexus Skin Sensitization (https://www.lhasalimited.org/)
- Danish QSAR Database (https://qsar.food.dtu.dk/)
- TIMES-SS (https://oasis-lmc.org/products/software/times.aspx)
- StopTox (https://stoptox.mml.unc.edu/)
- iSafeRat (https://isaferat.kreatis.eu/)

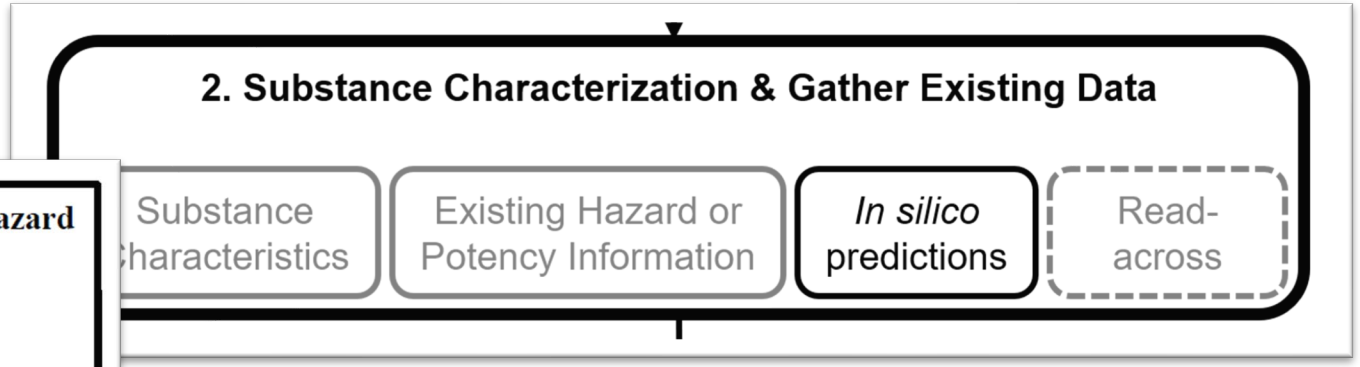
Potency predictions

Leadscope Model Profiler (https://www.instem.com/solutions/discovery/leadscope-model-applier/)

- Derek Nexus: Skin Sensitization EC3 (https://www.lhasalimited.org/)
- SARA-ICE (https://ntp.niehs.nih.gov/go/n465041)

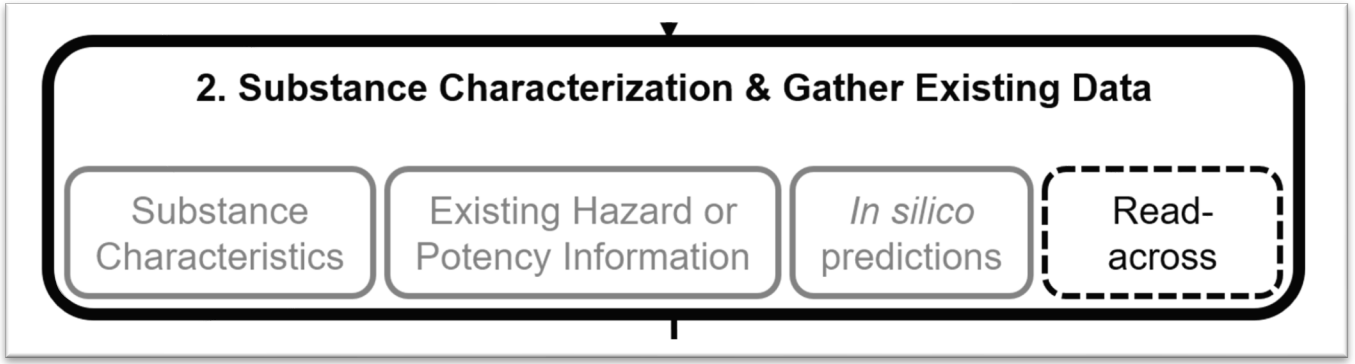
Mechanistic endpoints

- OECD QSAR Toolbox (https://qsartoolbox.org/)
- Leadscope Model Applier (https://www.instem.com/solutions/discovery/leadscope-model-applier/)



- Predictions should fulfil the OECD validation principles and the OECD QSAR Assessment Framework
- Version, platform, model should be captured

Step 2 – Substance Characterization & Gather Existing Data



Read-across in dashed box to indicate optional use at Step 2

- Read-across will **not** be described in detail in this BPG, however, rationale for analogue selection, groupings, similarity calculations, reasons for inclusions/exclusion should be documented
- ICCS read-across BPG to be published in 2026

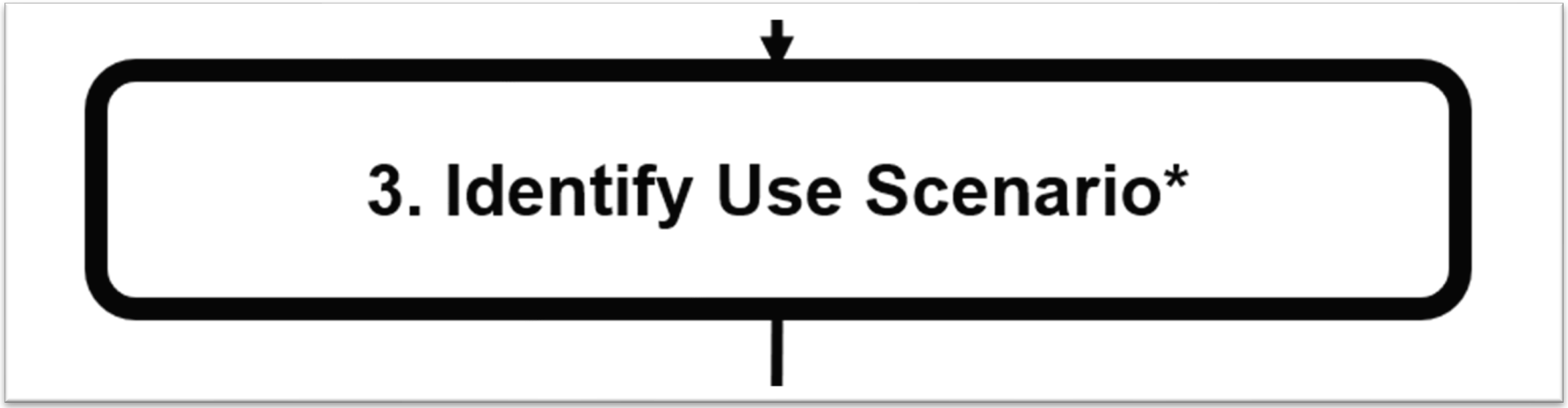
Assumption: We have no NAM data, and no analogues, and will generate NAM data as needed

Step 2. Substance Characterization & Gather Existing Data

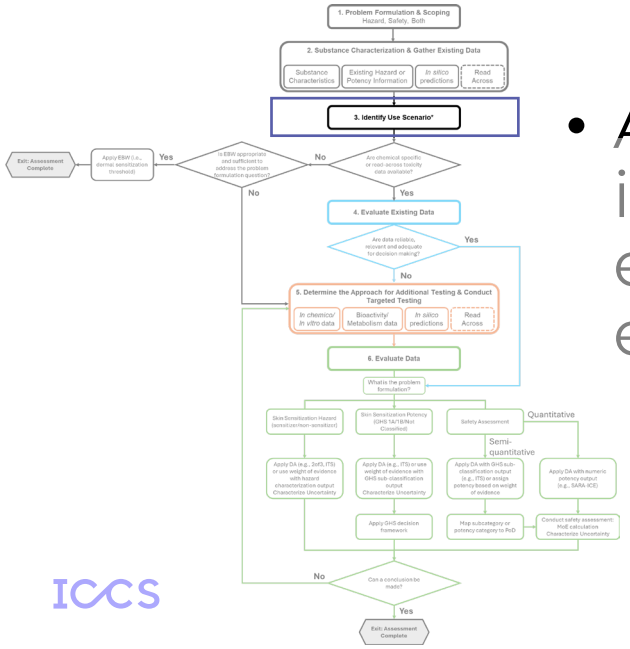
Substance Characterization	
Common name	Cinnamaldehyde
INCI name	CINNAMAL
Synonyms	Cinnamic aldehyde; trans-Cinnamaldehyde; Cassia aldehyde; 3-Phenyl-2-propenal
CASRN	104-55-2
Structure	C1=CC=C(C=C1)/C=C/C=O
Molecular formula	C9H8O
Molecular Weight (g/mol)	132.16
Particulate size or size range (if applicable)	Not applicable
Purity	Typically ≥95–99% (supplier dependent)
Physical form	Pale yellow oily liquid
Partition coefficient	LogP ~1.8–2.1
Non-cosmetic uses or exposures	Flavouring agent, fragrance ingredient, chemical intermediate

Step 2 Objective: Collect data on the substance that will inform the resulting skin sensitization assessment. The data collected should include substance physico-chemical properties, existing hazard and potency data, *in silico* prediction data (e.g., structural alerts, metabolites) and potential analogue compounds.

Step 3 – Identify Use Scenario



*not relevant if only hazard-based assessment



- A **use scenario** is the specific way a substance is used in a cosmetic product, described in enough detail to estimate how much of the substance a consumer is exposed to

Step 3 – Identify Use Scenario

- Identify the product type and other relevant data to establish **how** the substance will be used
- Calculate a **Consumer Exposure Level** (CEL) using established consumer exposure values (e.g., SCCS Notes of Guidance)

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

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

Element	Description
Product type of interest	Face cream
Concentration of substance in each product	2%
Method and location of application for each product type	Applied to face and left on
Population, including targeted or special consumer groups (if applicable)	n/a

Assumption: A deterministic, single product exposure approach is assumed

Step 3. Identify use scenario

Data to Collect to Support 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, 2%	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					
Body lotion	7.82	123.2	1.00	**7.82**	**123.2**
Face cream	1.54	24.14	1.00	**1.54**	**24.14**
Hand cream	2.16	32.70	1.00	**2.16**	**32.70**
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

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

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

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} = (2/100) x 1.54

0.0308 (g/d)

30.8 (mg/d)

30800 (µg/d)

Step 3. Identify use scenario

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

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:

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

Where:

- CEL (µg/cm^2) = consumer exposure level
- E_{dermal} (µg/day) = the daily substance amount to which the skin is exposed
- SSA (cm^2) = 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.

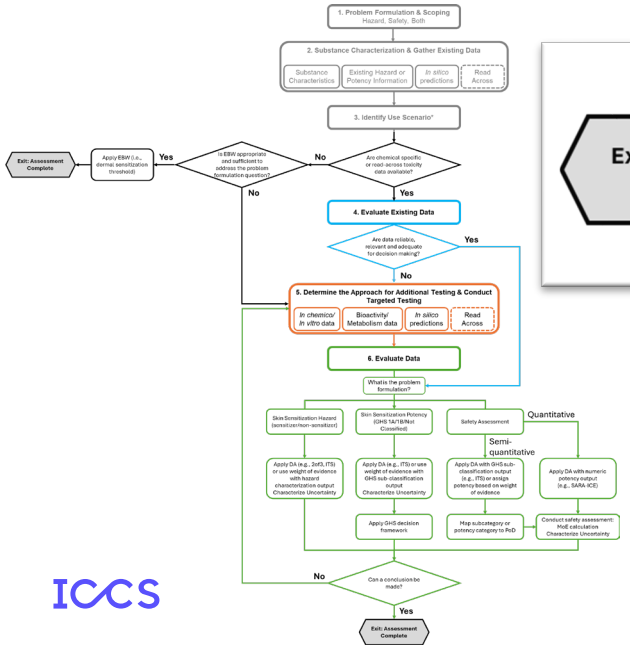
$CEL = E_{dermal} / SSA$

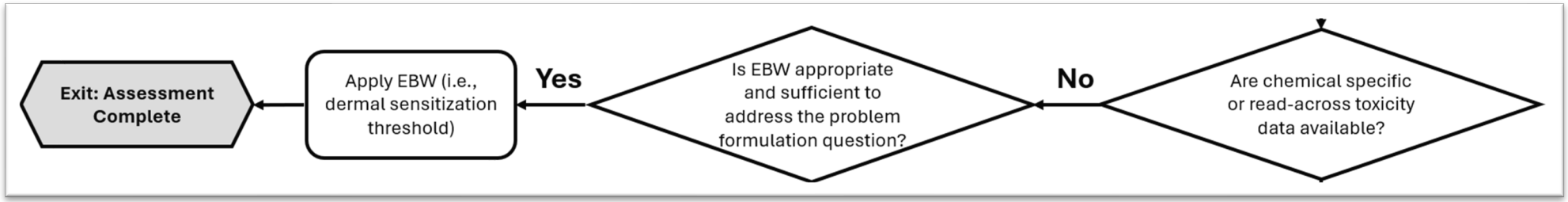
30800 / 565

54.5µg/cm^2

Can Exposure-Based Waiving be applied?

- Now we have calculated the exposure, evaluate if the exposure estimated is such that **exposure-based waiving** could be implemented
- **Exposure-based waiving is applied** when:
  - A full quantitative safety assessment is deemed unnecessary because the estimated exposure to a chemical is anticipated to be negligible or below a pre-defined safety threshold
  - Chemical exposure is calculated to be low
  - There are no chemical-specific (or read-across) toxicity data available





Can Exposure-Based Waiving be applied?

- For skin sensitization, EBW can be applied using the **dermal sensitization threshold** (DST):
  - A value that represents the estimated level of dermal exposure below which a chemical is not expected to induce skin sensitization (SS)
  - Conceptually similar to the Threshold of Toxicological Concern (TTC)

Table 5. Summary of Example DST Values from the Published Literature

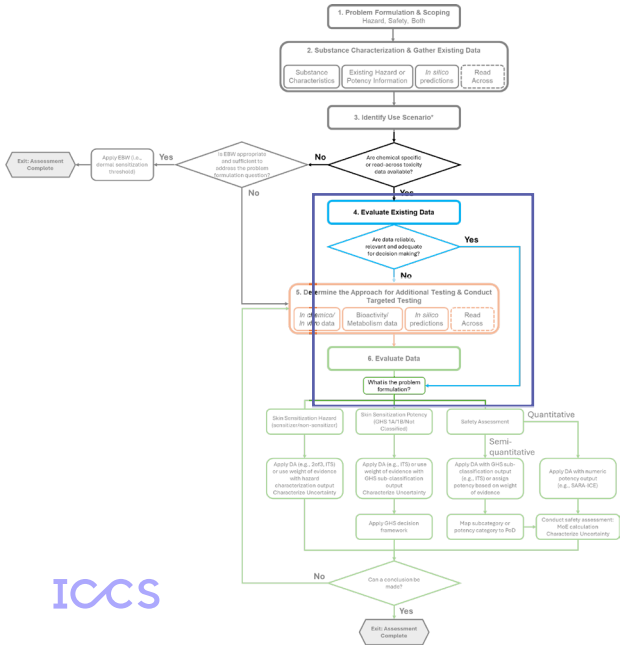
	Dermal Sensitization Threshold Value (µg/cm²)		
Publication	**Non-Reactive Substances**	**Reactive Substances[a]**	**High Potency Substances[b]**
Chilton et al. 2022	710	73	1.0
Nishijo et al. 2020; 2022	900[c]	64[c]	1.5
Safford et al. 2011; 2015	900	64	Not provided

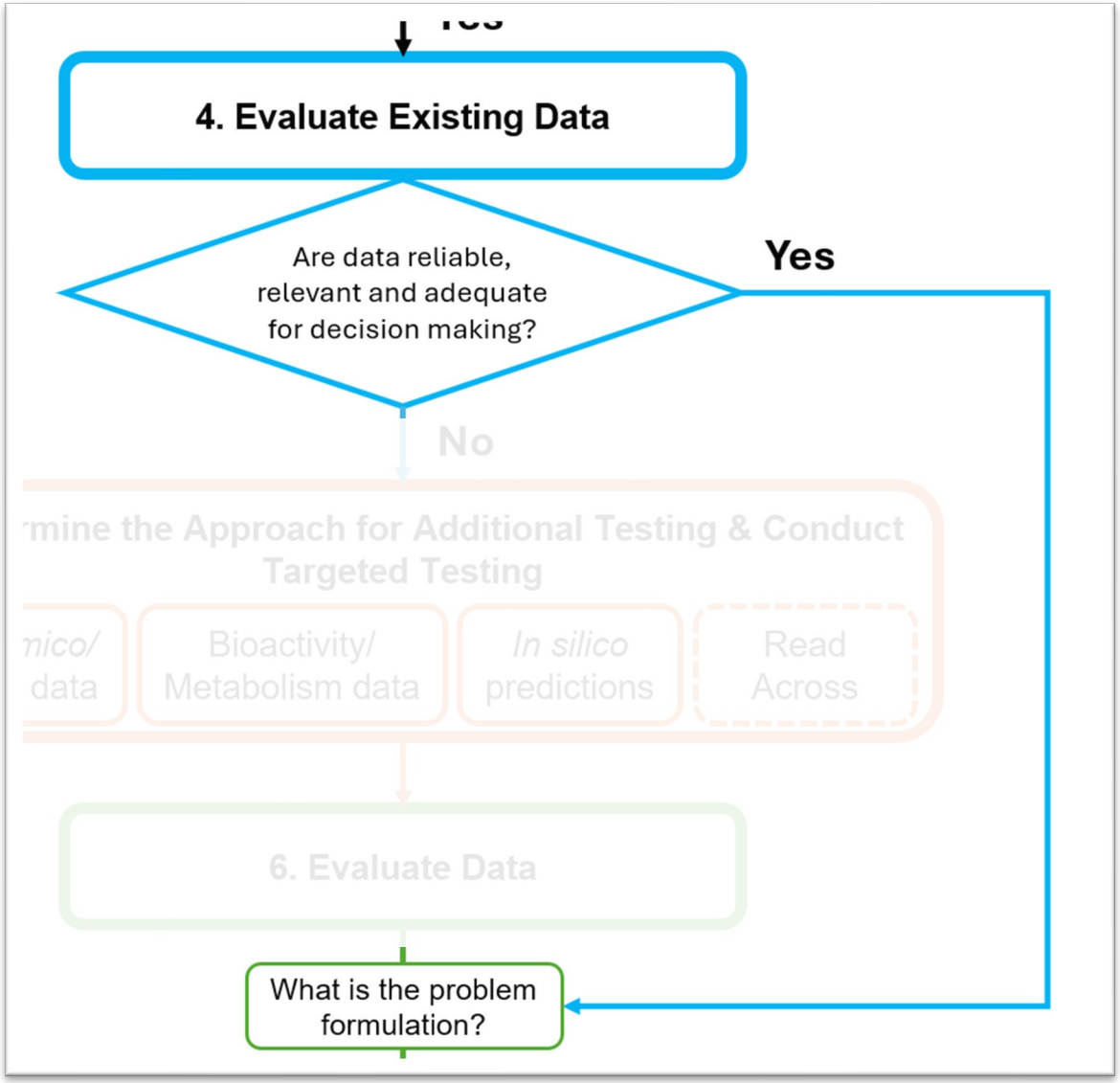
Can Exposure-Based Waiving be applied?

- Now we have calculated the exposure, evaluate if the exposure estimated is such that **exposure-based waiving** could be implemented
- Based on the calculated exposure of 54.5µg/cm^2, **EBW cannot** be implemented as the exposure is **not sufficiently low**
- NOTE: If existing data is available, the safety assessor should continue through the workflow

> **Step 3 Objective:** Define the exposure scenarios for the substance and estimate the quantitative exposure level of the substance to the consumer. With this data, an assessor may, if appropriate, evaluate whether exposure-based waiving may be used to assess skin sensitization potential.

Step 4 – Evaluate Existing Data





Step 4 – Evaluate Existing Data

- **Data map** can provide a structured way to organize data gathered

Table 6. Example Data Map for Organization Existing Data for Substance*

Evidence Stream	KE	Data availability	Data reliability	Result	Comment
Physico-chemical properties	NA				
Animal					
Buehler	AO				
GPMT	AO				
LLNA	AO				
Other	NA				
Human/Clinical					
HRIPT	AO				
HMT	AO				
Diagnostic Patch Testing	AO				
Other	NA				
In Chemico					
DPRA	MIE/KE1				
ADRA	MIE/KE1				
kDPRA	MIE/KE1				
Other	NA				
In Vitro					
KeratinoSens™	KE2				
LuSens	KE2				
EpiSensA	KE2				
h-CLAT	KE3				
U-SENS™	KE3				
IL-8 Luc	KE3				
GARD™skin	KE3				
Other Assay	NA				
In Silico					
Tool name & version	NA				
Metabolism	NA				
Other	NA				
Analog Data					
Read-across data**	NA				
Sufficient data for concluding hazard/safety?					

Step 4 – Evaluate Existing Data

- **Data map** can provide a structured way to organize data gathered
- **Reliability**, **relevance**, and **adequacy** evaluated
- This step may lead to **Step 6** and **conclude** the assessment, or indicate that **additional targeted testing** is required (**Step 5**)

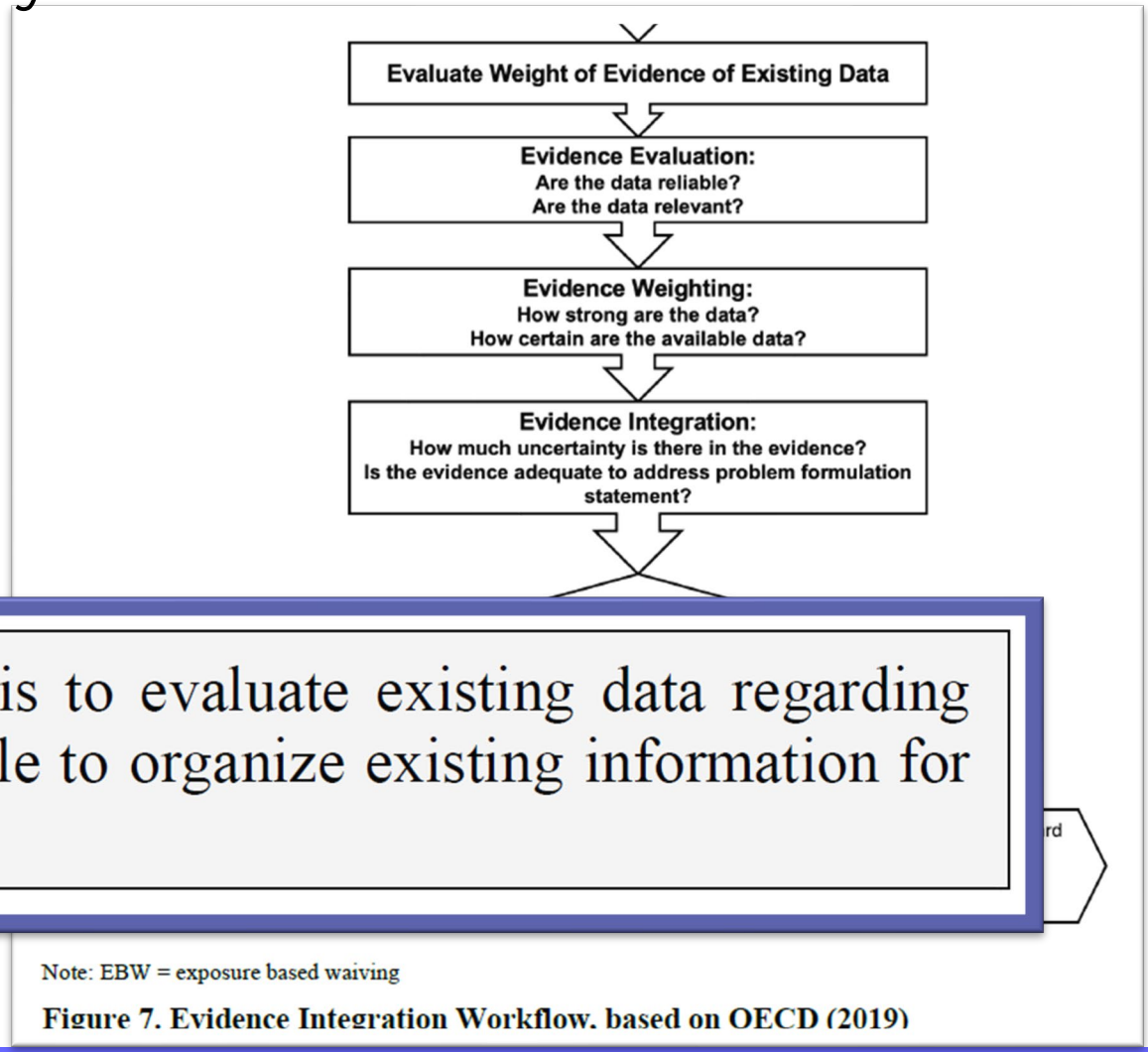
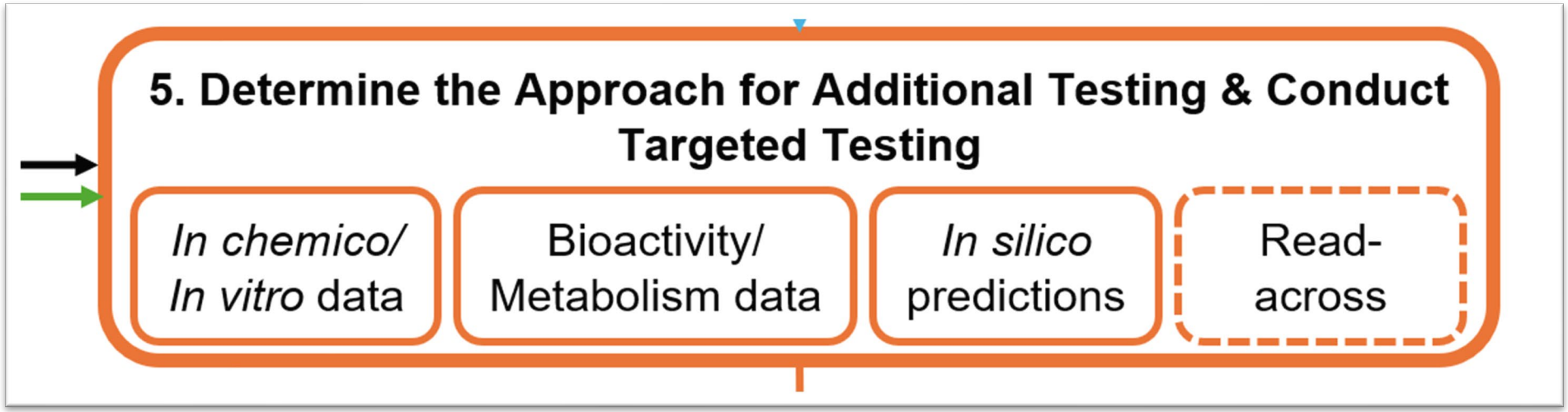


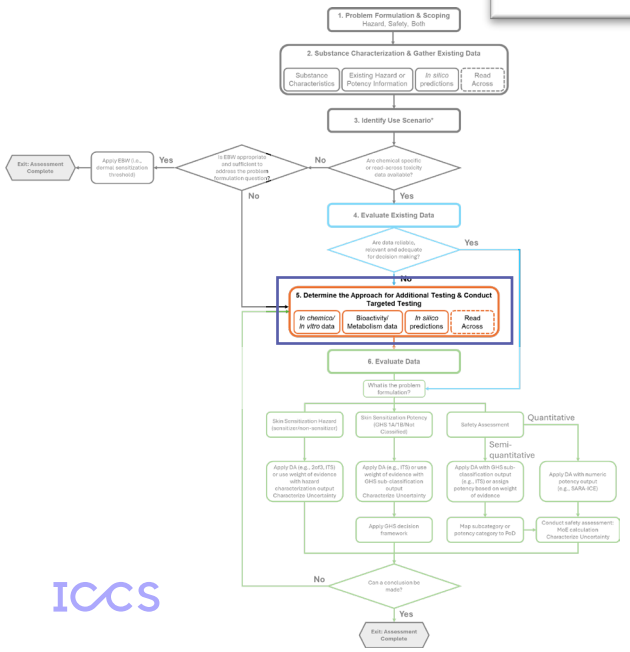
Figure 7. Evidence Integration Workflow, based on OECD (2019)

Assumption: We have no NAM data, and no analogues, and will generate NAM data as needed

Step 5 – Define the approach for additional testing & conduct targeted testing



Read-across in dashed box to indicate optional use at Step 5



In addition to determining which data gaps need to be filled, the scope of the evaluation should be considered (e.g., hazard assessment; safety assessment). Questions for consideration to help identify targeted testing needs include:

- Is qualitative hazard, hazard category, or quantitative point of departure information needed?
- Do relevant metabolic pathways in the skin need to be probed for more in-depth understanding?
- Which *in chemico* and *in vitro* methods, or *in silico* tools, will inform the identified data gaps?

Step 5 – Define the approach for additional testing & conduct targeted testing

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- Is qualitative hazard, hazard category, or quantitative point of departure information needed?
- Do relevant metabolic pathways in the skin need to be probed for more in-depth understanding?
- Which *in chemico* and *in vitro* methods, or *in silico* tools, will inform the identified data gaps?

- Revisiting our problem formulation

The assessment must address: The UN GHS classification of cinnamaldehyde and the risk of adverse effects at the proposed use levels (2% in a face cream).

Step 5 – Define the approach for additional testing & conduct targeted testing

BPG updated routinely – only currently includes TG methods/DAs

Table 7. Defined Approaches for Skin Sensitization using *In Chemico*, *In Vitro*, and *In Silico* Tools

Defined Approach	Problem Formulation Addressed	Input KE1: ADRA or DPRA	Input KE2: KeratinoSens™, EpiSensA, or LuSens	Input KE3: GARD™Skin, h-CLAT, IL-8 Luc, or U-SENS™	Input *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
		Input			
		KE1: DPRA, kDPRA	KE2: KeratinoSens™	KE3: h-CLAT, U-SENS™	*In Silico*
SARA-ICE°	Point of Departure (ED_{01}*)	X	X	X	N/A

°LLNA and HPPT data also may be used in SARA-ICE. Further information may be reviewed in OECD (2025).
*ED_{01} is the estimate of a dermal dose at which there is a 1% chance of inducing sensitization using a human predictive patch test.

- The ITS DA provides a GHS classification

Step 5 – Define the approach for additional testing & conduct targeted testing

Generating data for ITS DA

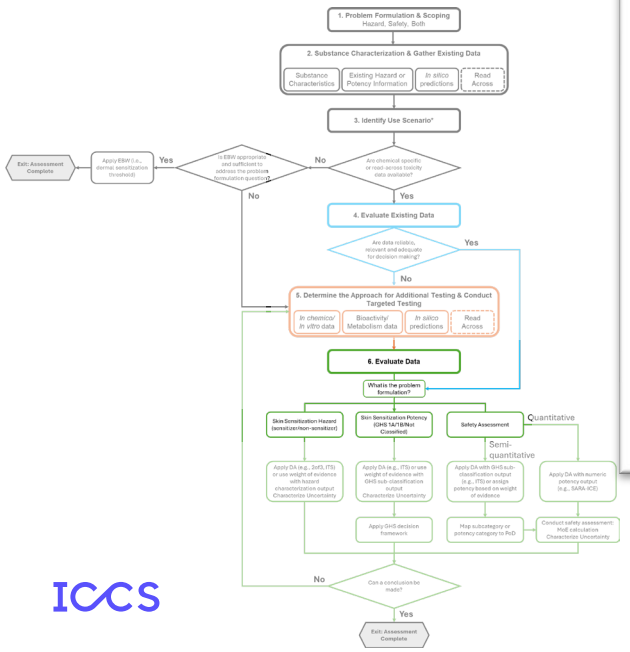
- Let's generate a KE1 assay result, KE3 assay result, and an *in silico* result

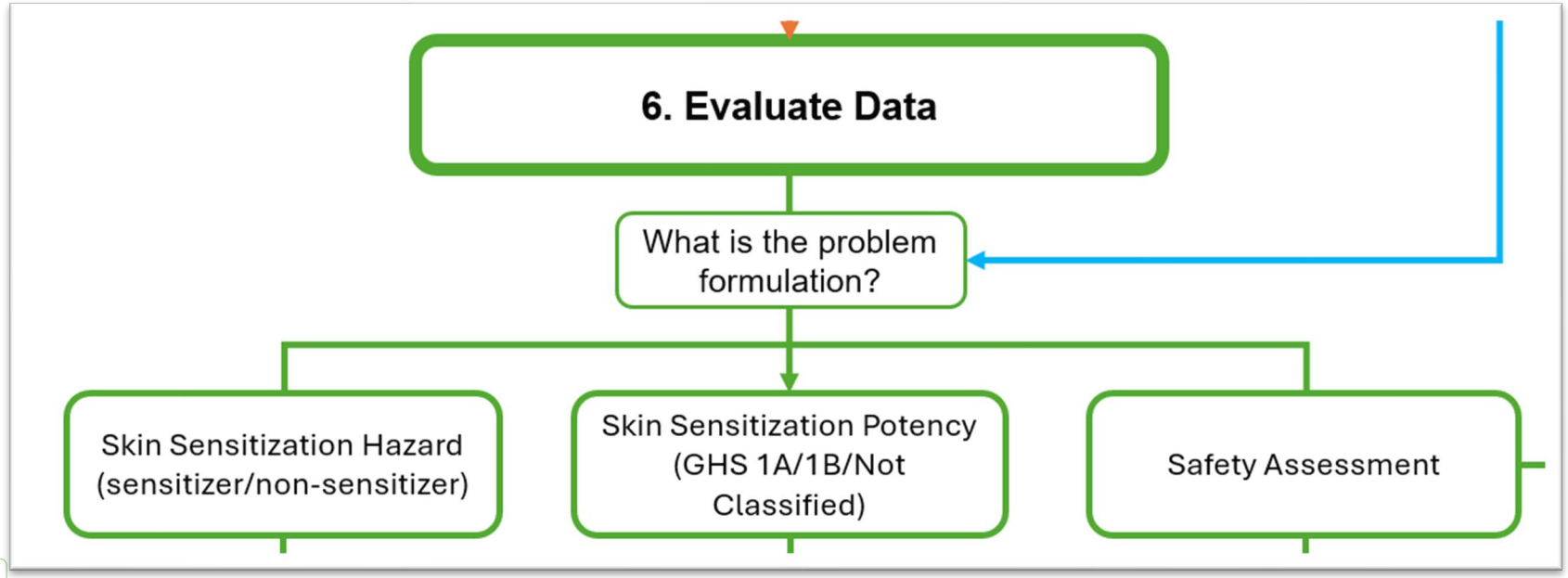
NAM	Unit(s)	Result	OECD TG
DPRA	Cys/Lys %	79.9/40.	442C
h-CLAT	(EC200/EC150, µg/ml)	14.5/10.3	442E
	(CV75, µg/ml)	12.7	
OECD Toolbox		Positive	As per GL 497

Step 5 Objective: Identify data gaps in the existing data for the substance of interest. In combination with the assessment scope and hypothesis, the test methods to fill the data gaps to assess skin sensitization potential can be identified and implemented in order to inform the skin sensitization assessment.

Step 6 – Evaluate Data

- All information, existing data, exposure estimates, newly generated data, and weight-of-evidence considerations, is **integrated** and the **problem formulation revisited**





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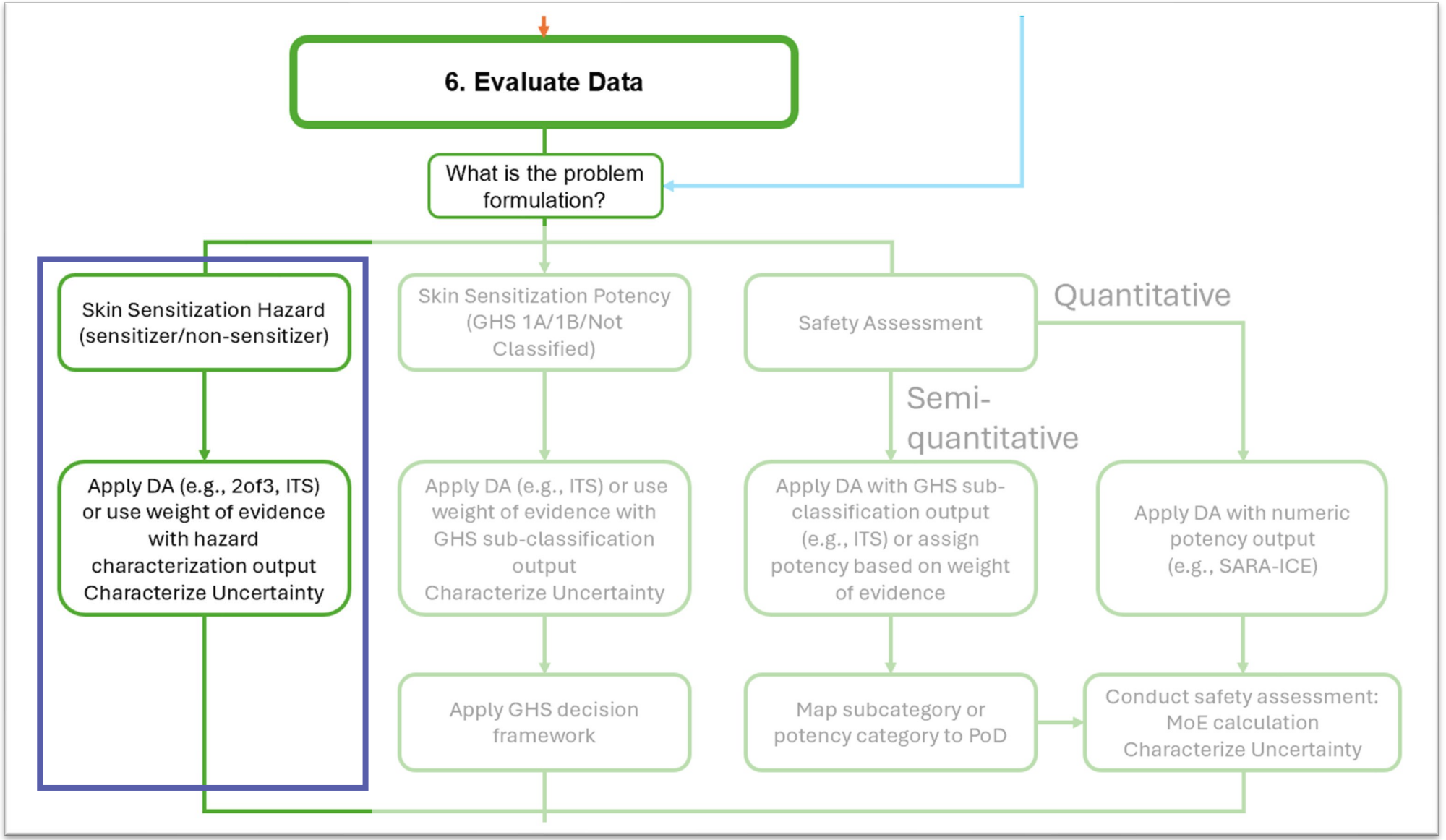
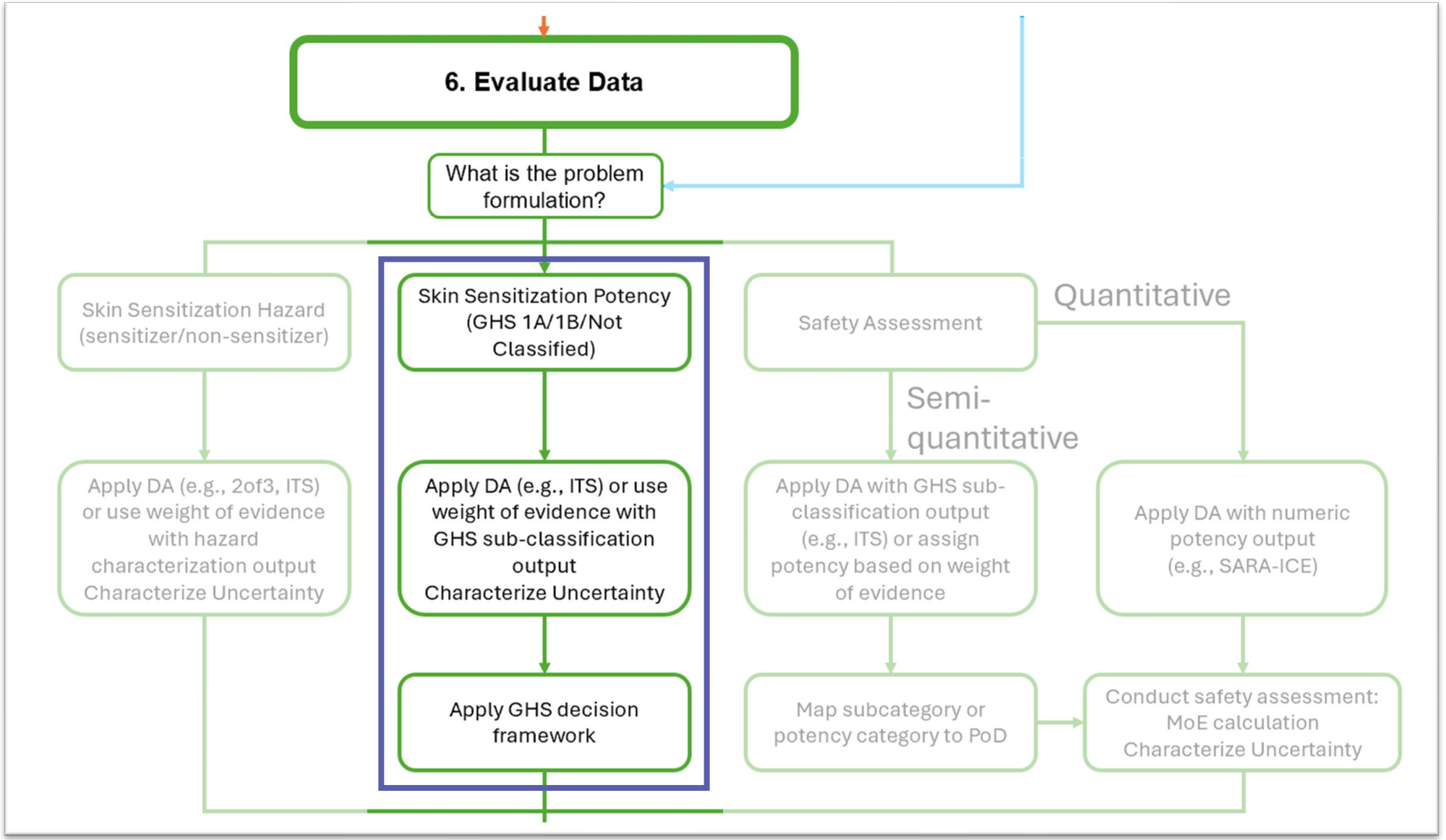
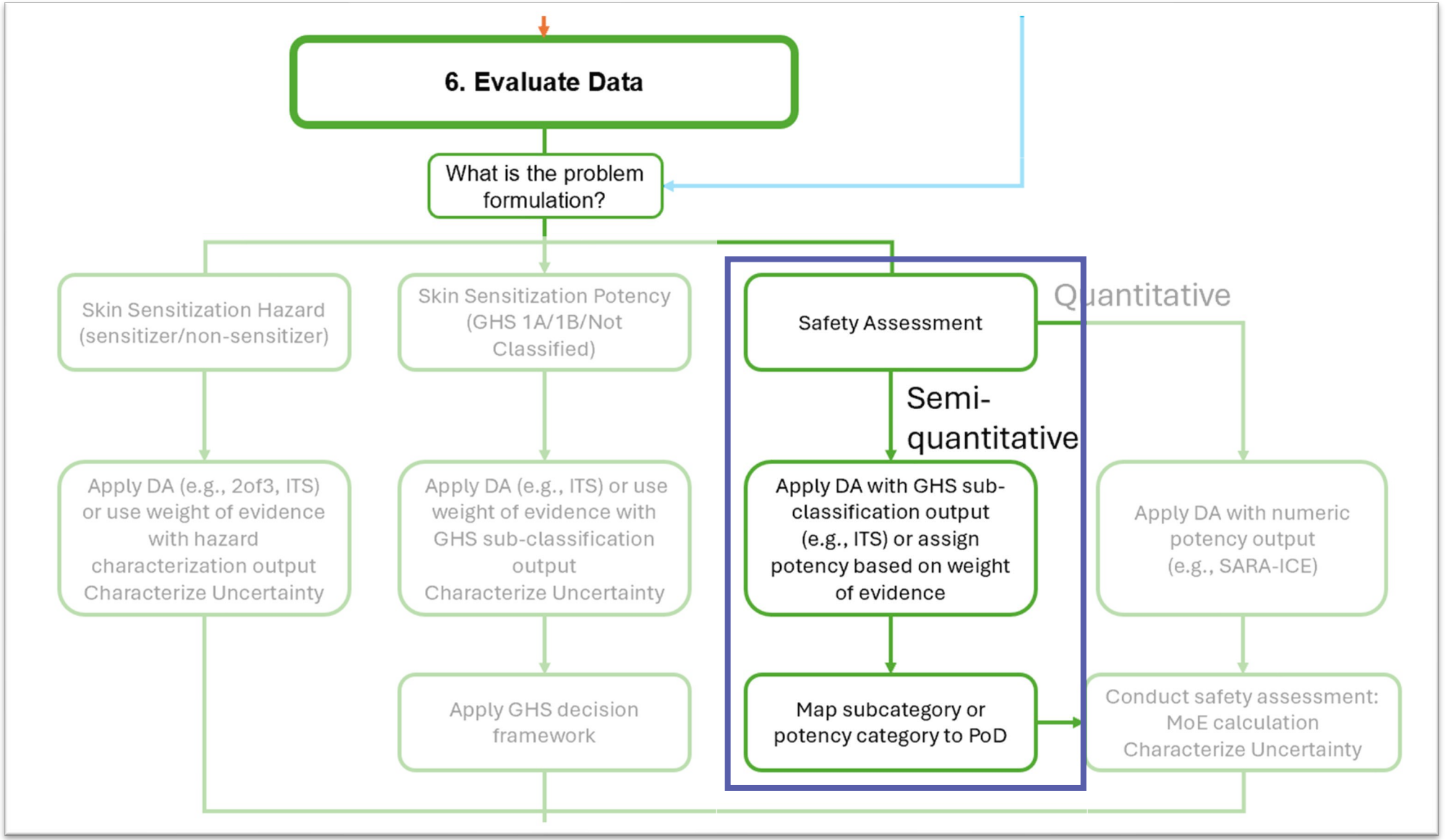
Step 6: Hazard assessment



Step 6: Potency assessment



Step 6: Safety assessment (semi-quantitative)



Step 6 – Evaluate Data

Converting data to ITS DA scores for hazard and potency assessment

- Let's convert the results to an ITS score

NAM	Unit(s)	Result	OECD TG	ITS Score
DPRA	Cys/Lys %	79.9/40.	442C	3
h-CLAT	(EC200/EC150, µg/ml)	14.5/10.3	442E	2
	(CV75, µg/ml)	12.7		
OECD Toolbox		Positive	As per GL 497	1
			Total Score	**6**
			UN GHS	**1A**

- Cinnamaldehyde is a **sensitizer**, and a **1A UN GHS sensitizer**

Step 6 – Evaluate Data

Semi-quantitative PoD derivation

- The substance is a **GHS 1A skin sensitizer**
- A PoD can be assigned for different GHS classifications
- The corresponding PoD would be 25-500 µg/cm^2

Table 11. Proposed Dose Ranges Associated with Skin Sensitization Potency, from Na et al. (2022)

Potency Category	Dose Range (µg/cm^2)	
	As proposed in Api et al. (2017)	As proposed in ECETOC 2003
Extreme	<25	<25
Strong	25-500	25-<250
Moderate	500-2500	250-<2500
Weak	>2500-10,000	2500-25,000
Very weak	>10,000	
Non sensitizer	--	--

As for GHS 1A substances, GHS notes these are classified as such if an HRIPT demonstrates a positive result at concentration ≤ 500 µg/cm^2 or an LLNA EC3 value ≤ 2%. Given the values provided in GHS for 1A are upper bounds (as opposed to lower bounds, as for GHS 1B). The NESIL for 1A substances is less clear. One option to select an appropriate NESIL in these instances involves a WoE approach. This approach results in the safety assessor assigning a potency category based on the available data, which can then be converted to a NESIL. This concept is presented in Na et al. (2022), who provide estimated dose ranges based on potency categories from two different sources, one from Api et al. (2017) and the other from ECETOC (2003). Once an assessor assigns the potency category, the NESIL can be selected as the lower end of the given dose range. As indicated in Table 11, the lower bound of the proposed moderate potency dose range from Api et al. (2017) is concordant with that used when considering a GHS 1B classification in Gilmour et al. (2023).

Step 6 – Evaluate Data

Semi-quantitative PoD derivation

- An illustrative PoD of 25 µg/cm2 will be used

$$MoE = \frac{PoD\ (or\ PoD_{NAM})}{CEL} \qquad \text{(Equation 5)}$$

MoE = 25 / 54.5

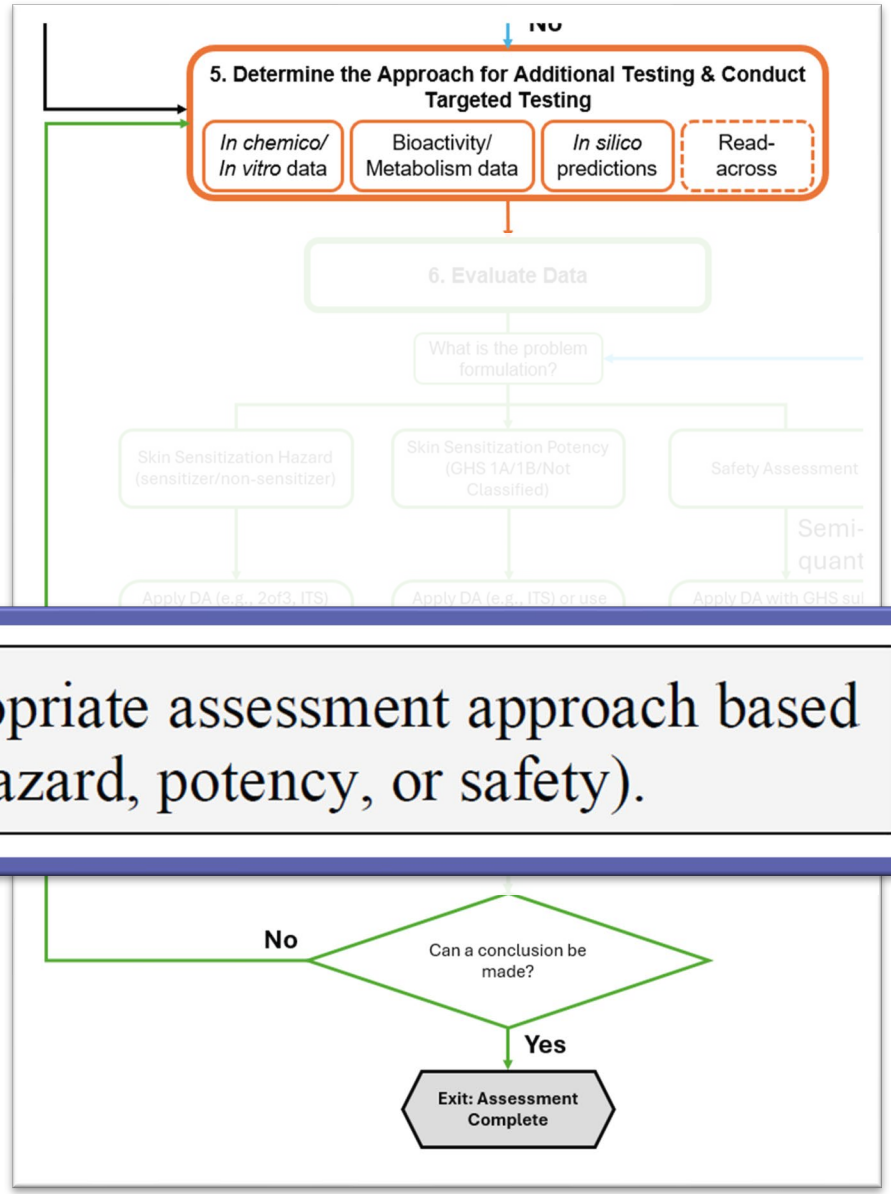
= 0.46

Acceptable MoE = 100

High risk as 0.46 < 100

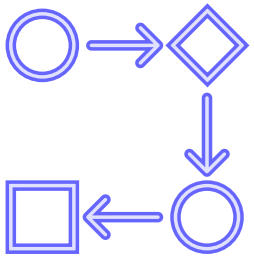
Decision: Can You Make a Conclusion?

- If a conclusion **cannot** be drawn, then the assessor may **iterate** back to Step 5
- If a conclusion can be made, then the assessment is **complete**



Step 6 Objective: Identify and apply the most appropriate assessment approach based on the defined problem formulation (i.e., assessing hazard, potency, or safety).

Conclusions



The ICCS BPG workflow enables transparent, science-based safety assessments for cosmetic ingredients

In the cinnamaldehyde case study, exposure exceeded EBW thresholds, requiring a full assessment

NAM data indicated strong sensitization potential (UN GHS 1A) with a high risk at the proposed use level (MoE = 0.46, below the acceptable threshold of 100)

The case study highlights the importance of robust evidence integration for regulatory decisions

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Thank You