An Introduction to the ICCS Best Practice Guidance Document on Skin Sensitization

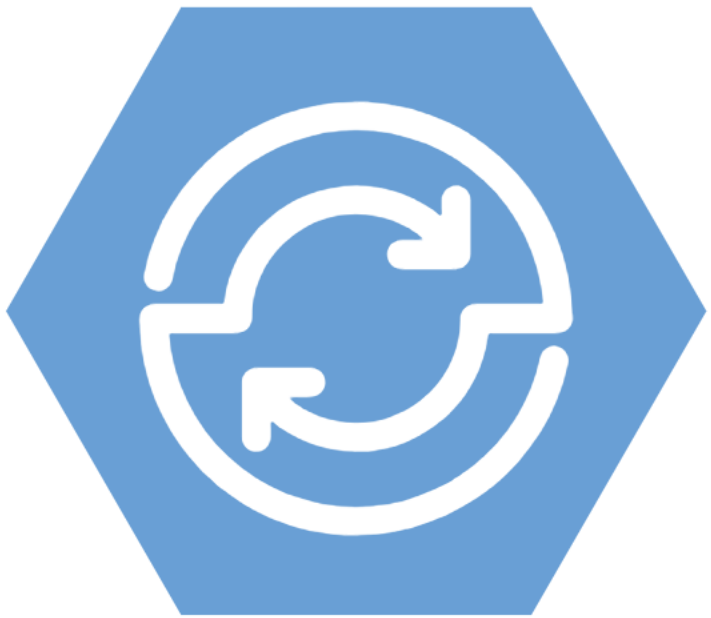
ICCS BPG Skin Sensitization: Safety Assessment Using NAMs for Substances in Cosmetics and Personal Care Products Webinar

Donna Macmillan, PhD
Director, Outreach and Capacity Building
ICCS

ICCS | INTERNATIONAL COLLABORATION ON COSMETICS SAFETY

Skin Sensitization Assessment: Using New Approach Methodologies for Substances in Cosmetics and Personal Care Products

Goals of ICCS Best Practice Guidance Documents



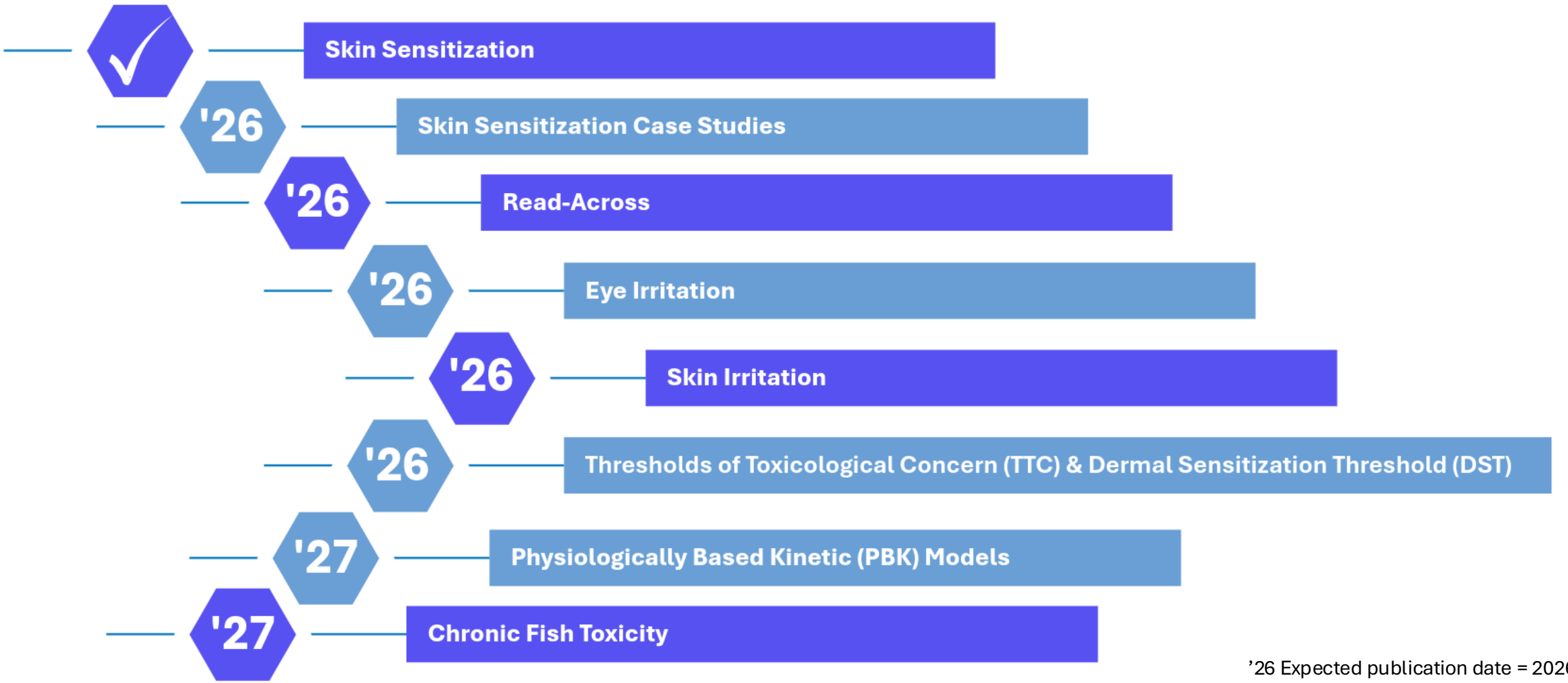
ENABLE BROADER ADOPTION OF NAMs
by providing practical, science-based guidance

IMPROVE THE QUALITY AND ROBUSTNESS
of safety assessments

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

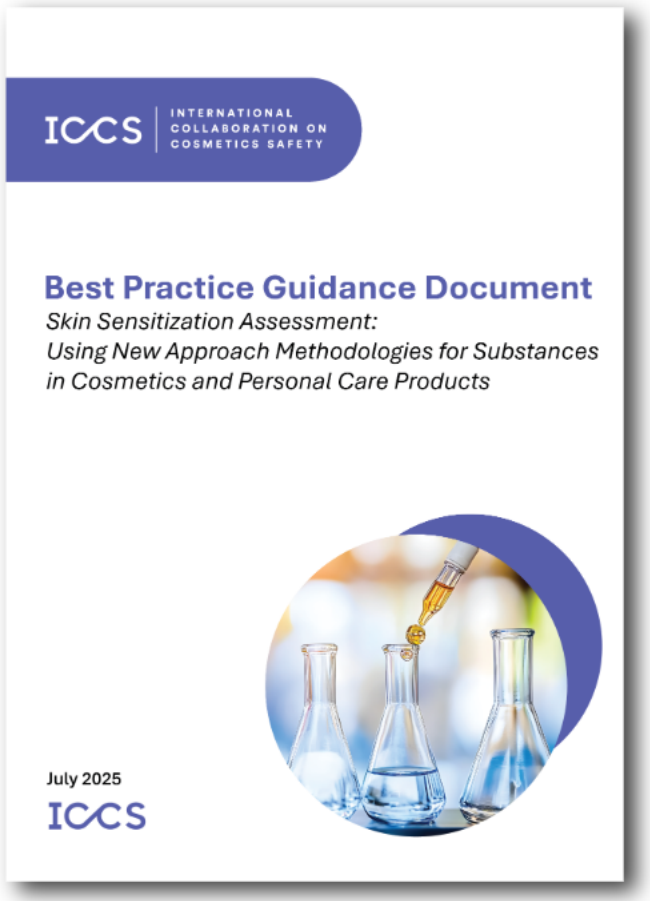
SUPPORT NGRA PRINCIPLES
through integrated evidence-based frameworks

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

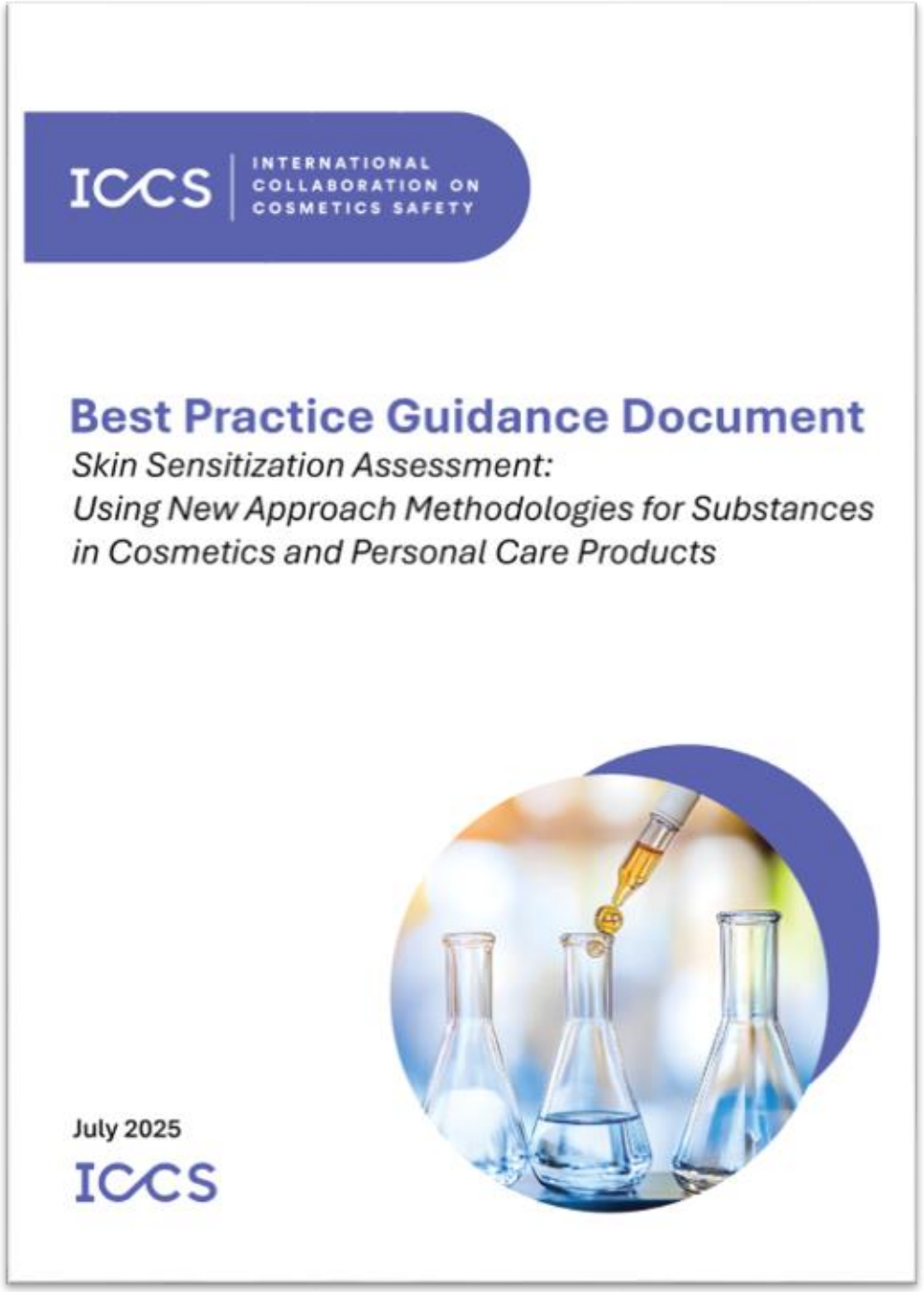
- Bridges the gap between advancing science and regulatory requirements
- Streamlines decision-making
- Supports consistency, transparency, and reproducibility enhancing global harmonization

HOW WAS IT DEVELOPED

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

WHO IT'S FOR

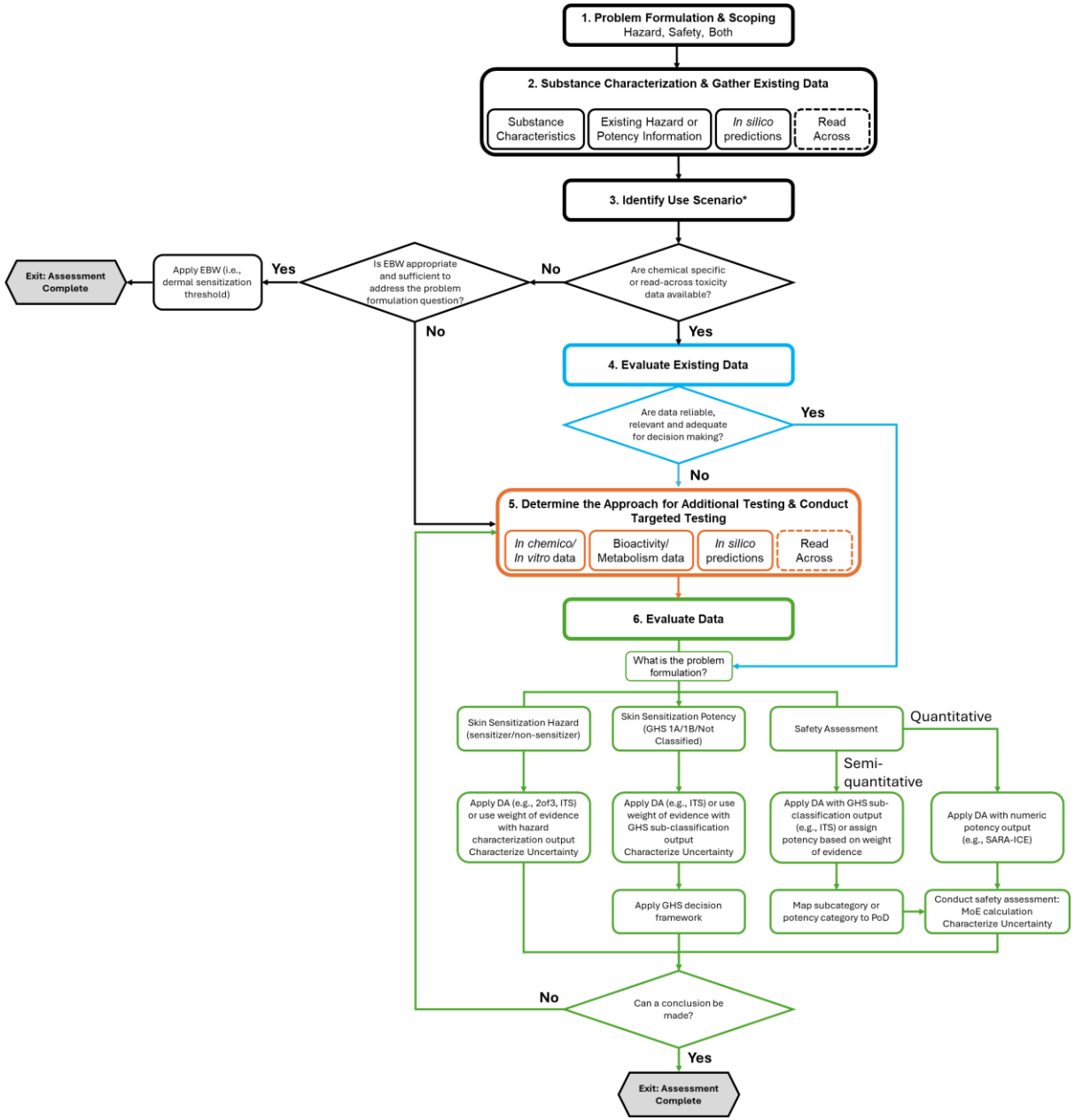
- Safety assessors and regulatory scientists integrating NAMs into safety assessments
- NGOs and government agencies engaged in risk assessment and policy development



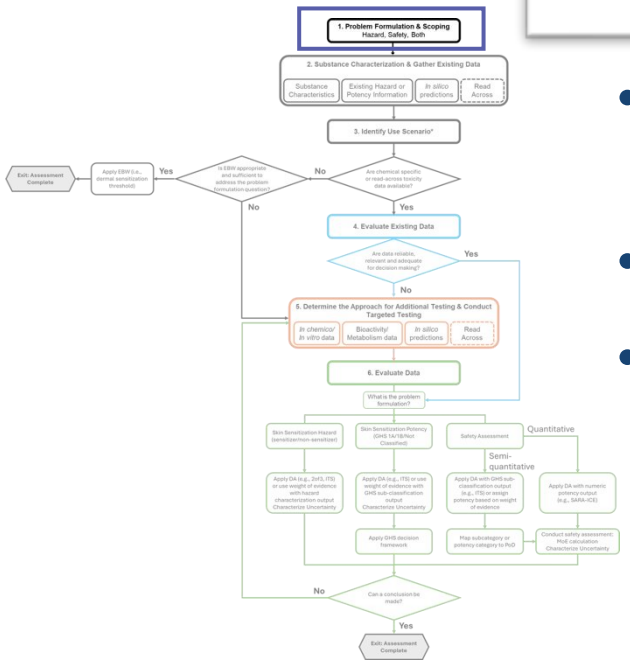
ICCS BEST PRACTICE GUIDANCE

https://www.iccs-cosmetics.org/education/best-practice-guidance/bpg-skin-sensitization-assessment-using-new-approach-methods

BPG Skin Sensitization Workflow



Step 1 – Problem Formulation & Scoping



- 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 (Cont.)

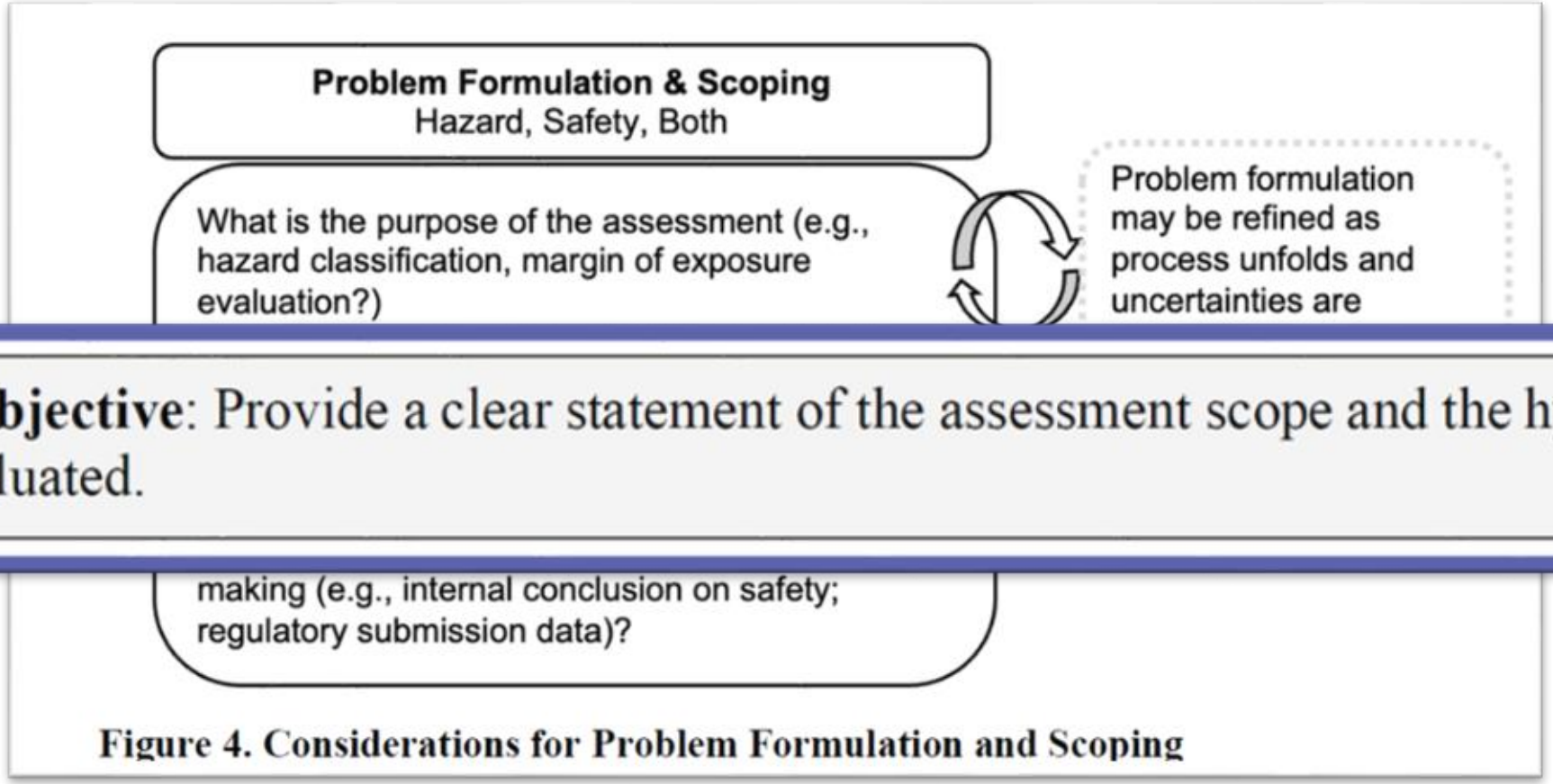
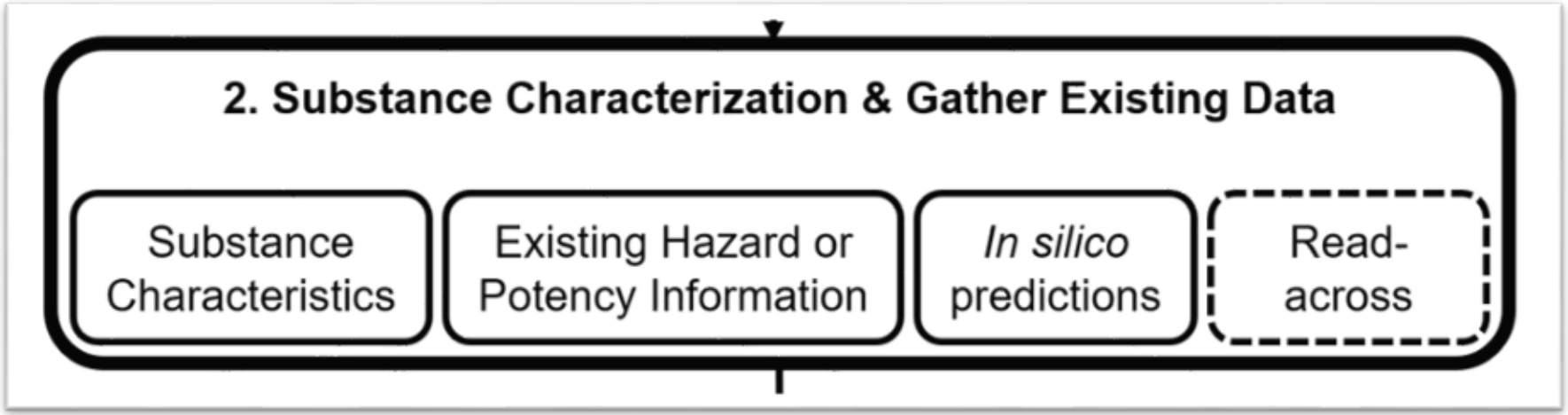


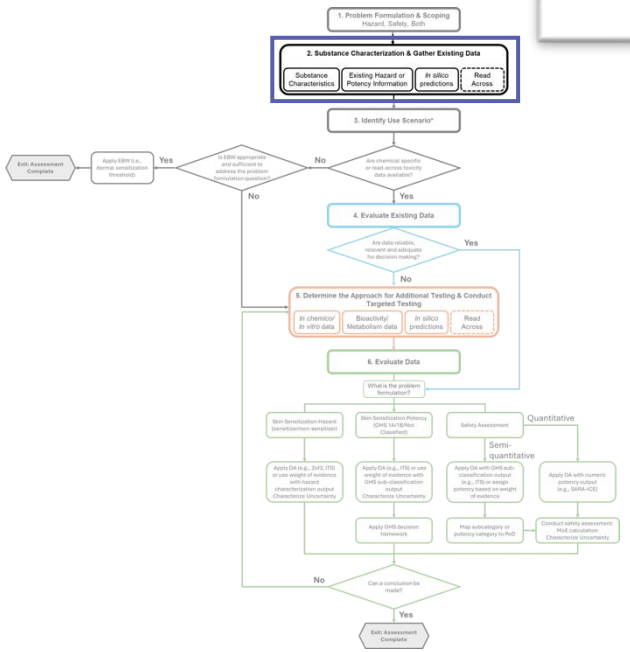
Figure 4. Considerations for Problem Formulation and Scoping

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 (Cont.)

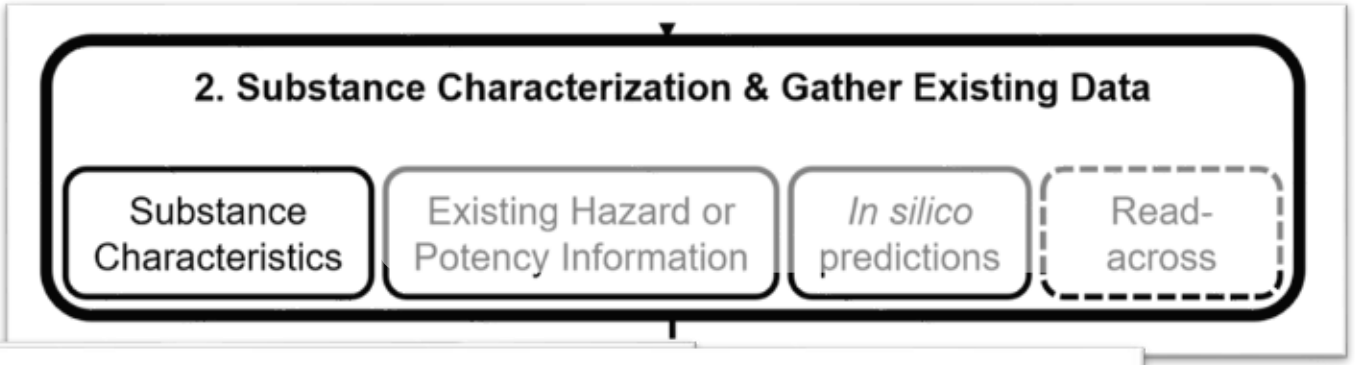
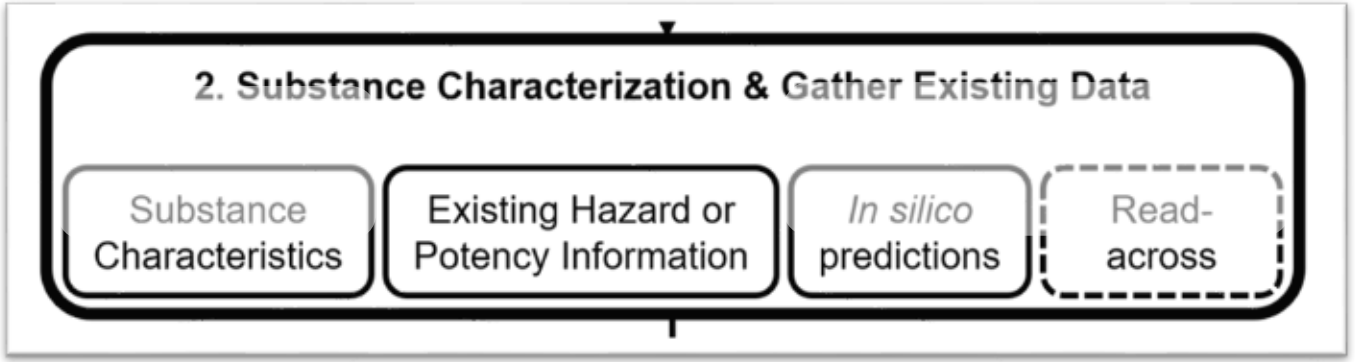


Table 3. Summary of Assessme

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 (Cont.)



- 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 (Cont.)

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/)

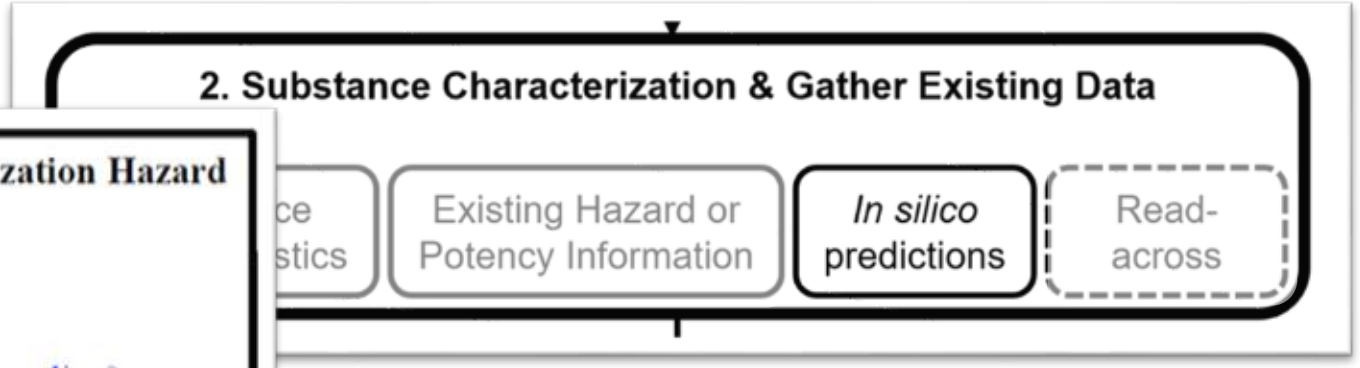
Potency predictions

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)

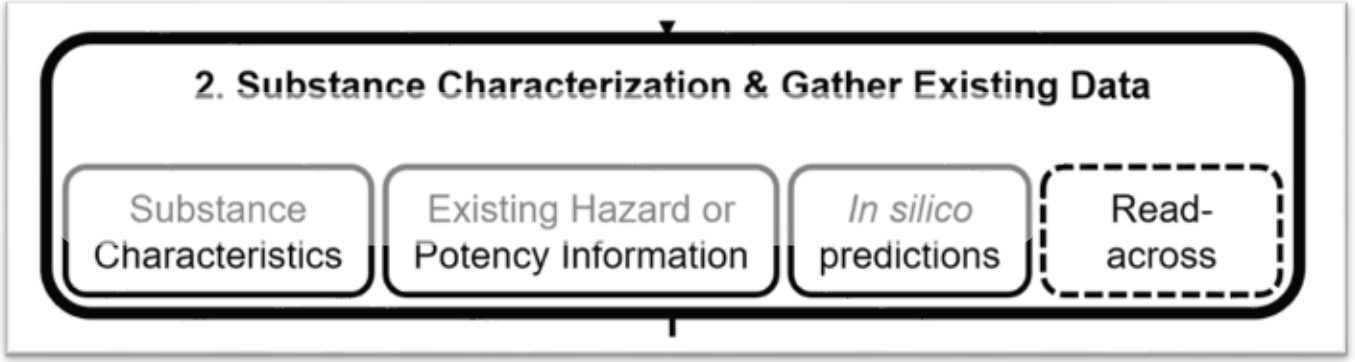
Mechanistic endpoints

- 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 (Cont.)



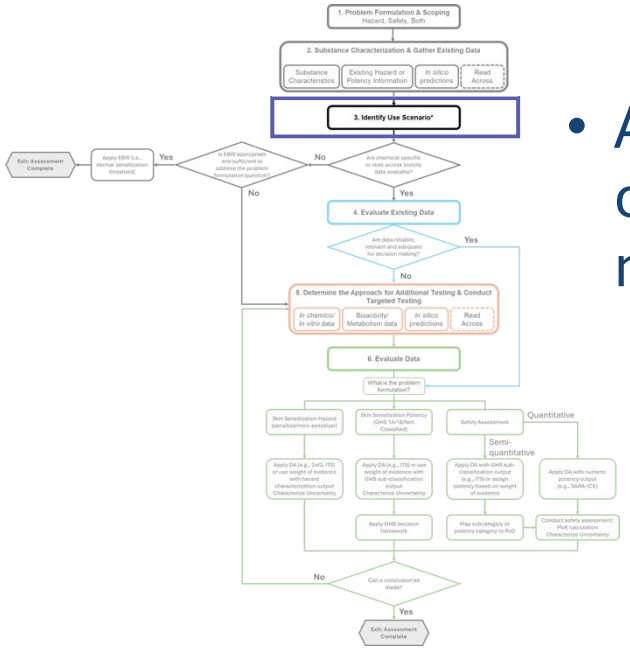
Read-across in dashed box to indicate optional use at Step 2

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

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 (Cont.)

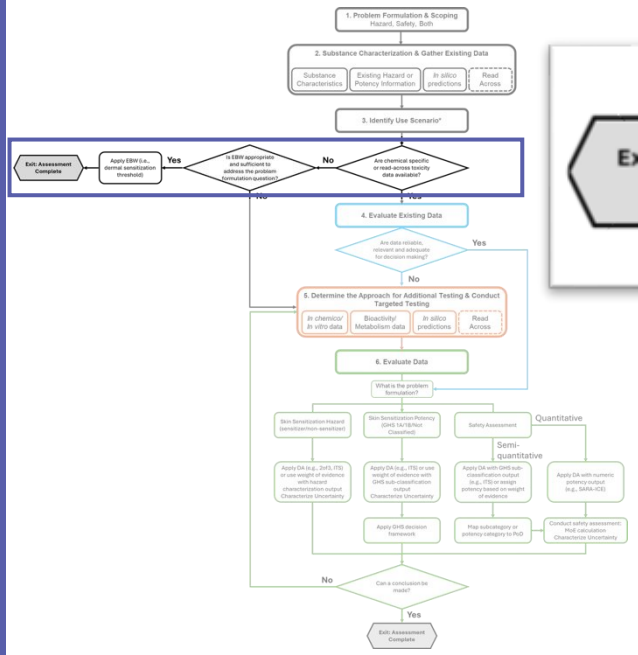
- Identify the product type and other relevant data to establish **how** the substance will be used
- Calculate a **Consumer Exposure Level** (CEL) using established consumer exposure values (e.g., SCCS Notes of Guidance)

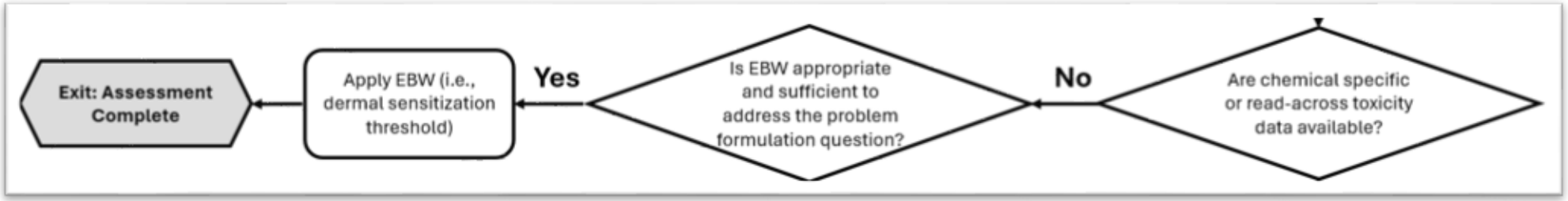
Table 4. Data to Collect to Support Derivation of a Consumer Exposure Level (CEL)

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

Decision: Can Exposure-Based Waiving (EBW) be Applied?

- **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





Decision: Can Exposure-Based Waiving (EBW) be Applied? (Cont.)

- 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

Decision: Can Exposure-Based Waiving (EBW) be Applied? (Cont.)

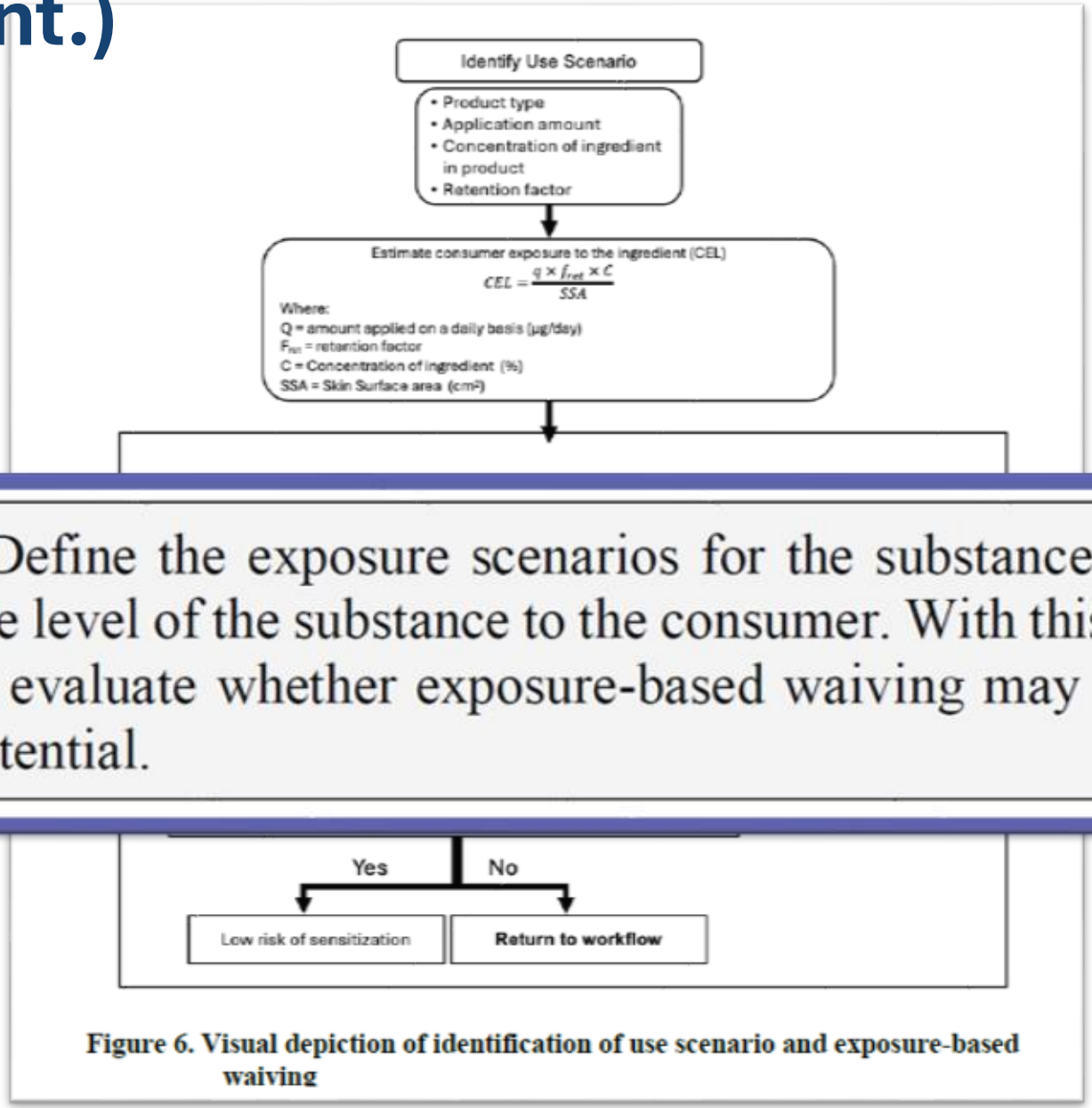
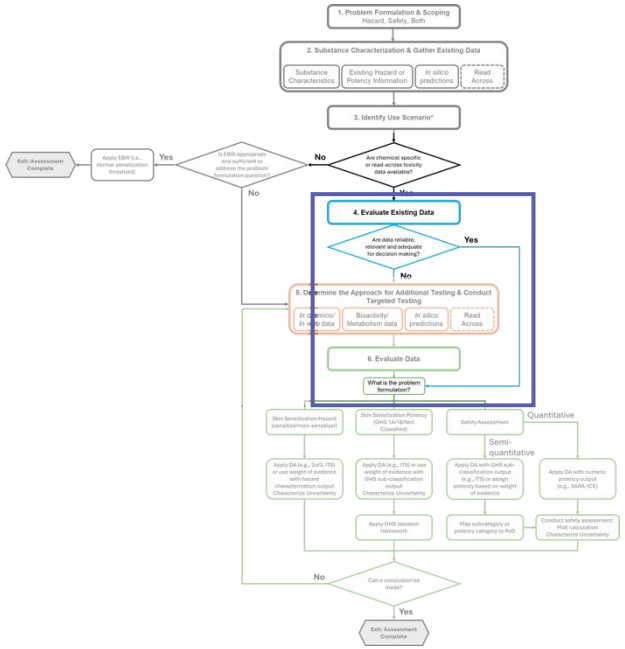
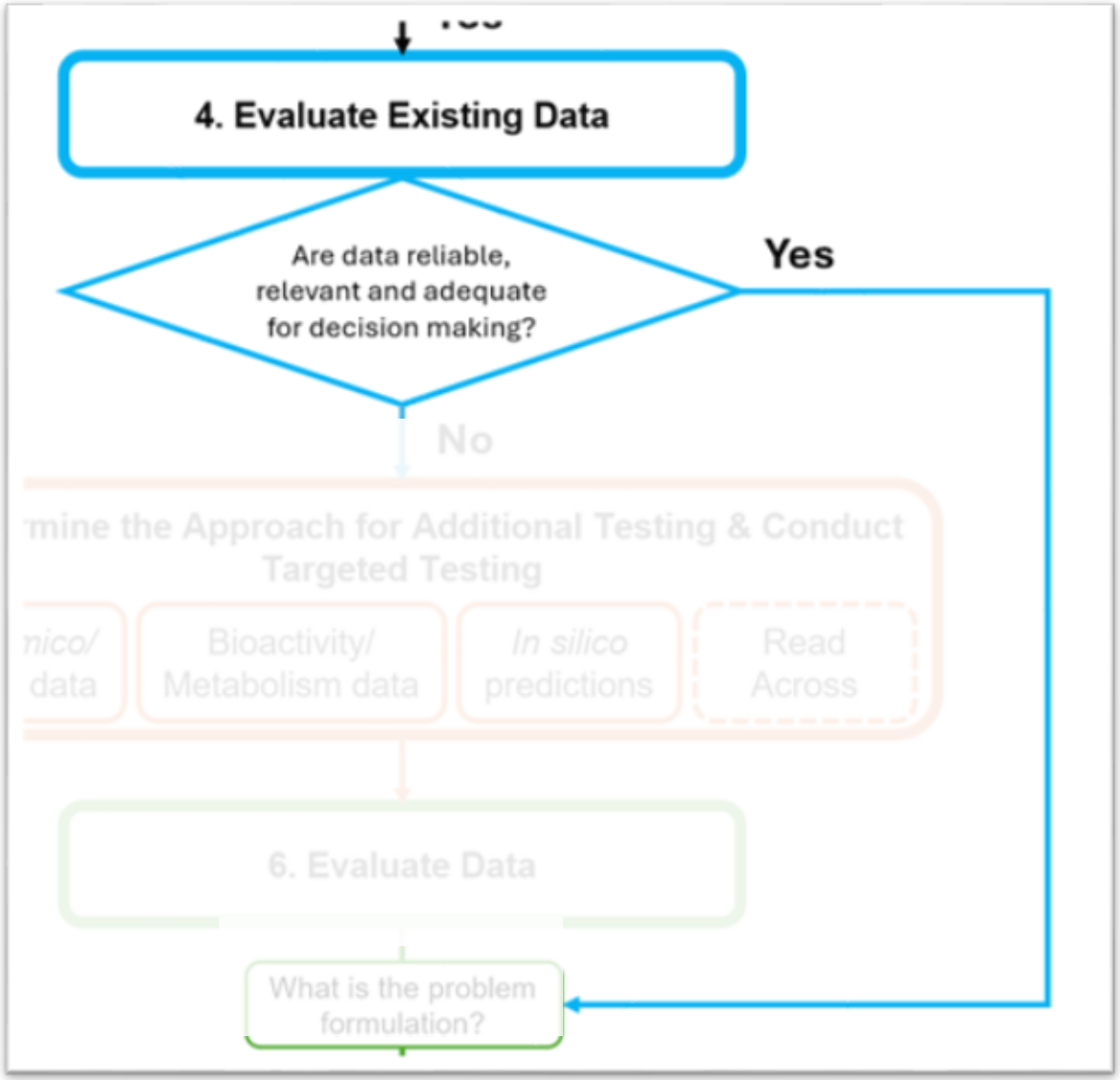


Figure 6. Visual depiction of identification of use scenario and exposure-based waiving

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 (Cont.)

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

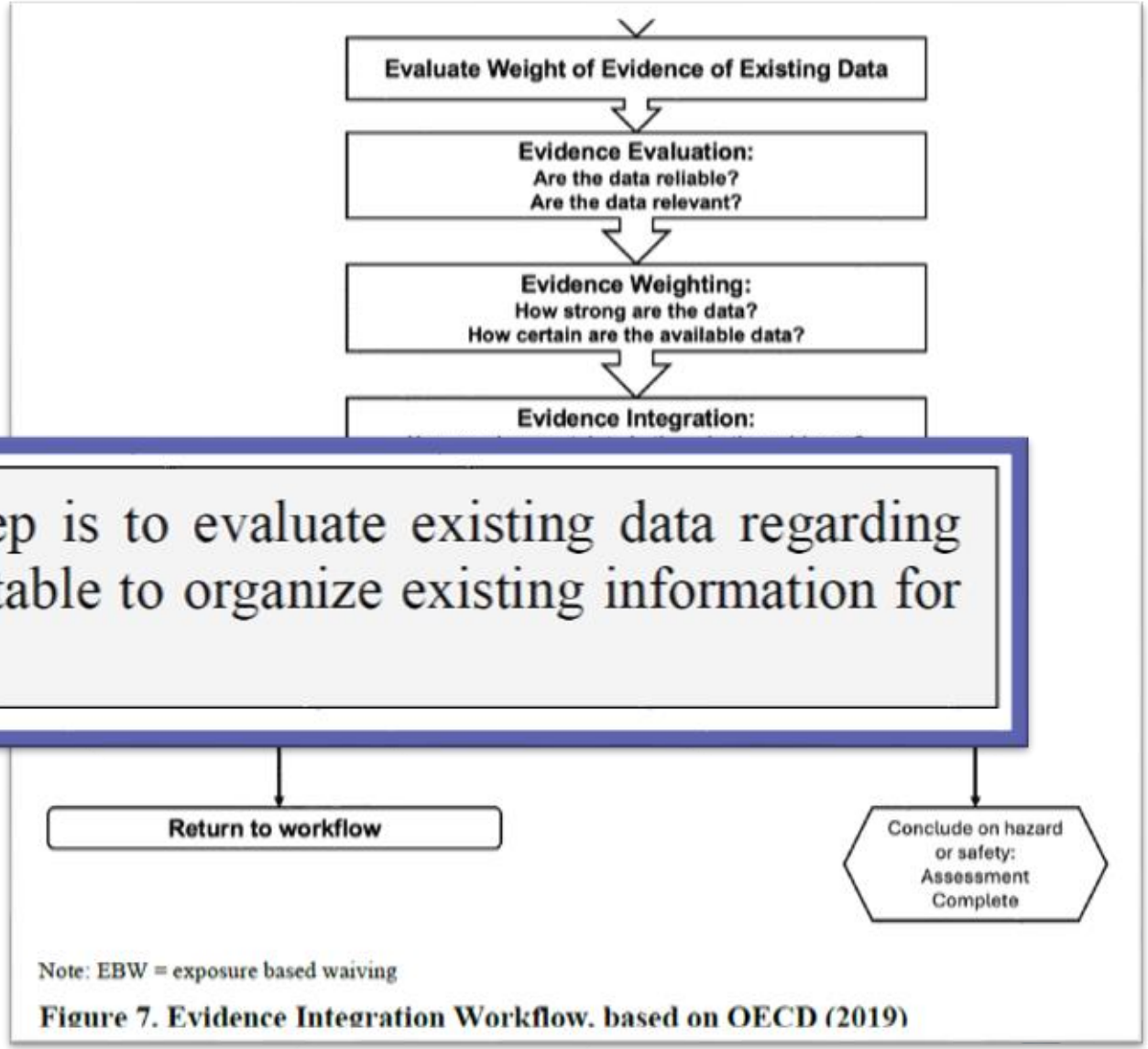
Table 6. Example Data Map for Organization Existing Data for Substance*

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 (Cont.)

- **Data map** can provide a structured way to organize data gathered
- **Reliability**, **relevance**, and **adequacy** evaluated

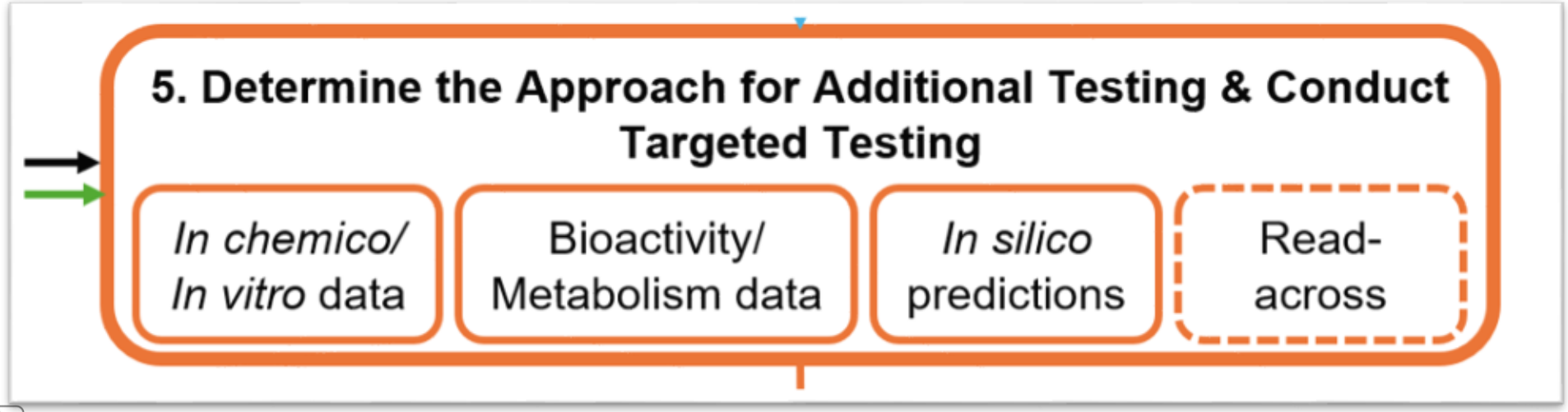
Step 4 Objective: The objective of this step is to evaluate existing data regarding reliability, relevancy, and adequacy. A data table to organize existing information for the substance of interest is recommended.



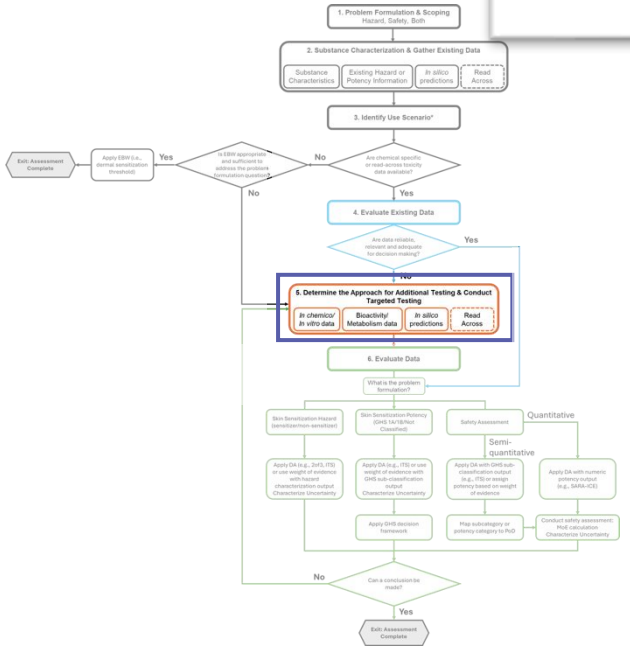
Note: EBW = exposure based waiving

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

Step 5 – Determine 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 – Determine the Approach for Additional Testing & Conduct Targeted Testing (Cont.)

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

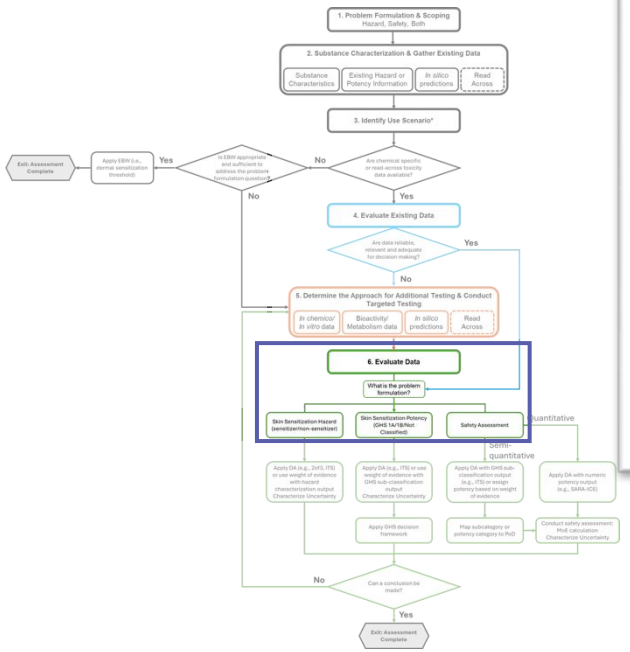
Defined Approach	Problem Formulation Addressed	Input KE1: ADRA or DPRA	Input KE2: KeratinoSens™, EpiSensA, or LuSens	Input KE3: GARD™Skin, h-CLAT, IL-8 Luc, or U-SENS™	Input *In Silico:* Derek Nexus, OECD QSAR Toolbox
2o3	Hazard (GHS 1 vs GHS NC)	X	X	X	--
ITS	Hazard (GHS 1 vs GHS NC) Potency Category(GHS 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

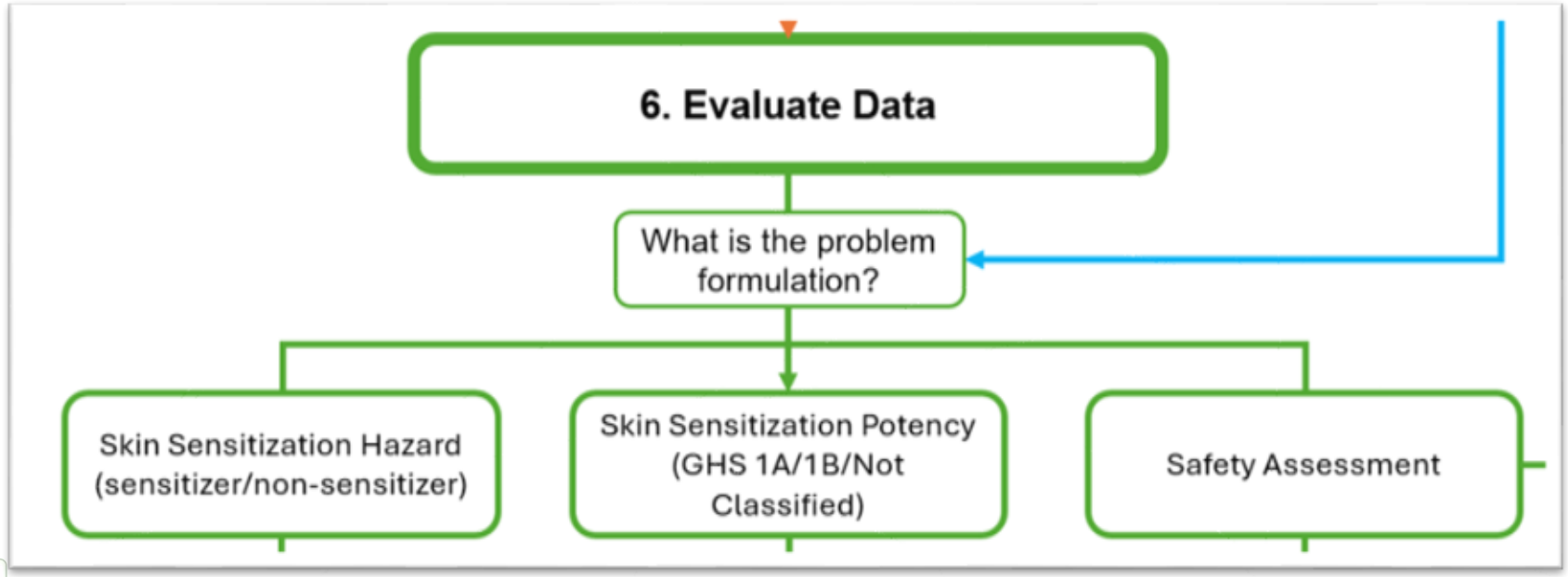
°LLNA and HPPT data also may be used in SARA-ICE. Further information may be reviewed in OECD (2025).
*ED_{01} is the estimate of a dermal dose at which there is a 1% chance of inducing sensitization using a human predictive patch test.

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.

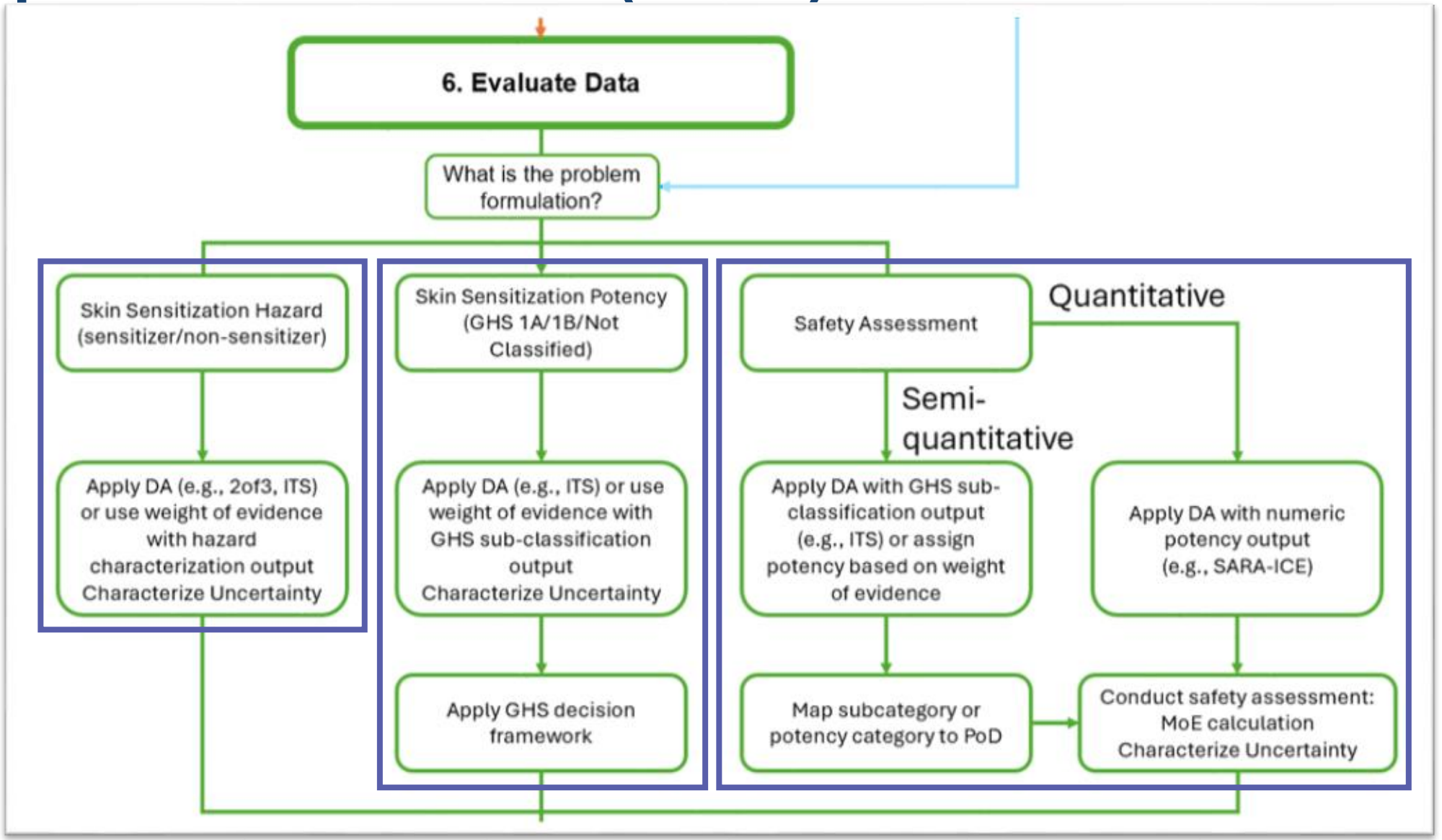
Step 6 – Evaluate Data

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



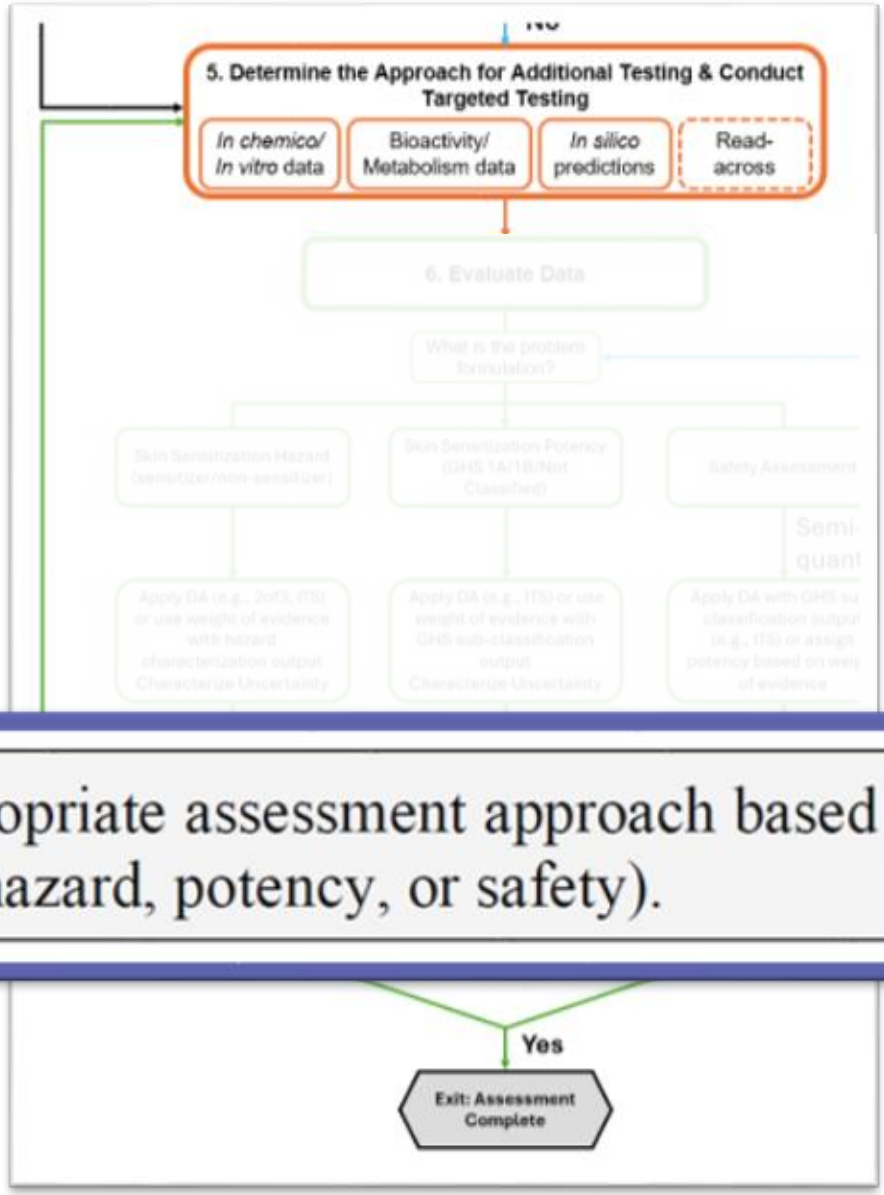


Step 6 – Evaluate Data (Cont.)



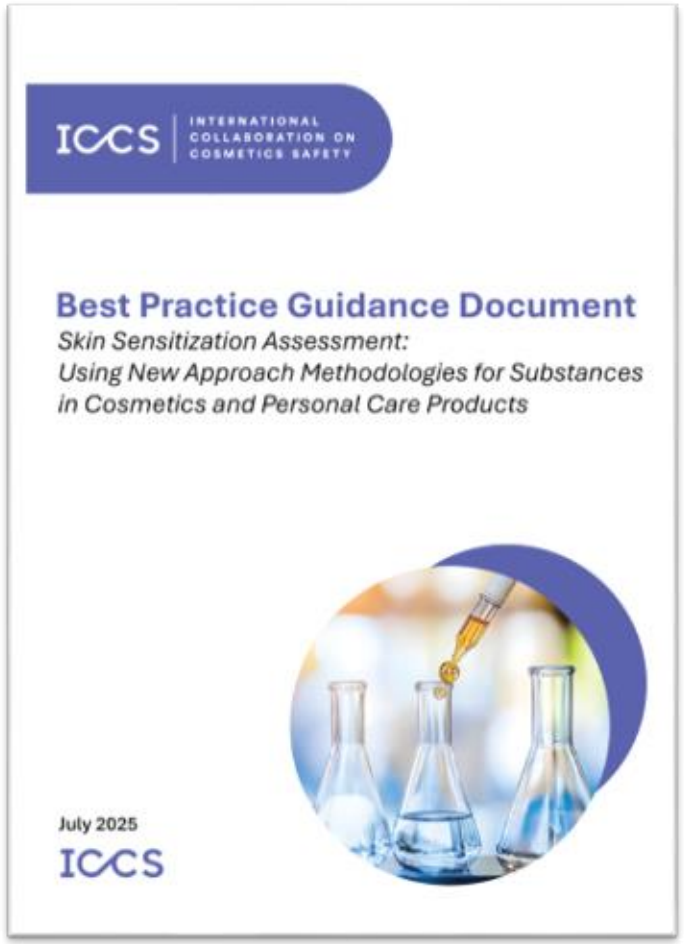
Can You Make a Conclusion?

- 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



- ICCS Best Practice Guidance provides a structured, step-by-step workflow aligned with NGRA principles, to conduct skin sensitization assessments using NAMs
- Bridges the gap between advancing science and regulatory requirements
- Supports consistent, transparent, and reproducible decision-making by guiding assessors through data gathering, evaluation, and interpretation, supporting global harmonization

THANK YOU!

ICCS | INTERNATIONAL COLLABORATION ON COSMETICS SAFETY