An Iterative and Multidisciplinary Framework for Determining Read-Across for Hazard Assessment

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GRADIENT

ABSTRACT

For global chemical compliance and safety data sheet (SDS) generation, we analyzed toxicological data for a comprehensive portfolio of chemicals. Many of these substances have no readily available toxicity data, necessitating "read-across" or "surrogate" identification. To facilitate adherence to a consistent and scientifically sound approach, we developed an iterative, multidisciplinary framework for identifying high-quality read-across chemicals that can inform the toxicological assessment of a data-poor chemical of interest (COI). Our read-across identification and evaluation approach involves consistently preserving COI reactive functional groups, considering structural alerts and bioavailability, and using an internally developed database of chemical groupings to validate or challenge potential hazard profiles. Mechanistic and metabolic data are incorporated when possible and necessary. We have reviewed over 700 COIs to date using our read-across framework and observed (1) chemical expertise and rationale documentation are particularly important for complex chemicals (*e.g.*, of unknown or variable composition, complex reaction products, and biological materials [UVCBs]), (2) systematic use of chemical groupings and structure-activity relationships streamlines read-across selection and ensures consistency within a large portfolio of chemicals, and (3) regular communication and collaboration between toxicologists and chemists is essential for successful application of the framework. Lastly, the framework includes quality assurance protocols and requires that users compare toxicity data for multiple surrogates to ensure concordance. Appropriate application of the read-across approach ultimately lowers analytical costs and dependence on animal testing, fosters safer chemical use, and increases compliance with hazard communication frameworks such as the Globally Harmonized System for Classification and Labelling of Chemicals (GHS).

OBJECTIVE

To fill toxicological data gaps by identifying appropriate chemical surrogates (a.k.a. analogues) or structural alerts and applying a read-across approach.

## WHAT IS READ-ACROSS? WHY USE IT?

- Properties of a known (data-rich) chemical (*i.e.*, surrogate or analogue) are "read across" to a new (data-poor) chemical. Toxicological data gaps exist for many new and existing chemicals.

- Alternatives assessments – analyses that inform the transition to safer/greener chemicals – can be conducted only if the toxicity of substitute chemicals is well-characterized.

- *In vivo*/animal testing may not be time- or cost-effective, and there may be ethical objections.

- Read-across ensures that new and existing chemicals are used more safely.

- Read-across facilitates compliance with hazard communication frameworks.

SURROGATE CHECKLIST/CONSIDERATIONS

- Document rationale, professional judgment, and uncertainty.

- Consider multiple chemical surrogates, if possible, and ensure that toxicity data are concordant.

- Ensure that suggested surrogates and COI contain the same functional groups and no other reactive functional groups.

- Search Gradient's chemical portfolio and list of chemical groupings for previously assessed compounds that may inform surrogate identification.

- Use National Industrial Chemicals Notification and Assessment Scheme (NICNAS) structural alerts to identify chemicals, functional groups, or substructures that are linked to a particular toxicity endpoint.

- Consider physical and chemical properties, *e.g.*, solubility, that might affect bioavailability and reactivity.

- Check resources: European Chemicals Agency (ECHA) 2015 Read-Across Assessment Framework (RAAF); NICNAS Structural Alert Tables.

METHODS

Figure 1 Framework for Identifying Chemical Surrogates
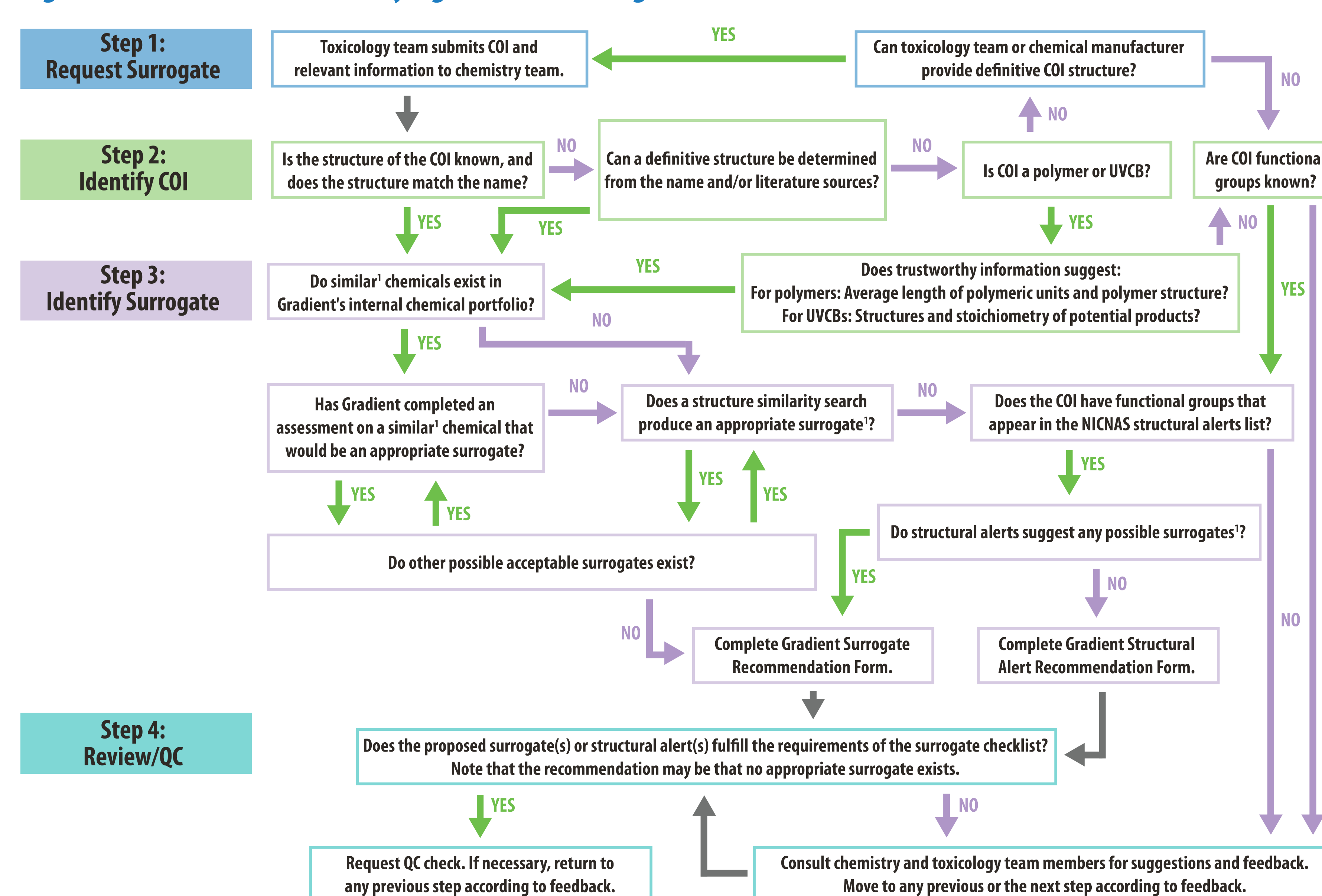
Notes: ▇ - Yes; ▇ - No; ▇ - Neutral. (1) Consider structure, physicochemical properties (e.g., K_{ow}, aqueous solubility, reactivity), metabolism, and/or biological similarities. COI = Chemical Interest. QC = Quality Control. UVCB = Unknown or Variable Composition, Complex Reaction Products, and Biological Materials.

RESULTS

- Our read-across framework is iterative and multidisciplinary.

- The use of chemical groupings streamlines surrogate selection and ensures consistency.

- The use of structural alerts can provide insight when chemical surrogates are not obvious or available.

- The framework includes quality assurance protocols.

- Our read-across framework has been used to review over 700 COIs to date.

Case Study: Cationic Detergent

Step 1: Limited toxicological data was available for Benzyldimethylhexadecylammonium chloride (CAS RN 122-18-9), an antimicrobial and surfactant. Please suggest a surrogate.

Step 2: Identify COI
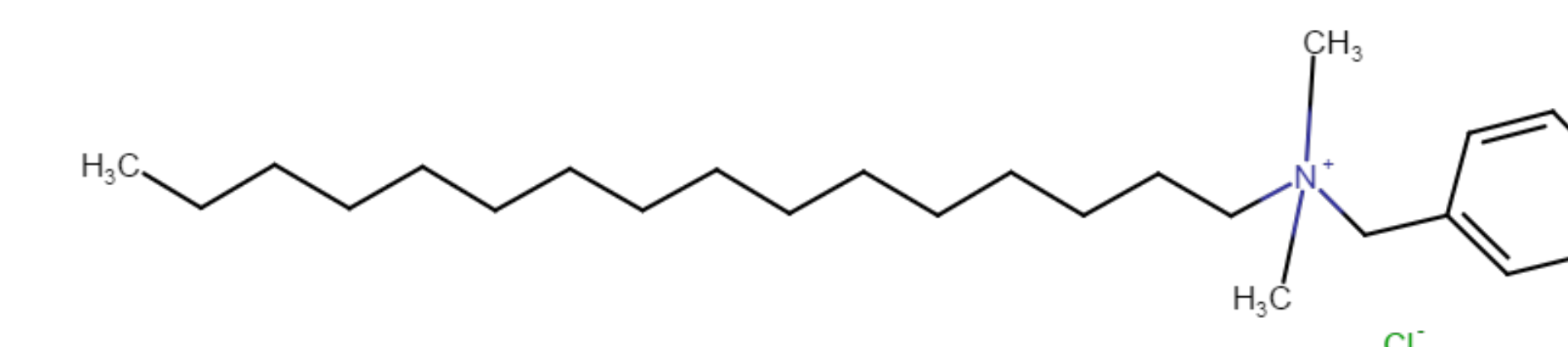
Step 3: Identify Surrogate(s)

CAS RN	Structure	Considerations	Decision
3529-04-2		The counter ion (Br⁻) differs from that of the COI (Cl⁻): May introduce uncertainty.	Not suitable
37139-99-4		The C chain is unsaturated and slightly longer (C18) than that of the COI (C16): May affect physical/chemical properties.	Suitable, with reservations
139-07-1		The alkyl chain is slightly shorter (C12) than that of the COI (C16): May affect physical/chemical properties.	Suitable, with reservations
68424-85-1		This mixture includes the COI and other quaternary ammonium compounds that may be conservative.	Suitable

Note: Structures copied from National Library of Medicine.