Approaches to Identifying Potential Candidate Chemicals for Prioritization: **Functional Category Approach Based on Chemical Structure and Function**

Clive Davies and Lauren Sweet
U.S. EPA, Office of Pollution Prevention and Toxics
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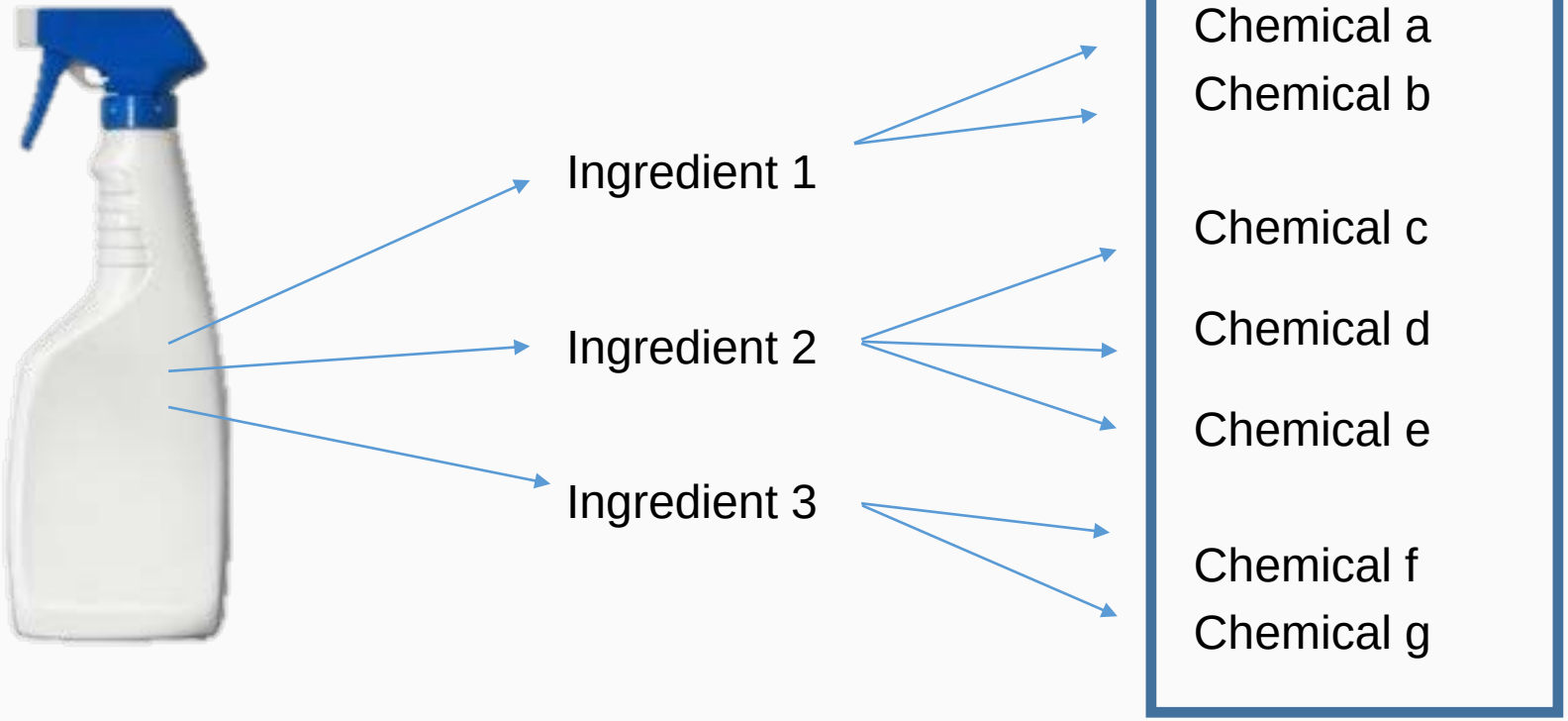
Outline

- Functional use in this approach
- Introduction of high-throughput models used in this approach
- Methodology for organizing and identifying candidates for prioritization
- Benefits & caveats

Key Points

- Focus at the chemical-structure level
- Promotes efficiency by taking advantage of:
  - Existing EPA high-throughput tools
  - Lessons learned from developing SCIL
- Compatible with OECD functional use categories
- Could complement other organizing approaches to identify functionally-related priority candidates from the active TSCA inventory

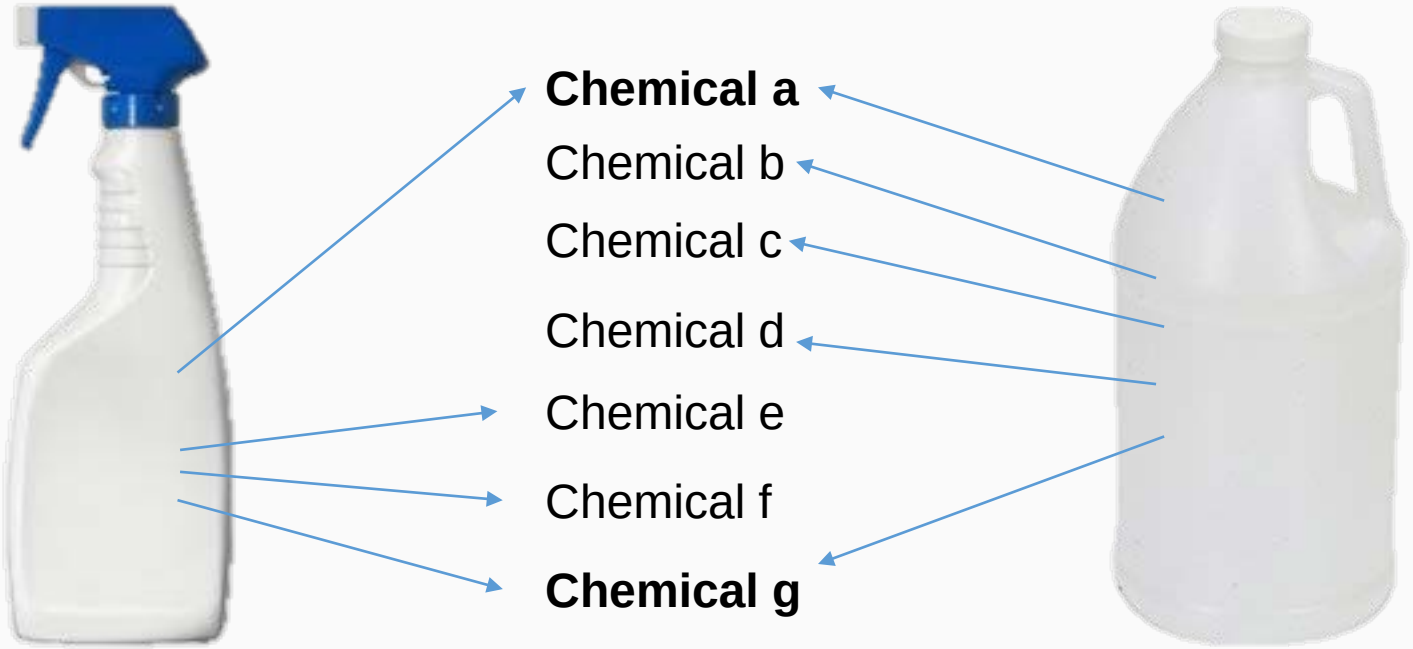
➢ Proof of concept was successful, generating clusters of chemicals based on functional use



Product ingredients are often made up of multiple chemicals of diverse structure, function and toxicity.

Product A

Product B



A chemical may serve the same function in many product types.

Functional Uses* – First Ten Chemicals

- Asbestos (specialized industrial chemical)
- 1-bromopropane (solvent)
- Carbon tetrachloride (processing aid)
- 1,4 Dioxane (processing aid)
- Cyclic Aliphatic Bromide Cluster (flame retardant)
- Methylene chloride (processing aid, solvent)
- N-methylpyrrolidone (processing aid, solvent)
- Perchloroethylene (processing aid, solvent)
- Pigment Violet 29 (pigment)
- Tetrachloroethylene (solvent)

* Simplified for illustrative purposes

Safer Chemical Ingredients List

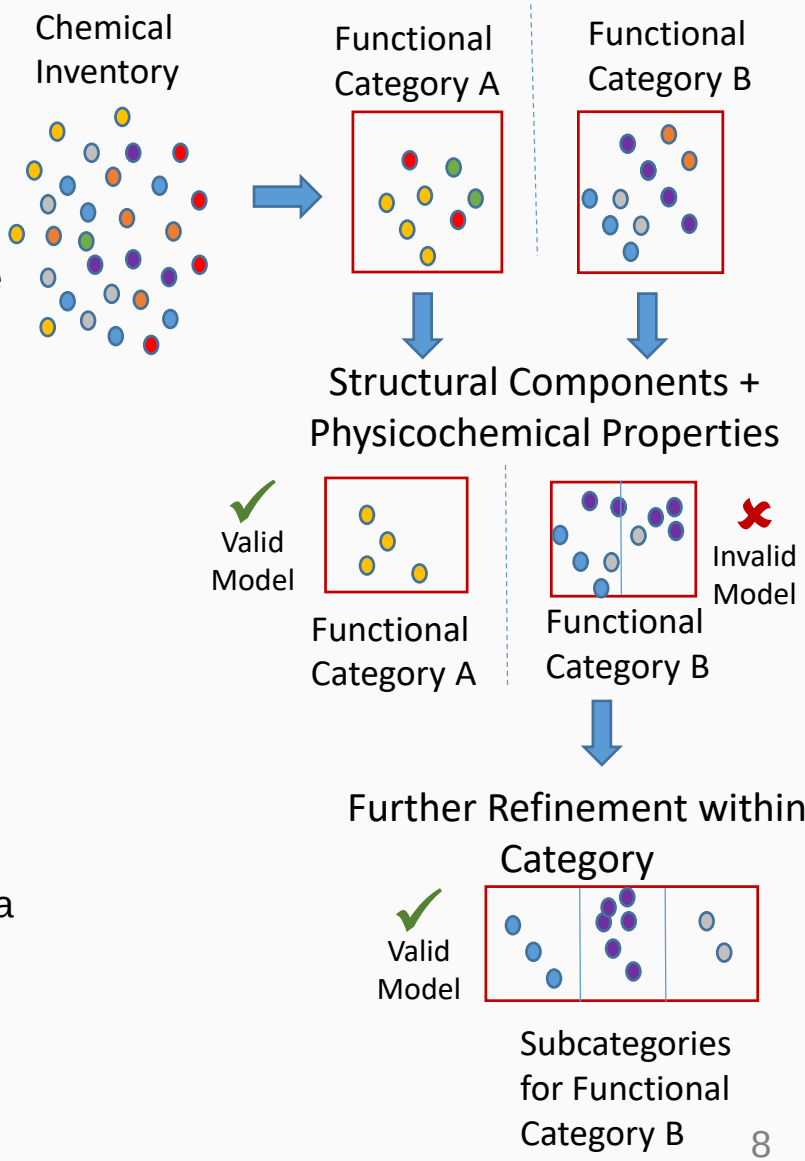
918 chemicals & **987** listings on SCIL as of November 2017

By functional ingredient classes:

- Antimicrobial Actives (7)
- Chelating Agents (22)
- Colorants (44)
- Defoamers (12)
- Emollients (26)
- Enzymes & Enzyme Stabilizers (30)
- Fragrances (152)
- Oxidant & Oxidant Stabilizers (19)
- Polymers (59)
- Preservatives & Antioxidants (34)
- Processing Aids & Additives (149)
- Skin Conditioning Agents (46)
- Solvents (67)
- Specialized Industrial Chemicals (14)
- Surfactants (282)
- Uncategorized (24)

Elements of the Model

- Functional Use database
  - EPA Office of Research and Development tool[1]
  - Functional use is assigned based on publicly available information
- Refine reported functional use information with predictive models[2] based on:
  - Structural components
  - Physicochemical properties (molecular weight, vapor pressure, water solubility, etc.)
- Refine functional categories if needed based on additional analysis of chemical properties or structures
  - Chemicals with same function but markedly different properties or chemical substructures
  - Example: a “rheology modifier” may be a thickener or a thinner; these subgroups could be identified via a clustering based on properties



[1]Isaacs et al. (2016) *Toxicology Reports*, 723-732.

[2]Phillips et al. (2017) *Green Chemistry*, 1063-1074.

Examples of Functional Use Categories

- Adhesion promoter (129, 5)
- Antioxidant (221, 46)
- Antistatic agent (409, 10)
- Catalyst (171, 4)
- Chelator (167, 60)
- Colorant (657, 98)
- Crosslinker (491, 15)
- Emollient (467, 72)
- Emulsifier (495, 110)
- Emulsion stabilizer (154, 54)
- Film forming agent (290, 46)
- Flame retardant (124, 7)
- Fragrance (2707, 311)
- Heat stabilizer (63, 2)
- Humectant (130, 46)
- Lubricating agent (88, 30)
- Oxidizer (38, 11)
- pH stabilizer (106, 30)
- Plasticizer (204, 23)
- Preservative (181, 62)
- Rheology modifier (87, 27)
- Skin conditioner (848, 103)
- Solvent (372, 131)
- Surfactant (855, 384)
- UV absorber (133, 6)
- Viscosity control agent (561, 70)
- Whitener (14,1)

First number: Number of Functional Use Database chemicals in the functional group
Second number: Number of SCIL chemicals identified by ORD's Functional Use Database

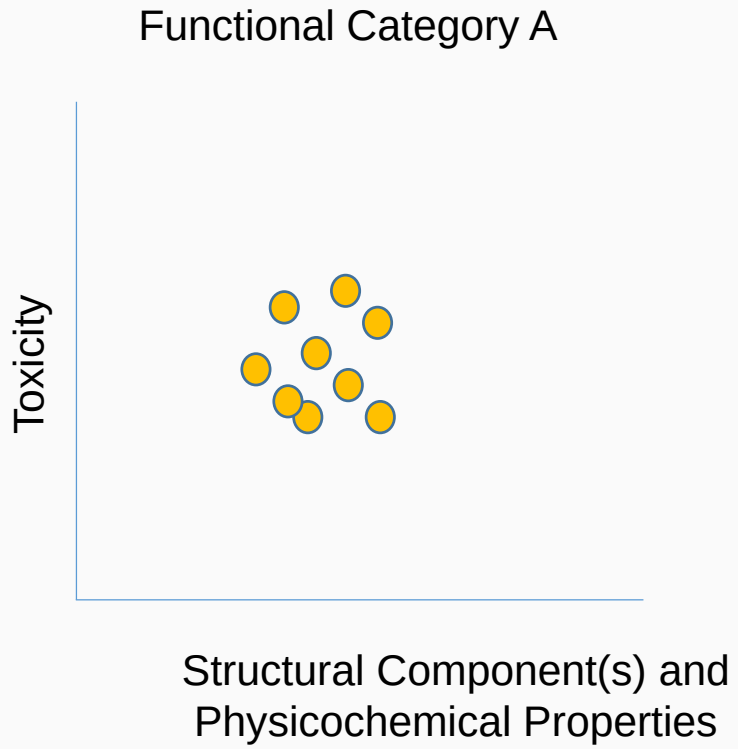
Goal in Applying this Approach

- Identify clusters of structurally and functionally related chemicals
- Provide a spectrum of functional options across a range of toxicities
- Identify potential high priority and low priority chemicals

➢ *Goals could be addressed through tailored Quantitative Structure Use Relationship (QSUR) models for function*

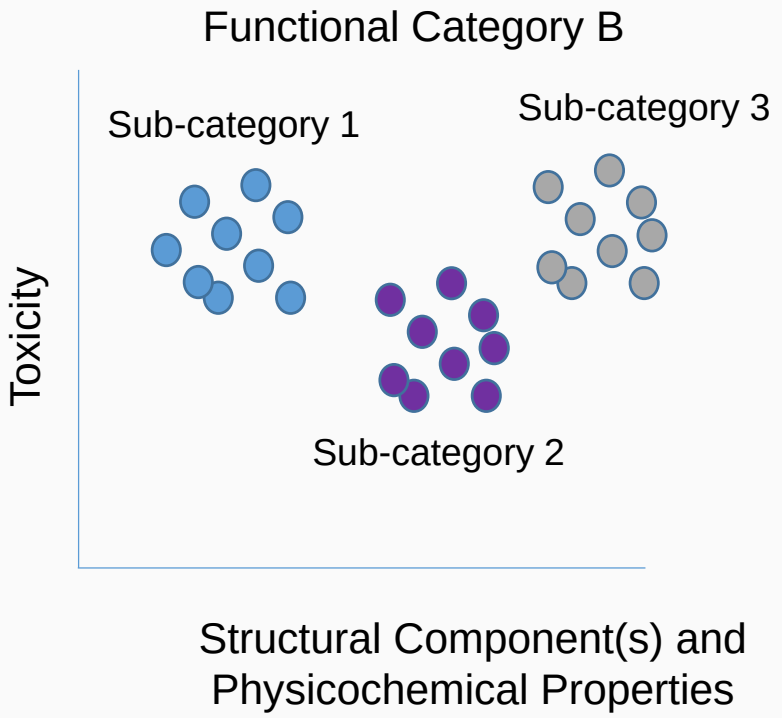
QSUR Model for a Homogeneous Functional Category

A cluster of chemicals with a common physical property that drives its functionality

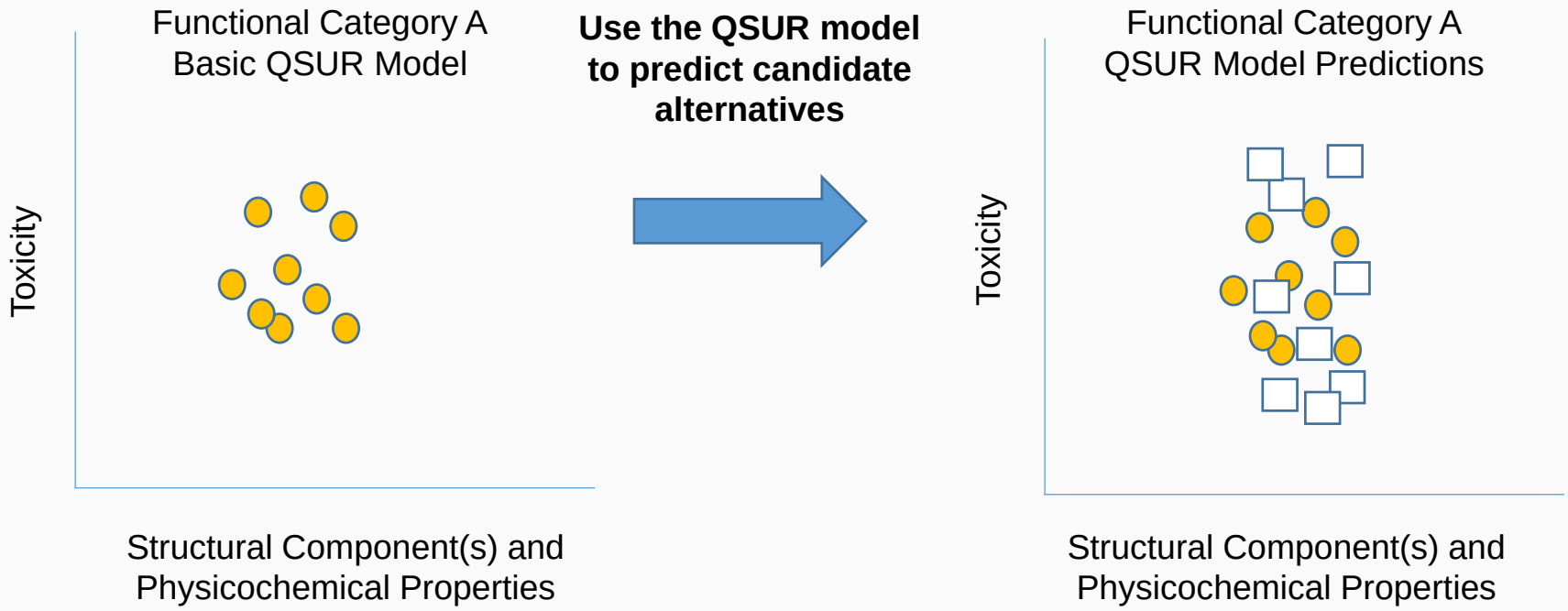


QSUR Model for Heterogeneous Functional Category

Several clusters of chemicals, each with a distinct physical property that drives function

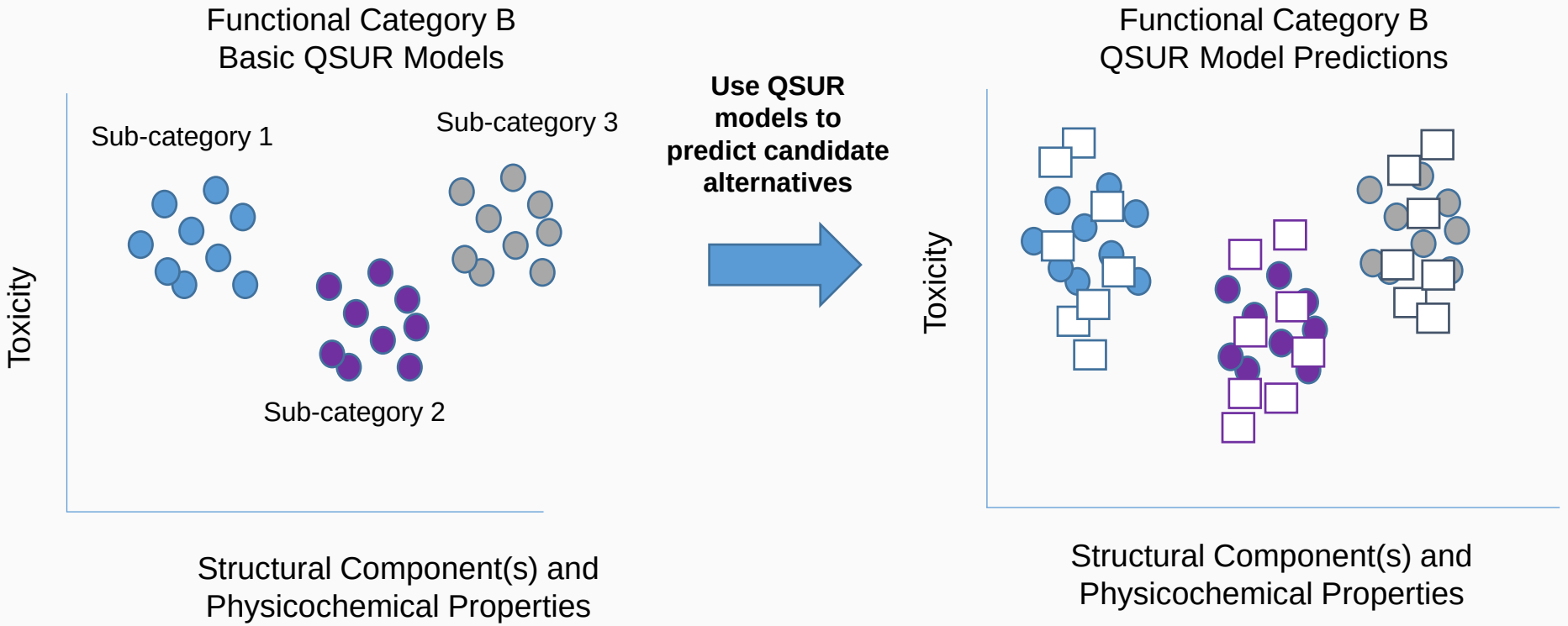


Applying QSUR Model for a Homogeneous Category to Existing Chemicals



- Chemical with known functional use
- Chemicals from the TSCA inventory that are predicted by the QSUR to be functionally similar

Applying QSUR Models for a Heterogeneous Category to Existing Chemicals



Methodology

Once existing chemicals have been filtered through the FUse database and QSUR modeling…

- Step 1: Select a functional use category:
  - Explore low hazard alternatives
  - Identify chemicals that may pose a concern in a given class
  - Focus on chemicals with highest exposures
- Step 2: Identify candidate chemicals in the category for prioritization:
  - Filter based on hazard and exposure
  - Use tools such as high-throughput screening

Benefits

- Takes advantage of tools that EPA ORD has developed and lessons learned from SCIL development
- Compatible with OECD functional use categories and New Chemical Program categories
- Could be used with a variety of hazard metrics
- Could provide a resource for chemical manufacturers and product formulators:
  - Increases the likelihood of the availability of alternative chemicals
  - Addresses uncertainty in the marketplace
  - Stakeholder input could confirm viability of alternatives

Caveats

- Functional uses are based on publicly available information—i.e., chemicals may have additional functional uses that are not captured in databases
- Current ORD QSUR approaches would have to be rebuilt to use this methodology
- This high-throughput approach may not be useful for functional categories with unique chemistries
- A focus on structurally similar chemicals may not always identify safer alternatives
- This approach would be most effective when paired with other organizing approaches

Thank you