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.
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

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\(^1\) Isaacs et al. (2016) *Toxicology Reports*, 723-732.

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 (141)

**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

- Functional Category B
  - Sub-category 1
  - Sub-category 2
  - Sub-category 3

- Structural Component(s) and Physicochemical Properties

- Chemical with known functional use
Applying QSUR Model for a Homogeneous Category to Existing Chemicals

Functional Category A
Basic QSUR Model

Use the QSUR model to predict candidate alternatives

Functional Category A
QSUR Model Predictions

Toxicity

Structural Component(s) and Physicochemical Properties

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

Functional Category B
Basic QSUR Models

Use QSUR models to predict candidate alternatives

Toxicity

Structural Component(s) and Physicochemical Properties

Chemical with known functional use

Chemicals from the TSCA inventory that are predicted by the QSUR to be functionally similar
Methodology

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

• Step 1: Select a functional use category:
  o Explore low hazard alternatives
  o Identify chemicals that may pose a concern in a given class
  o Focus on chemicals with highest exposures

• Step 2: Identify candidate chemicals in the category for prioritization:
  o Filter based on hazard and exposure
  o 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