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POSSIBLE FUTURE APPLICATIONS OF EMERGING CONCEPTS

QSURs and AEPs

5th Meeting of the Working Party on Exposure Assessment

June 28 – 29, 2021

United States Environmental Protection Agency

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QUANTITATIVE STRUCTURE-USE RELATIONSHIPS

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United States Environmental Protection Agency

CHEMICAL-RELATED USES FOR EXPOSURE SCIENCE

- **Functional Use**:

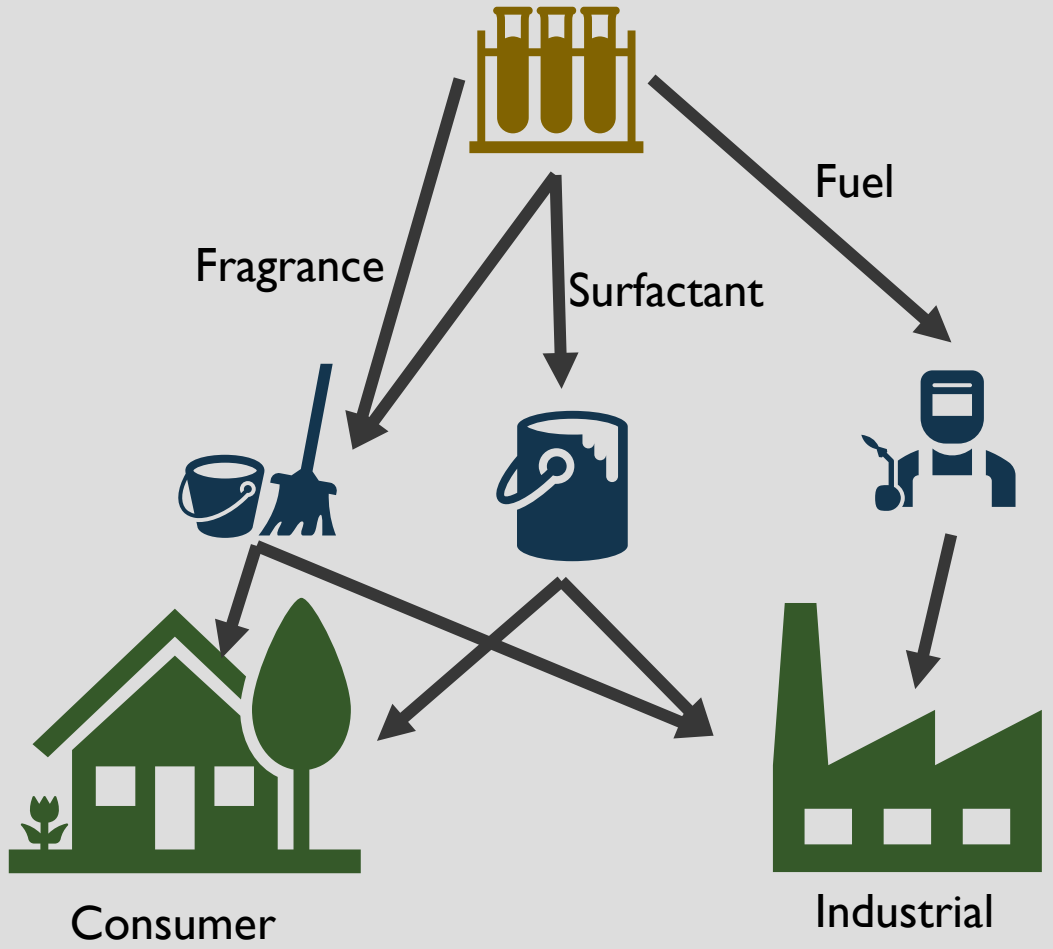
  roles a chemical can serve in products or processes due to its structure and properties

- **Product Use**:

  role of products or processes in which a chemical is used

- **Sector of Use**:

  groups which use a chemical (i.e., industrial process *versus* consumer product)



Tickner et al., *Environ. Sci. Technol.*, 2015

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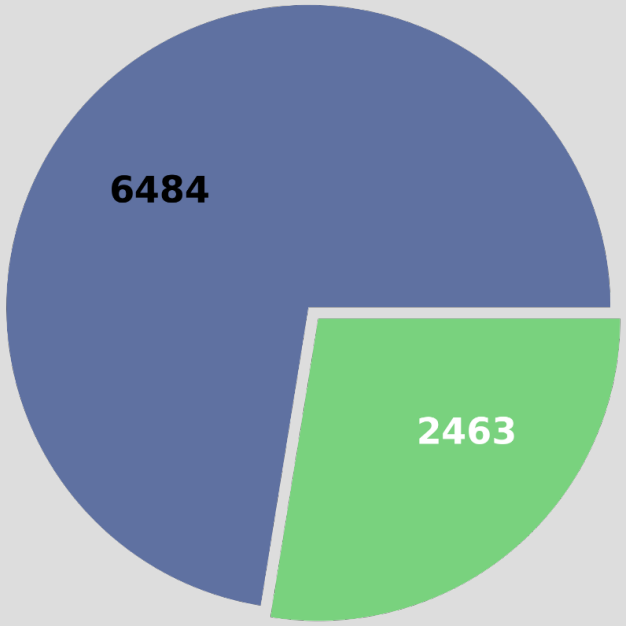
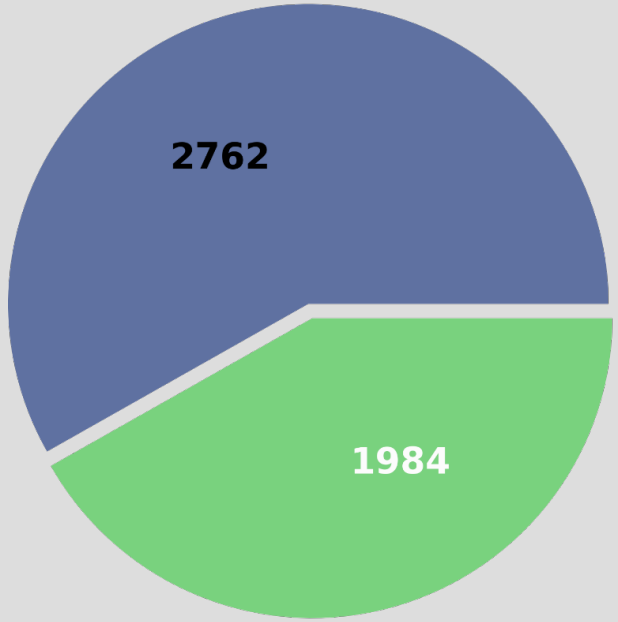
USE DATA ARE LIMITED

TOX21 CHEMICAL LIBRARY



TOXCAST CHEMICAL LIBRARY



Chemicals ***with*** functional use information

Chemicals ***without*** functional use information

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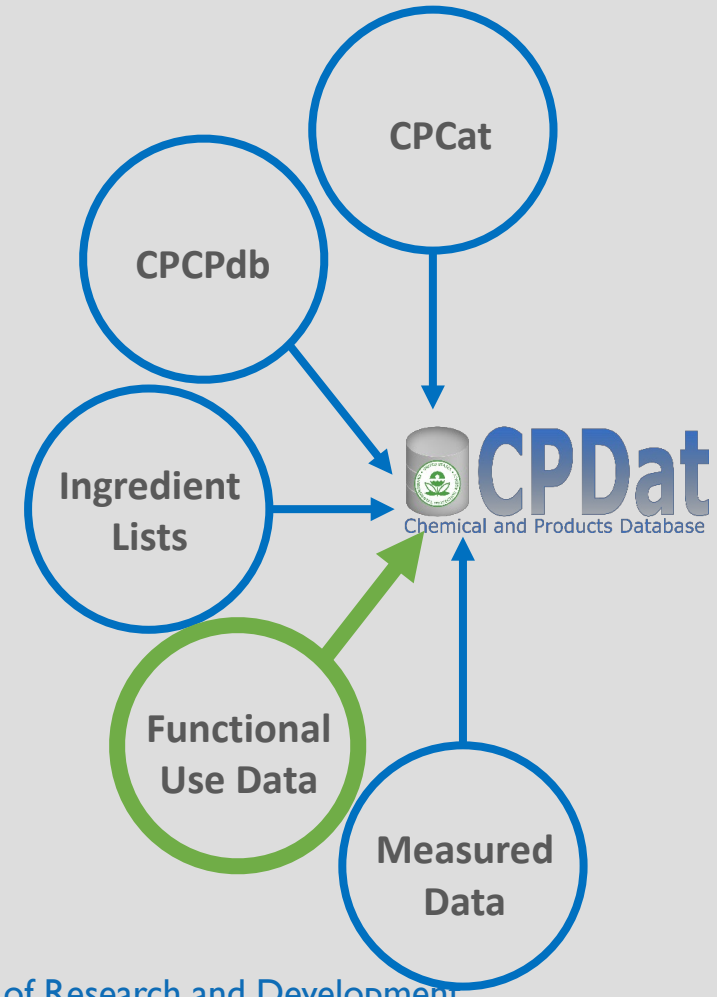
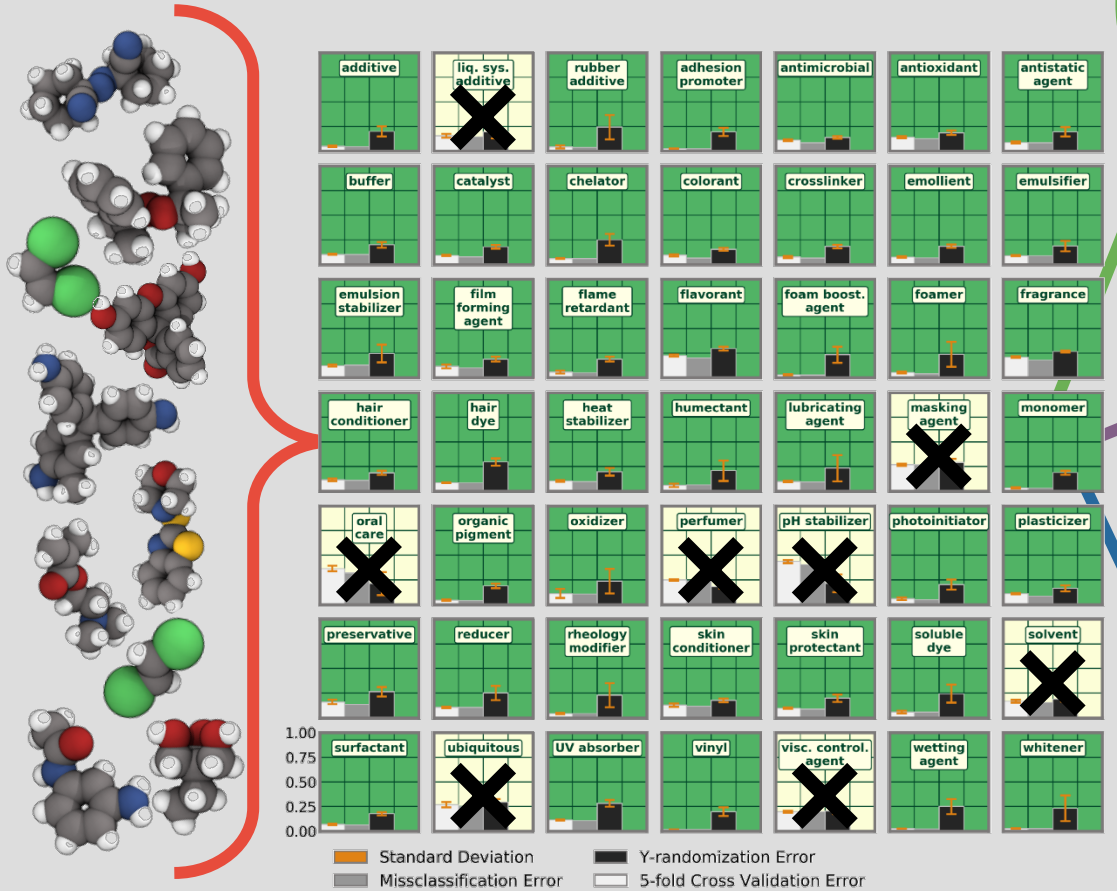
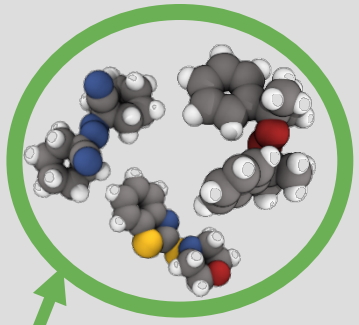
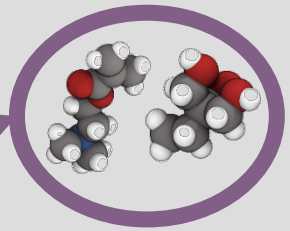
PREDICTING USE WHEN NEEDED



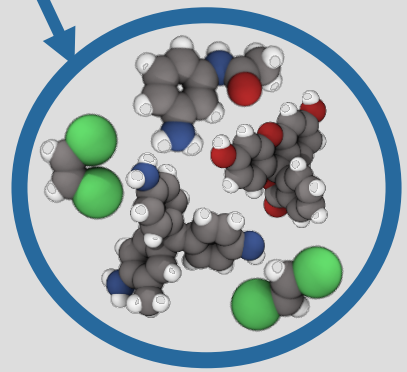




Catalysts



Crosslinkers



Colorants

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Phillips et al., *Green Chem.*, 2017

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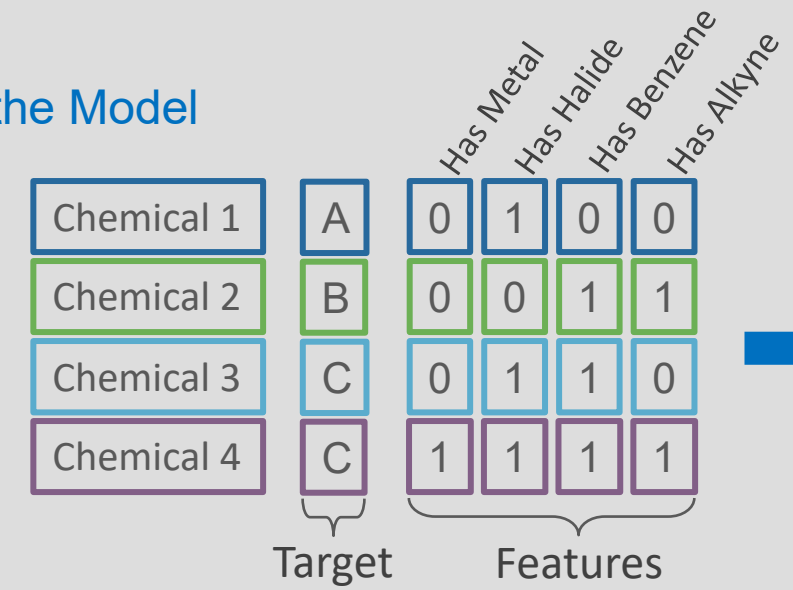
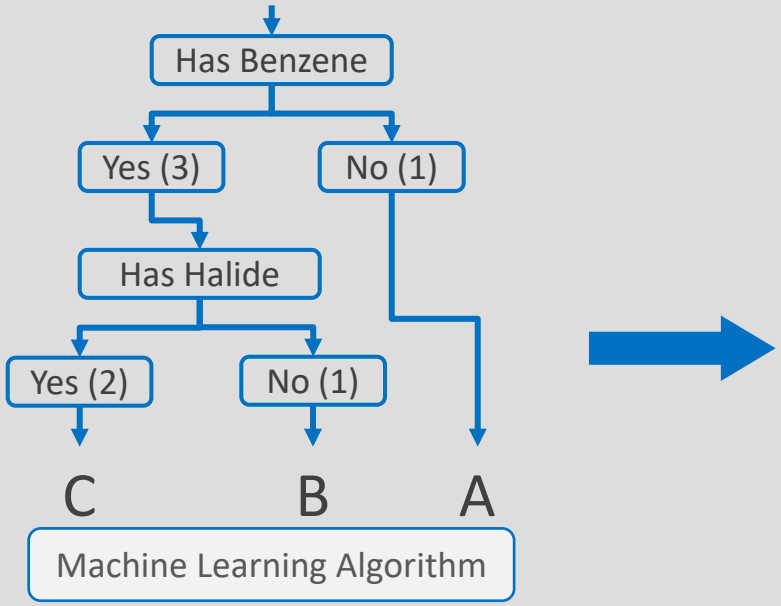
BRIEF OVERVIEW OF QSURS

Train the Model

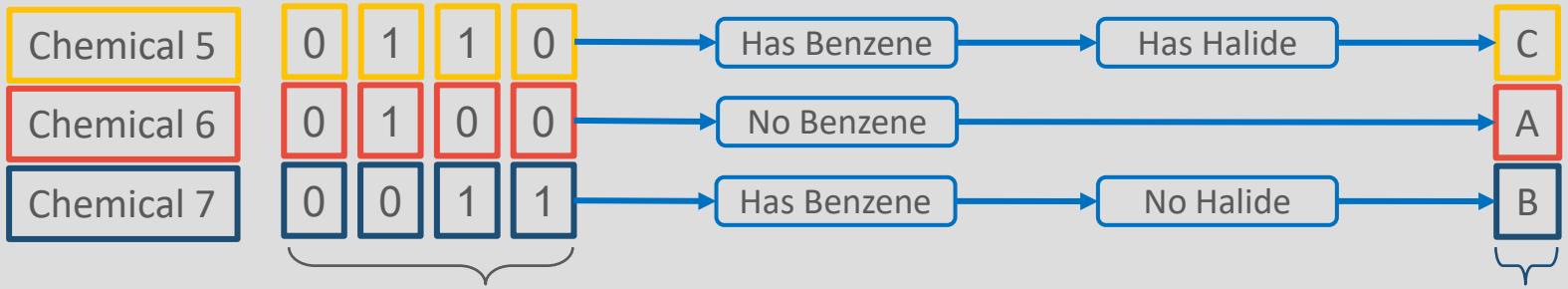




Valid models **must**:

- accurately predict the training set
- predict beyond the training set
- be more predictive than a model built on randomized data

Predict with the Model



Predict target with ***valid*** models using features

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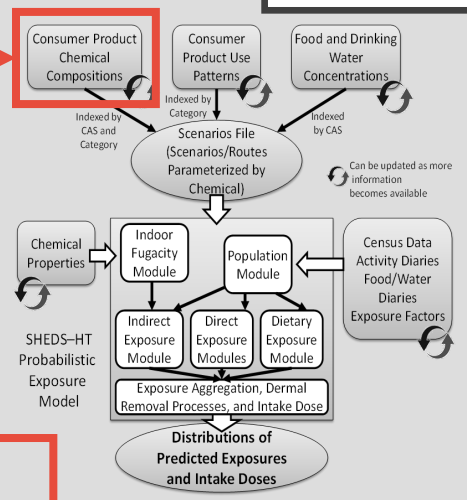
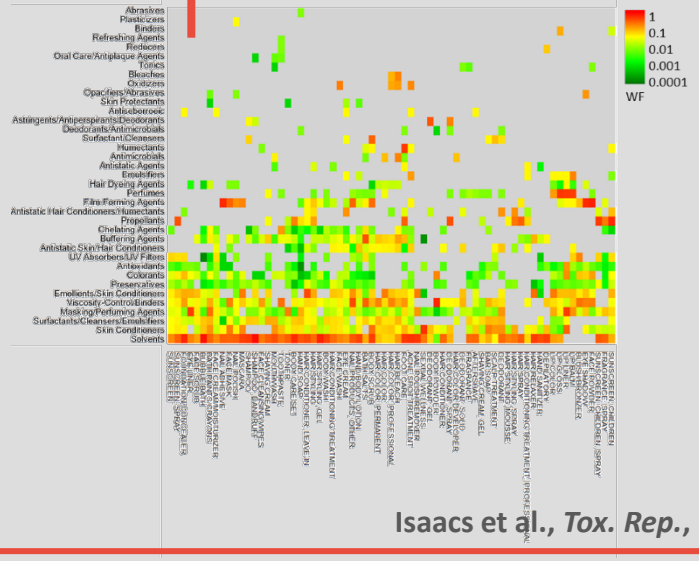
APPLICATIONS OF QSURS

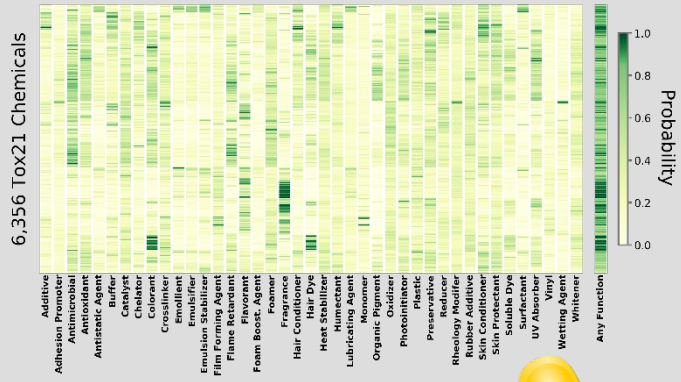


Isaacs et al., *Env. Sci. & Tech.*, 2014



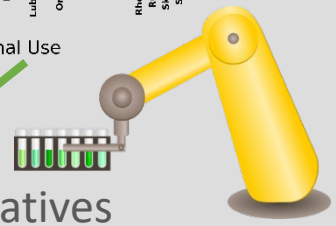
Isaacs et al., *Tox. Rep.*, 2016

Functional Substitutes

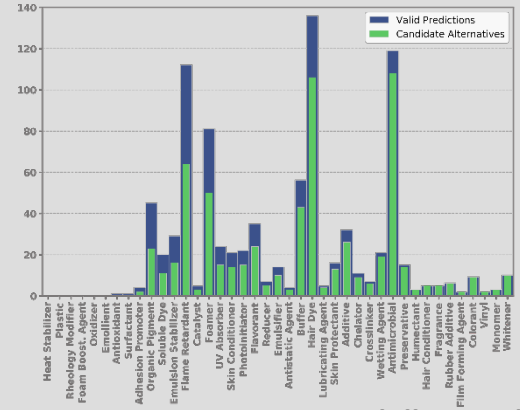


Threshold Bioactivity

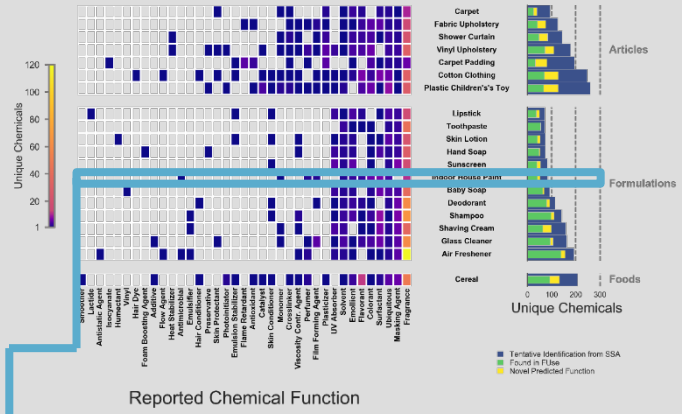
Functional Use



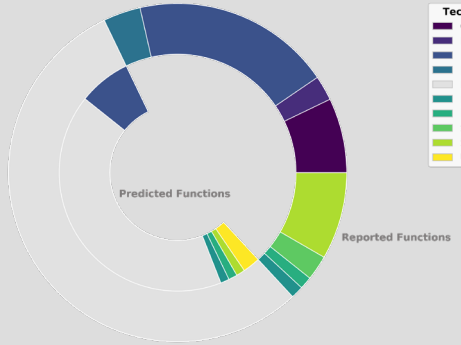
Candidate Alternatives



Phillips et al., *Green Chem.*, 2017



Reported Chemical Function



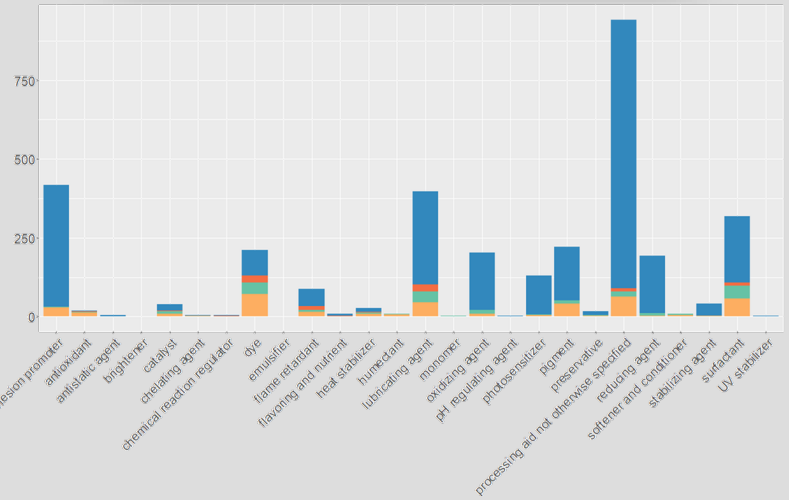
Phillips et al., *Environ. Sci. & Tech.*, 2018

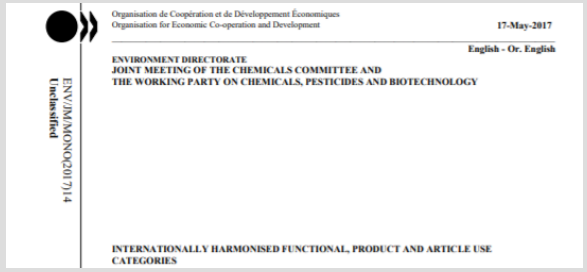
Exposure Estimate Parameterization

Alternatives Screening

Suspect Screening Identification

EFFORTS TO ADVANCE QSURS

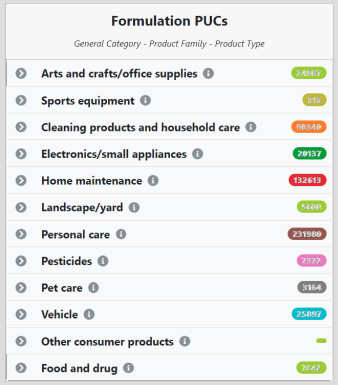


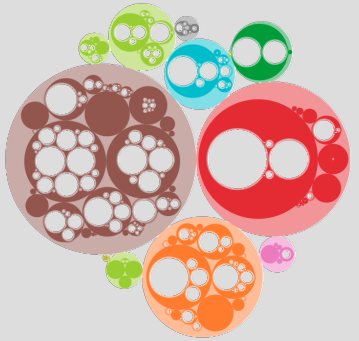

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development
17-May-2017
English - Or. English
ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY
Unclassified
ENV/JM/MONO(2017)14
INTERNATIONALLY HARMONISED FUNCTIONAL, PRODUCT AND ARTICLE USE CATEGORIES

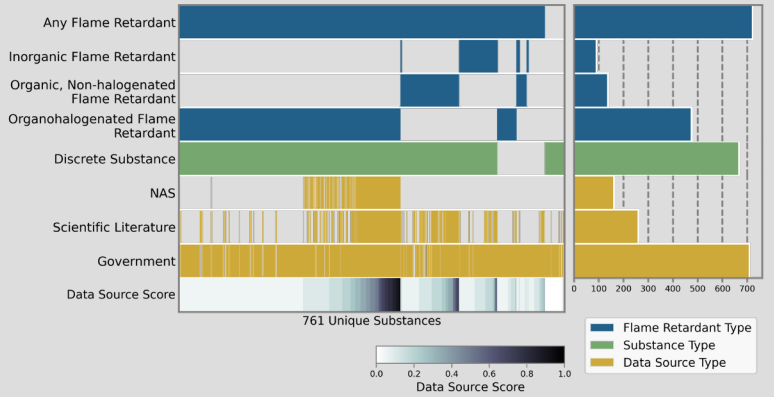
Welcome to Factotum

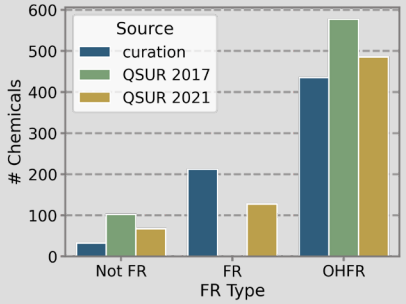
Documents	Products	Extracted Chemicals
528,431	701,506	3.9 million

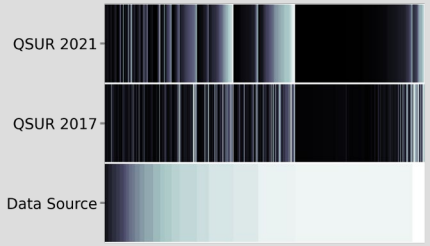
Products Linked To PUCs	Curated Chemical Records	Unique DTXSIDs
610,256	2.5 million	31,009











Evaluate with Government Data

Rebuild Models on New Information

Refine QSURs for Specific Needs

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*Trainee

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Aggregate Exposure Pathway: A framework for organizing exposure and dosimetry information

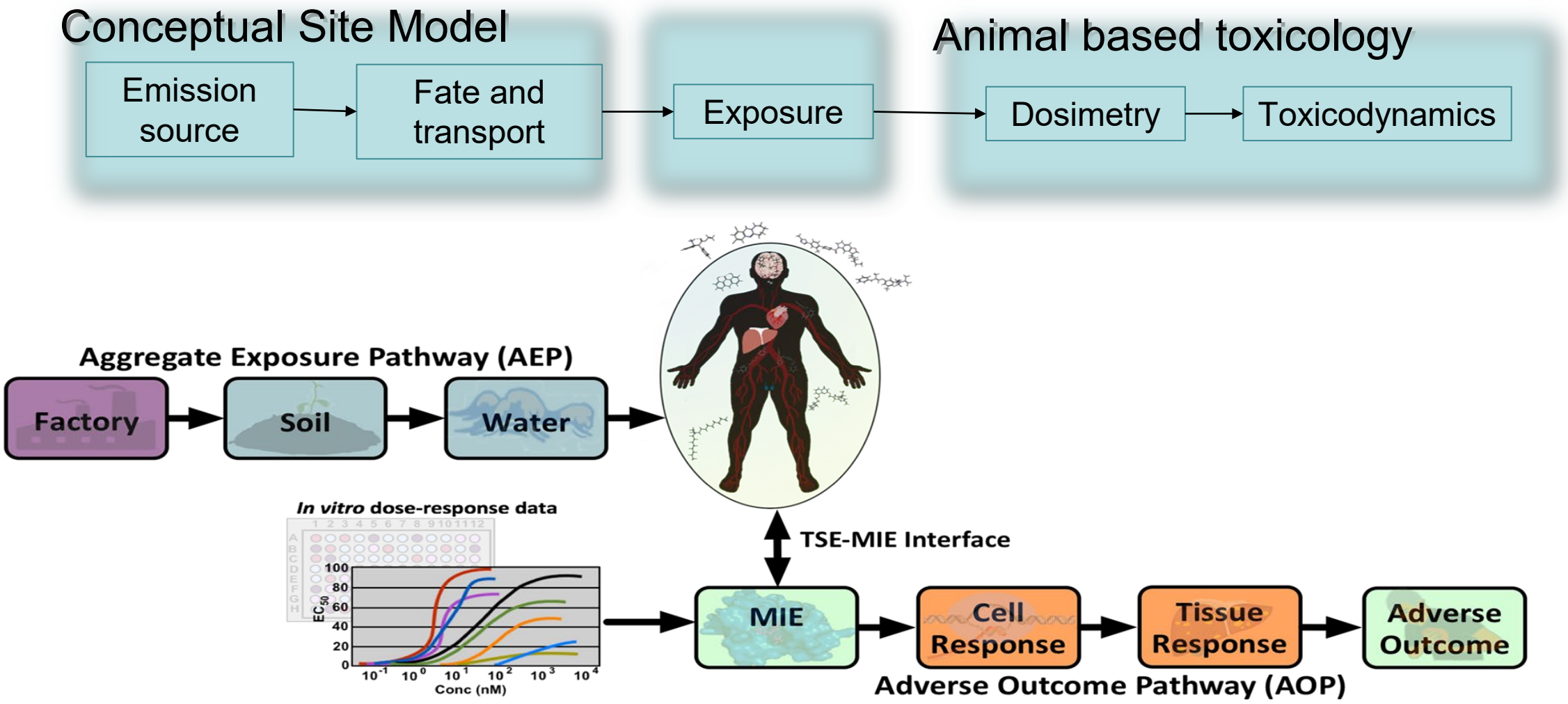
Completing the Link between Exposure Science and Toxicology for Improved Environmental Health Decision Making: The Aggregate Exposure Pathway Framework Environ Sci Technol,2016, 50(9): 4579-4892

- The Aggregate Exposure Pathway (AEP) concept was inspired by the Adverse Outcome Pathway (AOP).
  - Uses the same concepts of nodes (key exposure states) and edges (processes),
  - Ends where the AOP begins, and
  - AEP-AOP combined pathways map the entire source to outcome pathway.
- Aggregate Exposure Pathways differ from AOPs.
  - Chemical specific, and
  - Include chemical transformations.
- A similar concept to the earlier Conceptual Site Model.
  - AEP includes exposure, metabolism, and dosimetry and Conceptual Site Models do not.

A structured representation of exposure events The Aggregate Exposure Pathway (AEP)

- Connection between a **source** & a **target site exposure.**
- Processes considered
  - **Release from a source, environmental fate and transport, interaction of the receptor and exposure media, dose intake, adsorption, metabolism, transport, and excretion.**
- Does not include toxicity but gives the **target site exposure** (dose metric for the molecular initiating event).

A different way of dividing up the source to outcome continuum



Using the Aggregate Exposure Pathway

- The aggregate exposure pathway emphasizes the need to integrate exposure and PK models of dosimetry in risk assessments when toxicity is based on *in vitro* methods.
- Combined AEP-AOP pathways provide a basis for biologically-based-dose-response models
  - AEP covers the kinetics and AOP covers the dynamics portion of the modeling.
- Combined AEP-AOP pathways provide a bases for modeling source-to-outcome processes that determine risk.
- Combined AEP-AOP networks provide a basis for modeling chemical interactions and for characterizing risks from combined exposures.