Computational Exposure Science at the Environmental Protection Agency's Office of Research & Development

Presentation to the American Chemistry Council's Long Range Initiative Strategic Science Team

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Disclaimer: The views expressed in this presentation are those of the author and do not reflect the views or policies of the U.S. Environmental Protection Agency.

United States Environmental Protection Agency

Evolving Emphasis on Exposure Science

- TT21: Exposure must be integrated with toxicity testing at every step of risk assessment to guide development and use of toxicity information
- Predictive models are needed to screen chemicals based on exposure
- ExpoCast created to complement ToxCast by building on the technological and computational advances in exposure science
- Our goal has been to advance the characterization of exposure to inform chemical prioritization for evaluation as well as to translate results of high-throughput toxicity testing

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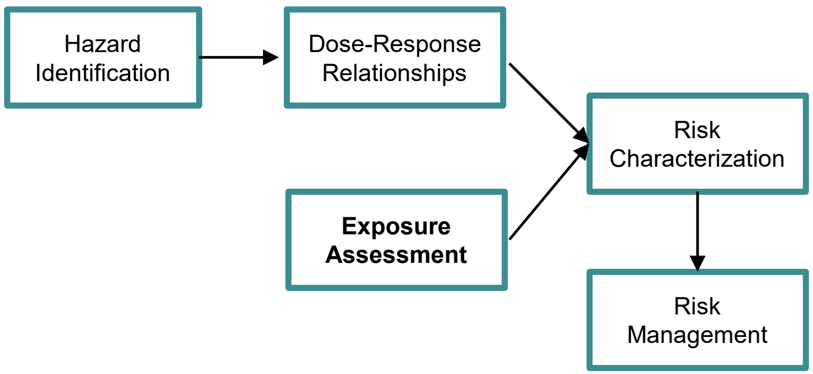
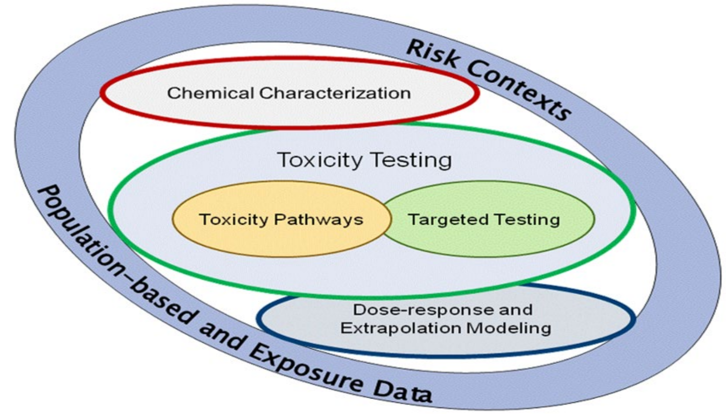
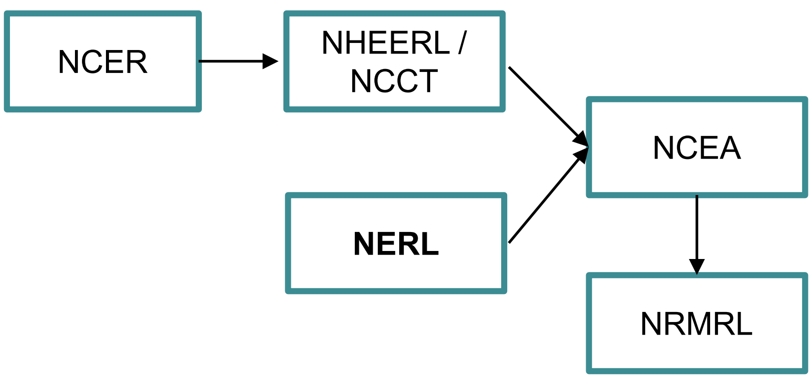
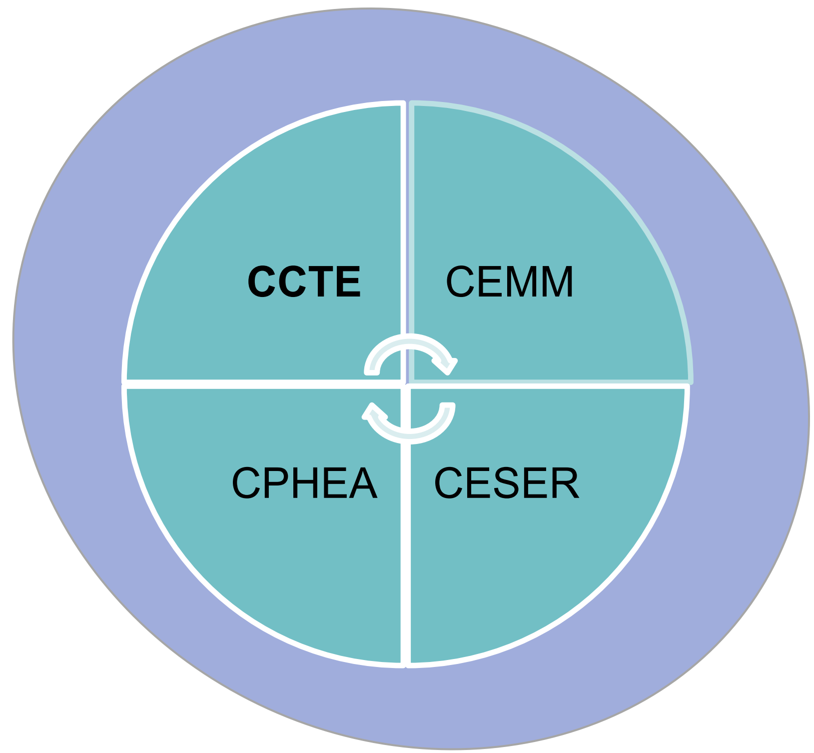
Transition to 21st Century Risk Assessment









https://www.epa.gov/sciencematters/epas-office-research-and-development-reorganizes-better-support-epas-mission

Center for Computational Toxicology and Exposure: Integrated Disciplines

CCTE works to support Agency decisions by providing solutions-driven research to rapidly evaluate the potential human health and environmental risks. CCTE research strives to:

- Reduce the time required to thoroughly test chemicals and emerging materials for human and ecological toxicity from years to months.
- Expand our understanding of quantitative human and ecological exposures for thousands of chemicals and emerging materials.
- Develop a comprehensive system of actionable chemical safety and ecological data with the software tools to integrate them for a range of human health and environmental decisions.
- Demonstrate translation of CCTE data, models, and tools into regulatory decisions by EPA Program Offices, EPA Regions, and States to protect human health and the environment.

Using the knowledge and tools developed from this research, CCTE performs rapid chemical screening and evaluation that allows thousands of chemicals to be evaluated for potential risk in a very short amount of time. The data and tools produced by CCTE researchers are intended to help Region and Program Offices, states, tribes, and communities make decisions to sustain a healthy society and environment.

- Center for Computational Toxicology and Exposure (CCTE)
  - Evaluates chemical toxicity through a variety of novel methods, including HTT, AOPs, VTM, and ETAM
  - Models chemical exposure (Rapid Exposure Modeling and Dosimetry, ExpoCast) to contextualize hazard
  - Disseminates chemical toxicity and exposure data and predictive tools (e.g., through the “CompTox Chemistry Dashboard”)
- CCTE has Four Divisions
  - Biomolecular & Computational Toxicology Division
  - **Chemical Characterization & Exposure Division**
  - Great Lakes Toxicology & Ecology Division
  - Scientific Computing & Data Curation Division

https://www.epa.gov/aboutepa/about-center-computational-toxicology-and-exposure-ccte

Chemical Characterization and Exposure Division (CCED)

CCED) performs research to develop and advance experimental chemistry approaches that are critical to the rapid characterization of the presence, structural characteristics, and properties of chemicals that are of interest to EPA scientists due to their potential environmental fate and toxicity. In addition to chemical characterization, CCED develops computational models to predict external exposure and internal doses for large numbers of chemicals based on minimal data.

CCED strives to reduce the time to conduct toxicity and exposure assessments from years to months by developing:

- Chemoinformatic tools and knowledgebases
- Rapid analytical methods for identifying environmental chemicals in environmental and biological samples
- Predictive models of both exposure and dose for environmental chemicals
- Absorption, Distribution, Metabolism and Excretion approaches for environmental chemicals and model parameterization

Examples of Research in CCED:

- ExpoCast
- HTTK R Package
- Non-Targeted Analysis Collaborative Trial (ENTACT)
- CompTox Chemicals Dashboard
- Chemical and Products Database (CPDat)
- DSSTox
- Toxicity Estimation Software Tool
- Adverse Outcome Pathway

Predicting screening-level population exposure and intake dose rates by strengthening linkages from structure, to function, to use scenarios, to dose by combining information on:

- Chemical properties
- Product formulations
- Mechanistic fate and transport processes
- Consumer behavior informatics
- Improved methods for extrapolating across chemicals

https://www.epa.gov/aboutepa/about-chemical-characterization-and-exposure-division

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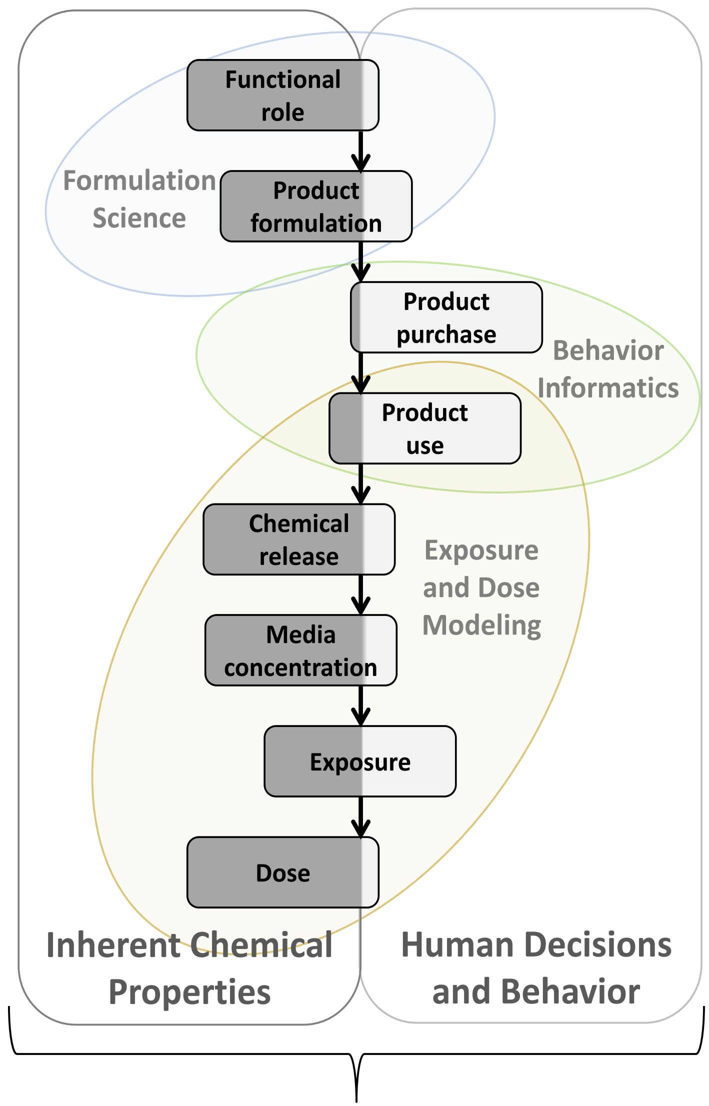
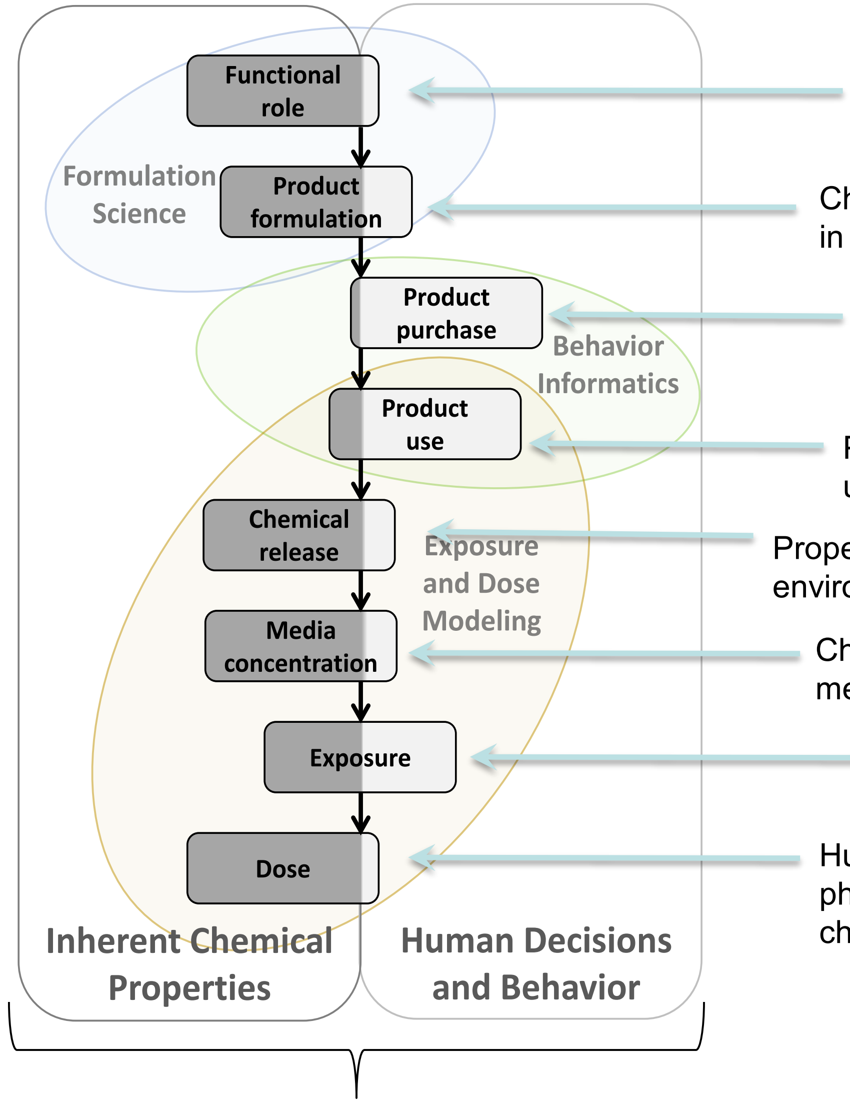
Computational Exposure Science: Integrating Data Streams and Models



High-throughput Predictions of Population-Level Chemical Exposures and Intake

Egeghy et al., EHP, 2016

Computational Exposure Science: Integrating Data Streams and Models



Datasets

- Chemical molecular structures and chemical function
- Chemical end-use including presence in consumer products
- Population patterns of consumer product purchasing
- Patterns of consumer product use
- Properties of homes and indoor environments
- Chemicals measured in residential media
- Human activity patterns and exposure factors
- Human physiology and pharmacokinetic properties of chemicals

High-throughput Predictions of Population-Level Chemical Exposures and Intake

Computational Exposure Science: Integrating Data Streams and Models

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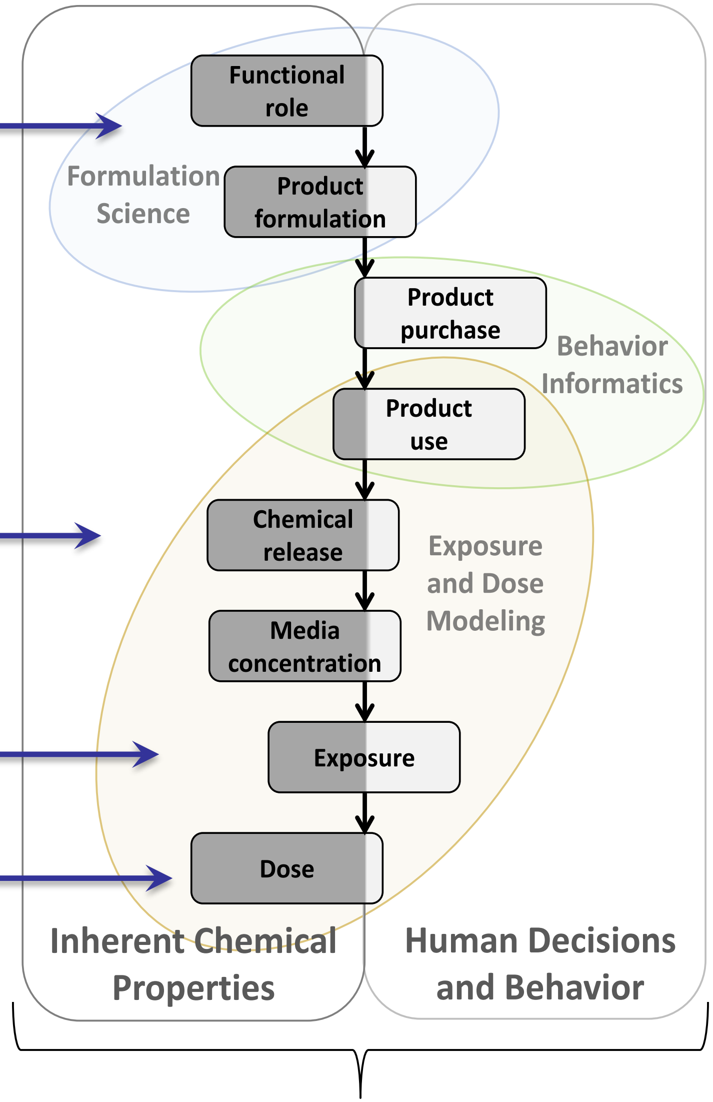
Models

Models predicting chemical function from chemical properties or structures

Models describing fate and transport of chemicals within a residence

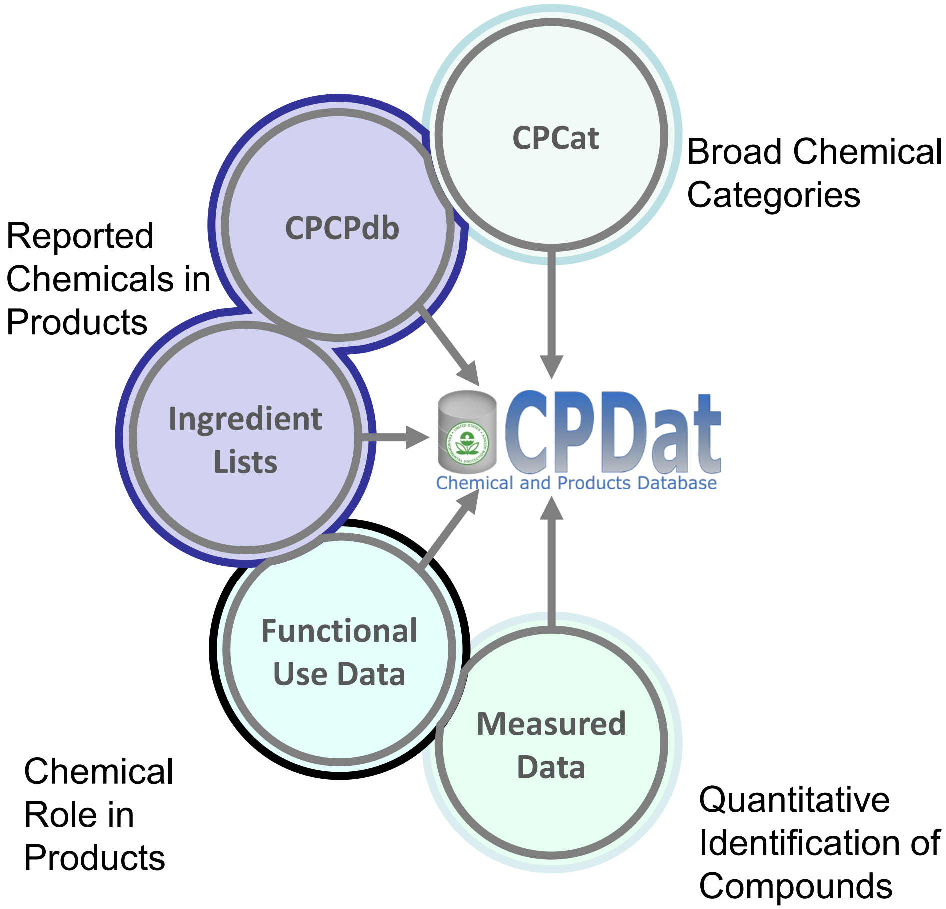
Probabilistic human exposure models

Dosimetry/ pharmacokinetic models



High-throughput Predictions of Population-Level Chemical Exposures and Intake

The Chemicals and Products Database (CPDat)

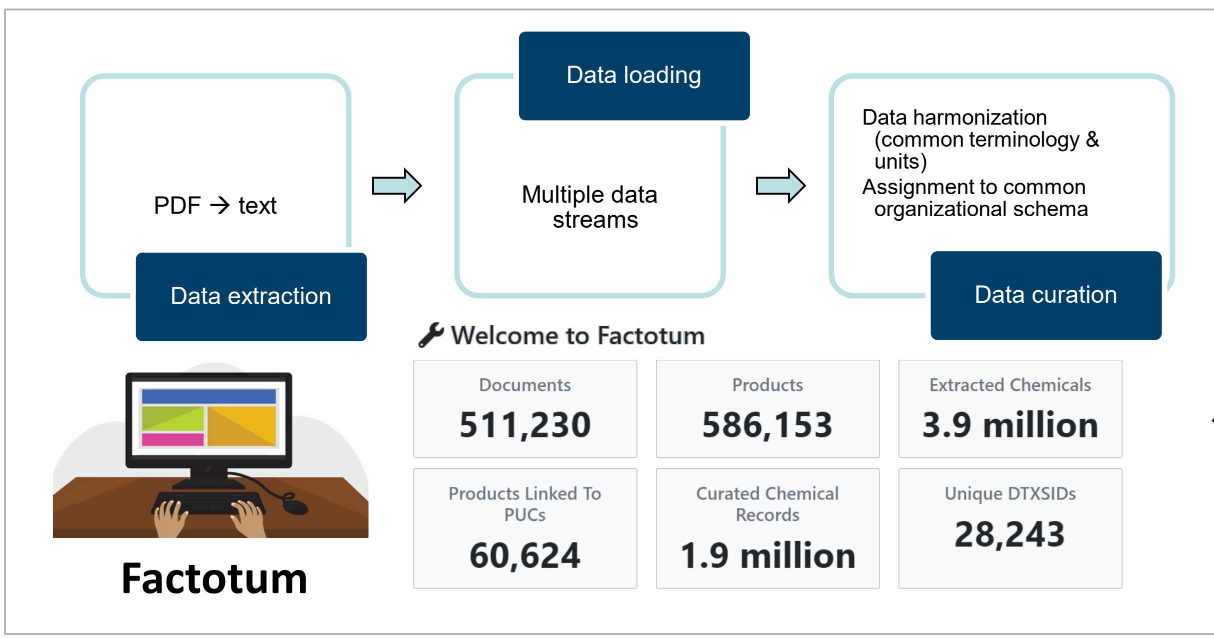


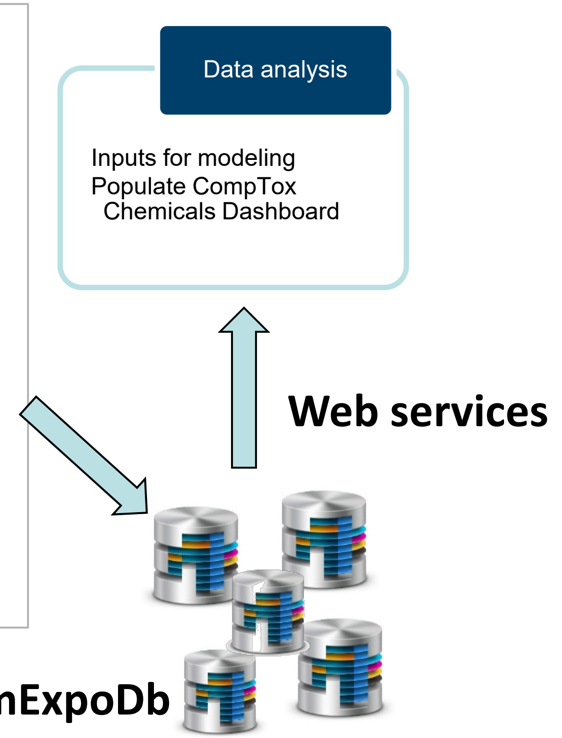
- ~60,000 chemicals
- ~16,000 products
- ~300 consumer product categories

Dionisio et al., Sci Data, 2018
Isaacs et al., JESEE, 2018
Phillips et al., Green Chem, 2017
Phillips et al., ES&T, 2018

ChemExpoDB/Factotum

- Factotum- web interface for exposure data curation
- ChemExpoDb – integrated family of databases to hold exposure data (use, monitoring data, product information, toxicokinetic data)
- Internal (and eventually external) webservices are being built to provide data in a machine-readable form to the CompTox Chemicals Dashboard and stakeholders





Courtesy of K. Dionisio

EPA United States Environmental Protection Agency

Refining and Improving Product Use Data

– Developed partnership with retailers and national marketing research companies to obtain geographically-specific data on purchasing habits (use surrogate), including household-level purchasing frequency data
– Refinement of consumer product categories
– Identifying and incorporating other available sources of consumer product use data
  • National Institute of Environmental Health Sciences' Sister Study
  • Small-scale studies
– Still exploring use of innovative web-based **infoveillance** methods

The Sister Study
A Study of the Environmental and Genetic Risk Factors for Breast Cancer
National Institute of Environmental Health Sciences • National Institutes of Health • Department of Health and Human Services

nielsen

Google

Courtesy of T. Buckley

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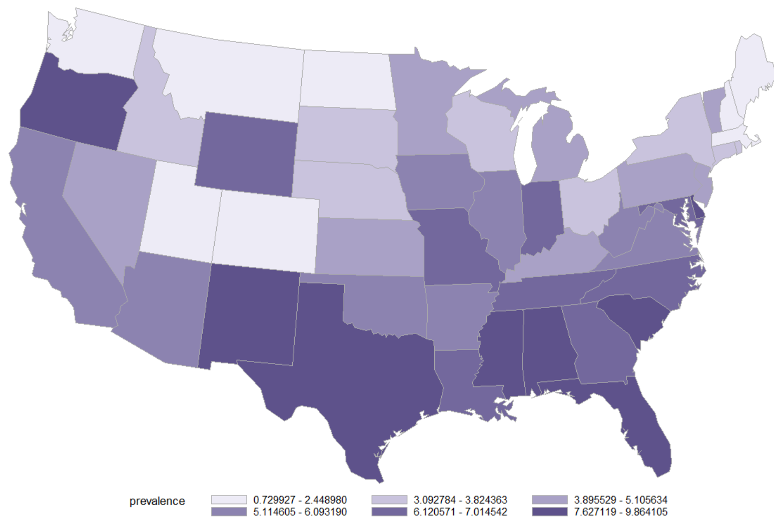
Consumer Product Purchasing Datasets

- Research Question: What chemical-containing products are U.S. households purchasing and in what amounts and how often?
- Methods
  - Collaboration with the Nielsen HomeScan Panel

Insecticide- Ant Killer (Liquid)



- Resulting Data and Ongoing Analyses
  - Longitudinal data for 2012 for 60,000 U.S. households
  - >4 million individual purchases of 200 product types
  - Understanding unique patterns of product purchases: demographic or geographic patterns of high consumer product use or co-occurrence patterns of products
  - Merging databases of consumer product ingredients with product purchase: ultimately identifying chemical co-occurrence patterns and potential cumulative exposures

nielsen

Courtesy of K. Isaacs

Market Basket Analysis of Product Purchase Data

Product Category	Global Rank	Asian	White	Black/ African American	Hispanic	No Children Under 18	Children Under 6	Children Under 13	Children Under 18	Lower Income	Mid Lower Income	Mid Higher Income	Higher Income	Grade and High School Education	College Education	Post College Education
Detergents	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Vitamins	2	0	0	-4	-3	0	-2	-4	-4	0	0	0	0	0	0	0
Hair Care	3	0	0	-6	1	-2	0	1	1	-3	-2	0	0	-1	0	0
Personal Soap and Bath	4	0	-2	2	1	-2	2	1	1	-1	-2	-1	0	-2	0	0
Laundry Supplies	5	-3	1	2	1	1	0	1	1	1	2	1	-1	2	0	-1
Household Cleaners	6	-1	1	2	0	3	-1	1	1	3	2	0	1	1	0	1
Oral Hygiene	7	1	0	2	0	0	-1	0	0	-1	0	0	0	0	0	0
Pet Care	8	-2	0	-7	-3	0	-4	-3	-2	1	0	0	-1	0	0	-1
Skin Care Preps	9	4	0	1	1	-1	0	1	0	-1	-1	-1	1	-1	0	1
Fresheners and Deodorizers	10	-2	0	3	1	1	-1	-2	-1	1	1	1	-1	1	0	-2
Deodorant	11	-2	0	1	1	0	1	1	3	0	0	0	1	0	0	1
Household Supplies	12	1	0	1	-2	0	-3	-3	-2	0	0	0	-1	0	-1	-1
Cosmetics	13	4	0	1	1	0	0	0	1	0	0	0	1	0	1	2
Paper Products	14	0	0	1	1	0	8	5	1	0	0	0	0	0	0	0
Insecticides	15	-2	-1	1	-1	0	-4	-3	-3	0	0	0	-1	0	-1	-1
Stationary & School Supplies	16	1	1	-3	1	-1	2	2	1	0	-1	0	1	-1	1	1
Automotive	17	-1	0	-1	-1	1	-3	-3	-2	0	1	0	-1	1	0	-2
Shaving Needs	18	-1	0	-5	1	0	0	1	1	-3	-3	0	1	0	-1	0
Medications, Remedies	19	3	0	-1	0	0	2	3	3	-1	0	0	0	0	1	2
First Aid	20	-2	-1	3	0	0	-1	-1	-1	2	2	0	-1	0	0	-1
Floral Gardening	21	1	1	-3	-2	0	-2	-3	-3	-2	-1	0	1	0	0	1
Tobacco & Accessories	22	-2	0	-3	-2	0	-2	-1	-1	3	2	0	-2	0	-2	-2
Baby Needs	23	2	0	2	2	0	7	4	3	1	0	0	1	-1	1	1
Fragrances- Women	24	1	0	2	2	0	2	2	2	0	0	0	1	1	1	1
Men's Toletries	25	0	0	-1	0	0	0	0	0	0	0	0	0	0	0	0
Ethnic HABA	26	-3	-3	10	-1	-1	0	0	0	0	0	0	-1	-2	0	0
Hardware, Tools	27	1	1	-1	-1	1	-1	-1	-1	-2	-1	0	1	0	0	0
Feminine Hygiene	28	1	1	1	2	0	1	1	1	1	1	0	0	2	0	0
Elec,Rec,Tape	29	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0

- Figure displays purchase prevalence ranking of product categories in Nielsen
- Colors illustrates the deviation of the category rank for specific demographic groups from global ranks
- Able to look at demographic differences
  - Example: Families with kids under 6 years
    - Upshift in Baby Needs (+7) and Paper Products (+6)
    - Downshift in rodenticides (-4)
- Purchase data combination with information on chemicals in consumer products may be used in high-throughput exposure modeling to screen for populations at potential risk

Courtesy of R. Tornero-Velez

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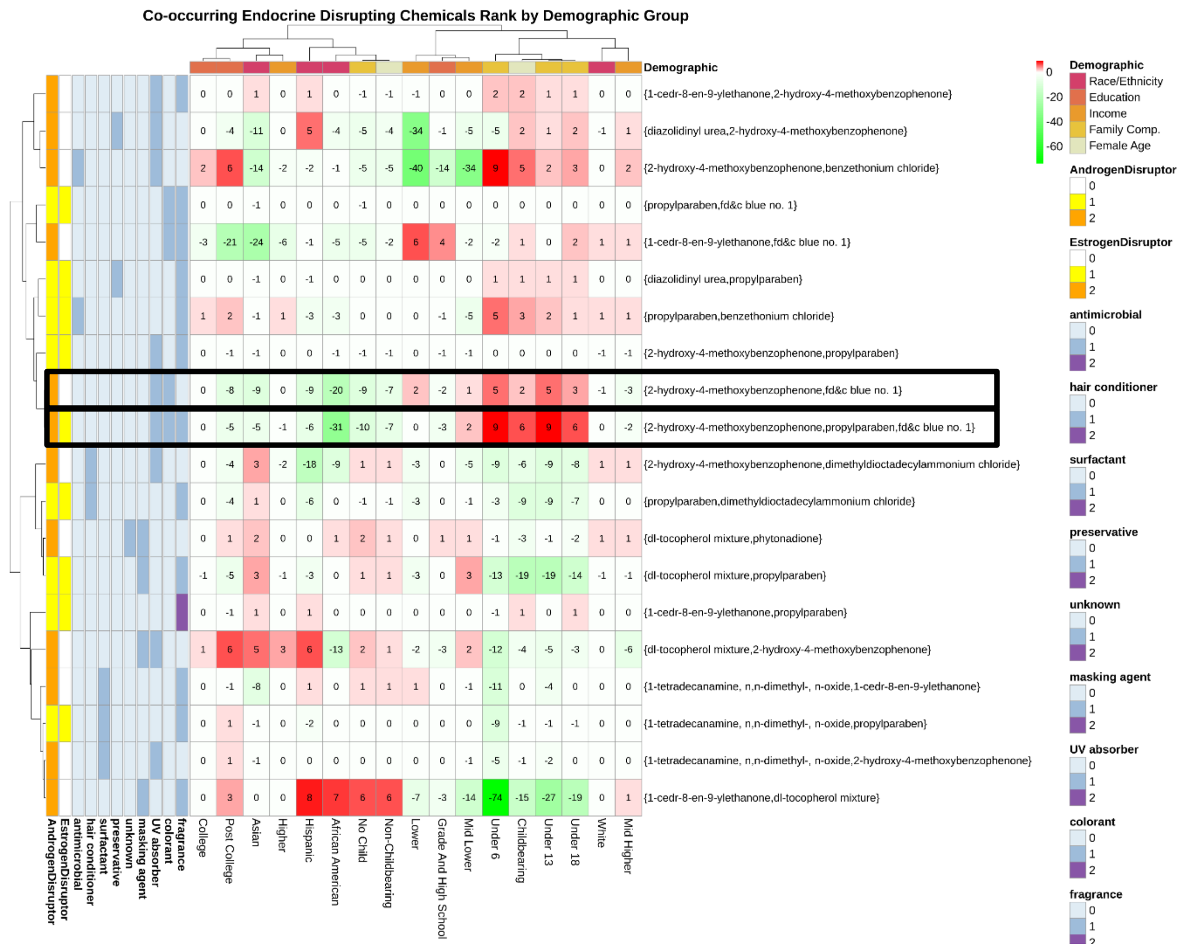
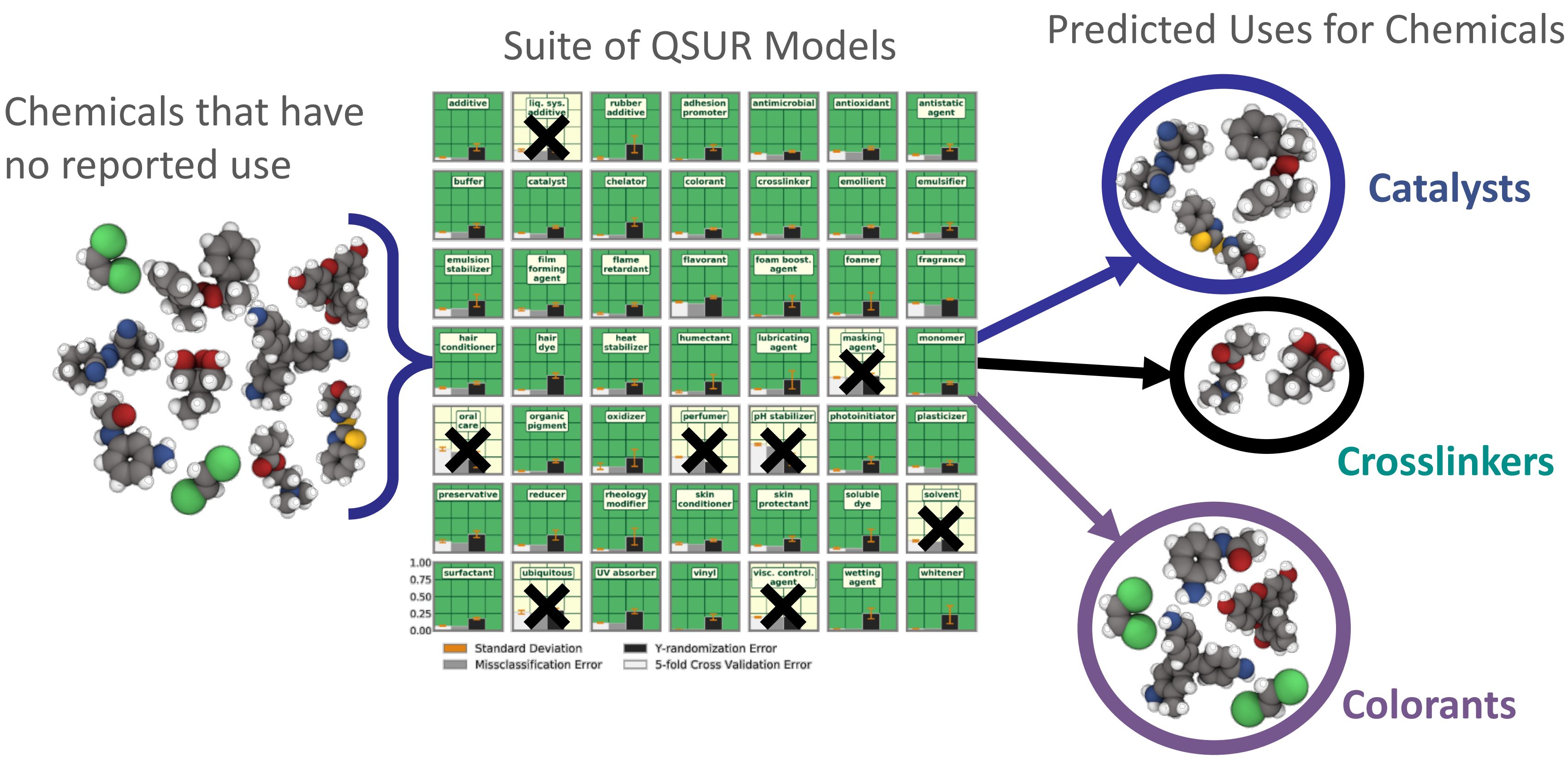
Investigate Product Purchase Data for Co-occurring EDCs

- Top 20 chemical sets occur in ~500 or more household-months
- Cooccurrence example:
- 2-hydroxy-4-methoxybenzophenone
  - used in sunscreens, widespread in things like plastics and toys
- FD&C blue no. 1
  - used in children's medications, cosmetics
- Higher preference: households with children; woman of childbearing age
- Lower preference: African American households



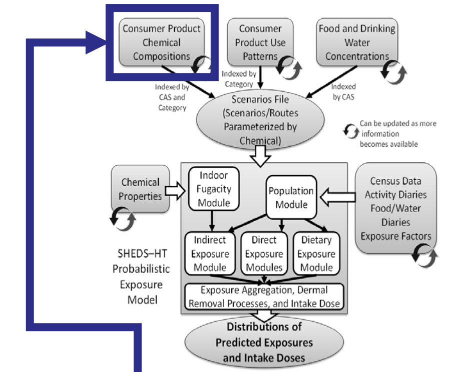
Courtesy of K. Isaacs

Quantitative Structure-Use Relationships (QSURs)

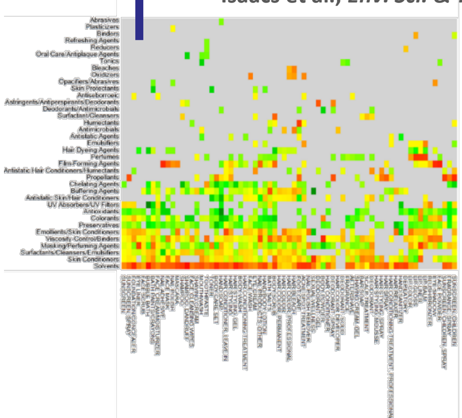


Phillips et al., *Green Chem.*, 2017

Applications of QSURs

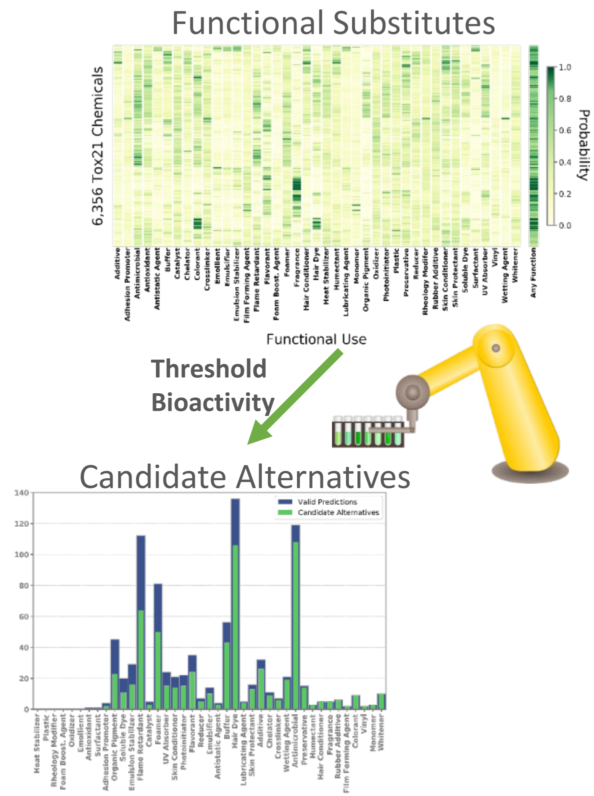


Isaacs et al., *Env. Sci. & Tech.*, 2014



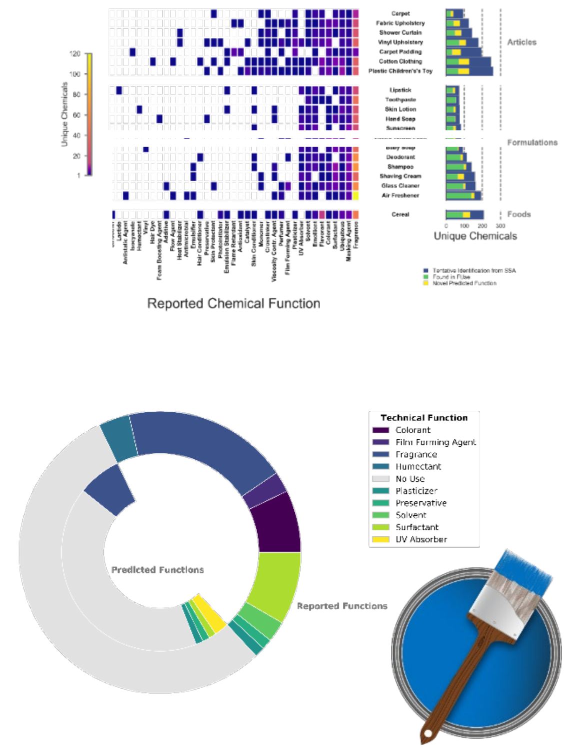
Isaacs et al., *Tox. Rep.*, 2016

Exposure Estimate Parameterization



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

Alternatives Screening



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

Suspect Screening Identification

Courtesy of K. Phillips

SHEDS-High Throughput: Merging Multiple Data Streams

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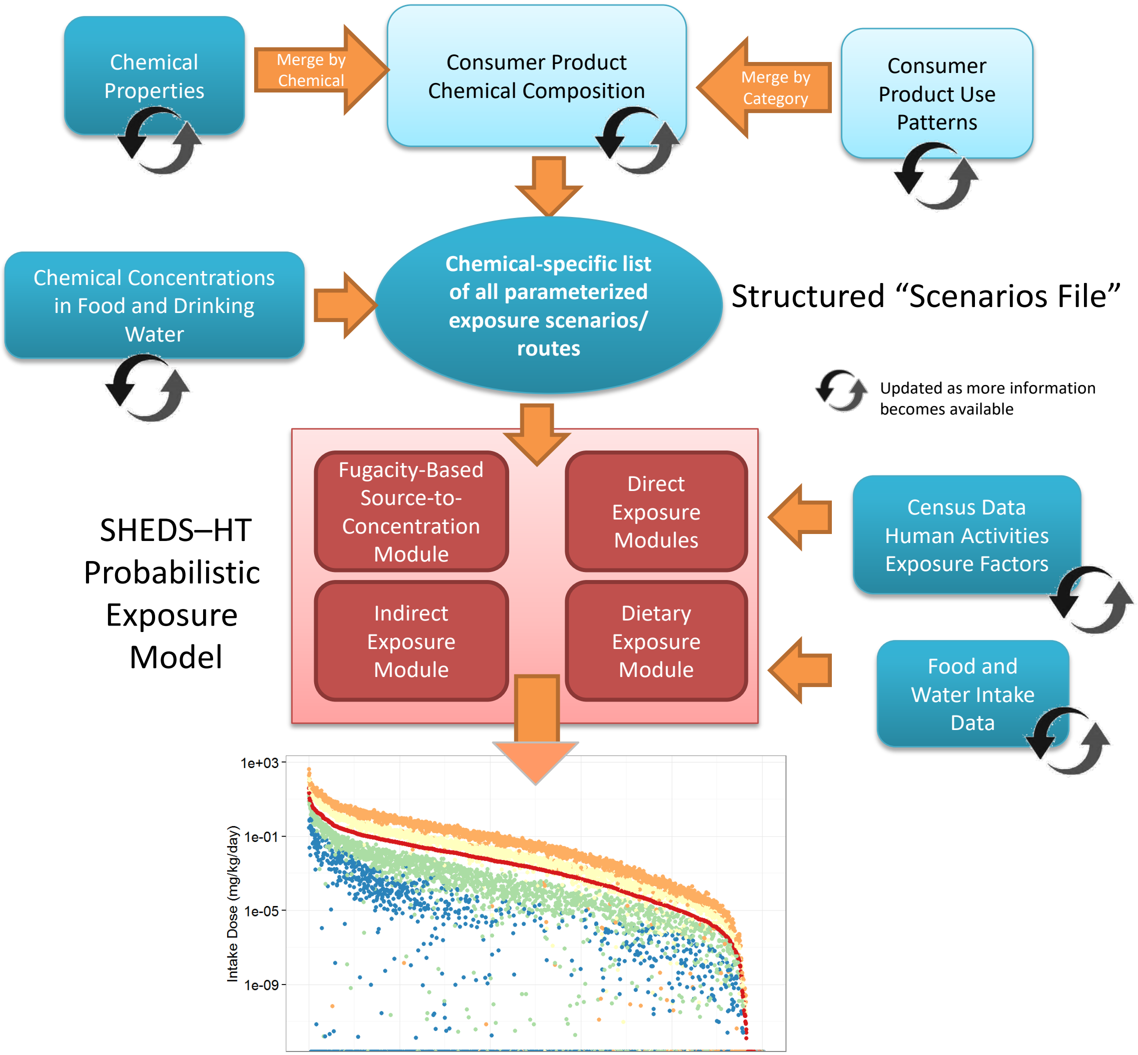
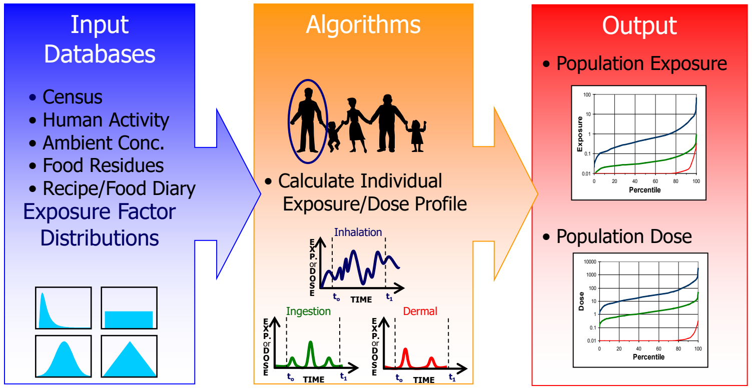




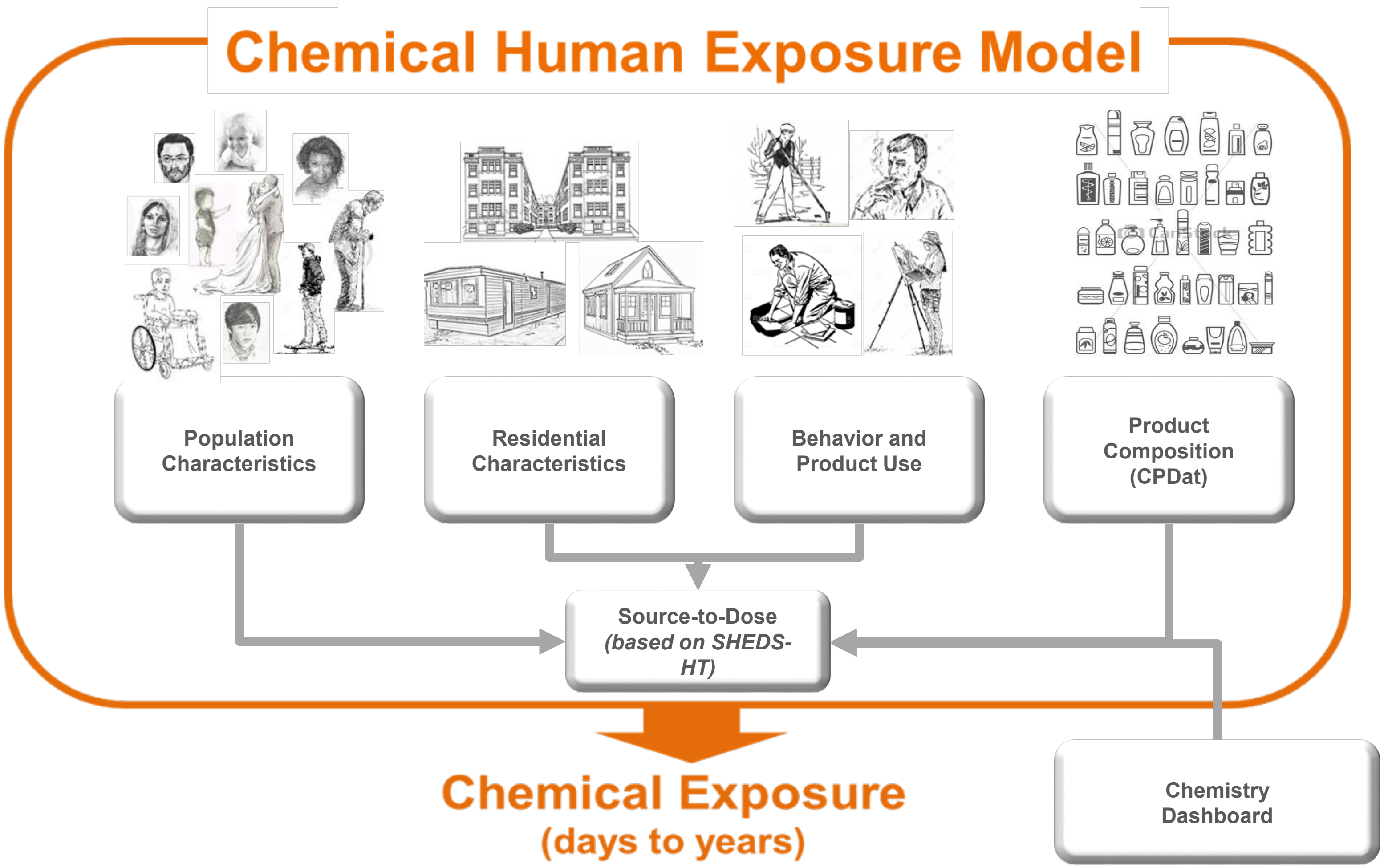
Source: H. Ozkaynak

- Reduced version of SHEDS-Multimedia; stochastic methods
- Available as R package
- Inputs
  - Use information and scenario mapping
  - Fugacity modeling methods used to determine air and surface concentrations for near-field indirect scenarios
- Outputs: Exposures for key cohort groups, by pathway(mg/kg/day)
- Updated to handle articles and dietary exposures
- Recently underwent external peer review
- Active collaboration with industry and academic partners on dietary and consumer chemicals

https://github.com/HumanExposure/SHEDSHTRPackage

Courtesy of K. Isaacs

Moving Towards Higher-Tier Applications



Courtesy of K. Isaacs

Understanding & Predicting Chemical Occurrence in Environmental Media

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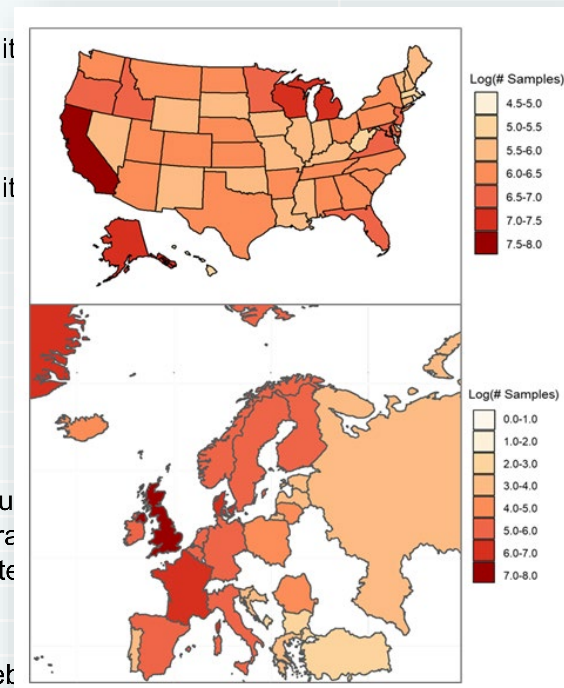
- Large database of multimedia monitoring information (~200 million records) obtained from 21 public databases
- Harmonized to chemical identifier (DTXSID) and 32 unique media
- Will allow for more efficient and rapid identification of available monitoring data for chemicals of interest
- Will form basis for machine-learning models of occurrence in media for use in non-targeted workflows and screening-level assessments

Medium	Unique Chemicals
ambient air	581
breast milk	93
drinking water	404
food product	201
groundwater	1178
landfill leachate	262
human (other tissues or fluids)	169
human blood (whole/serum/plasma)	354
indoor air	111
indoor dust	194
livestock/meat	104
personal air	32
product	131
raw agricultural commodit	10
other-ecological	92
other-environmental	32
precipitation	337
raw agricultural commodit	108
sediment	112
skin wipes	43
sludge	144
soil	151
surface water	484
unknown	767
urine	401
vegetation	104
wastewater (influent, efflu	788
wildlife (aquatic invertebra	536
wildlife (aquatic vertebrate	207
wildlife (birds)	170
wildlife (fish)	726
wildlife (terrestrial inverteb	67
wildlife (terrestrial vertebrates)	184



Courtesy of K. Isaacs

High Throughput Toxicokinetics (HTTK)

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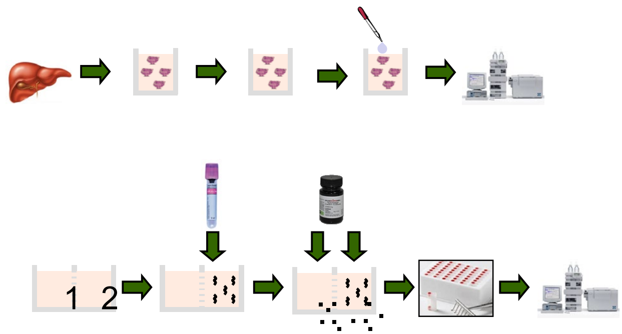
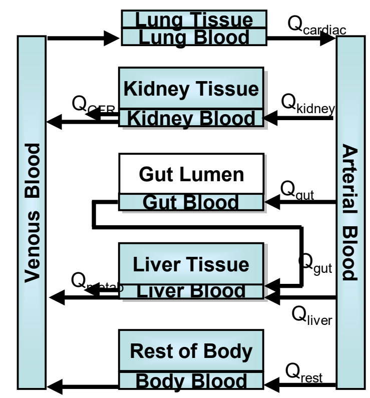
In vitro toxicokinetic data

In vitro hepatic clearanc
e

Plasma protein binding



generic toxicokinetic model



Administrator Wheeler (September, 2019):
"I am directing leadership and staff in the Office of Chemical Safety and Pollution Prevention and the Office of Research and Development to prioritize
…the reduction of animal testing while ensuring protection of human health and the environment."

= ***httk***

high(er) throughput toxicokinetics

Courtesy of J. Wambaugh

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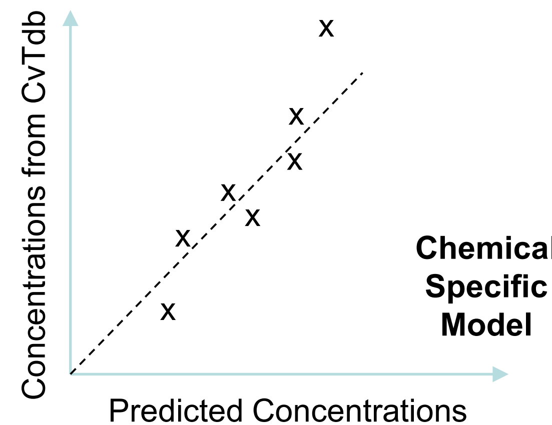
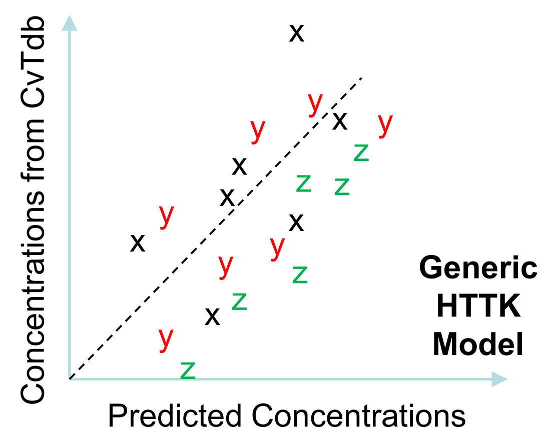
Building Confidence in TK Models

- **Chemical-specific TK model** allows comparison of predictions to *in vivo* data
  - Can estimate bias and uncertainty
  - Can **extrapolate to other situations** (dose, route, physiology) where you don't have data

- As most chemicals lack chemical-specific data, we need a **generic TK model**
  - Expect larger uncertainty, but also greater confidence in model implementation
  - Can estimate bias and uncertainty, and try to correlate with chemical-specific properties
  - Can use model to **extrapolate to other situations** (chemicals without *in vivo* data)

- Constructing an *in vivo* blood/plasma/tissue concentration vs. time (CvT) database to evaluate high throughput PBTK models for chemical prioritization and regulatory decision making





Cohen Hubal et al., JESEE, 2019

Summary

- Exposure science has a new setting in the Office of Research & Development
  - No longer isolated, now better integrated with toxicity testing
  - Follows the evolution of chemical evaluation
- The Center for Computational Toxicology and Exposure
  - Exploits advances in technology
  - Aims to be able to rapidly evaluate thousands of chemicals
  - Provides contextualization of high-throughput toxicology
  - Is problem-driven and solution-focused
- Broad applications beyond the Agency
  - Partnerships with Minnesota Dept. of Health and California Dept of Toxic Substances Control as examples

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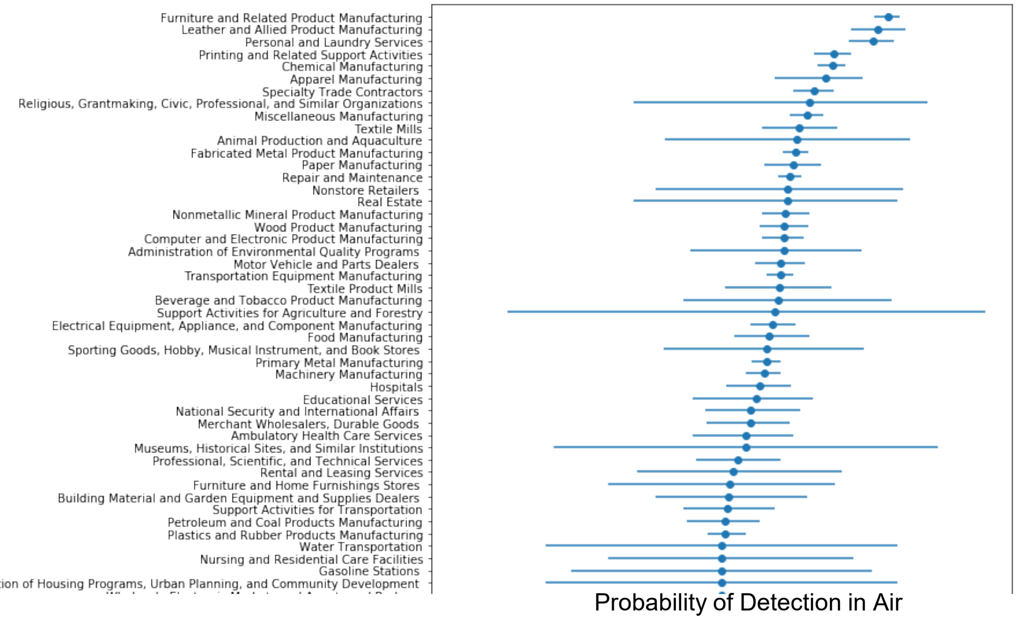
- Timothy Buckley
- Linda Sheldon
- Elaine Cohen Hubal

Occupational Exposure Models for Exposure-based Prioritization



- Need to parameterize for 1000s of substances lacking data
- Using existing workplace exposure data to develop a model that can predict air concentration based on chemical/physical properties and industry type
- Using Bayesian hierarchical logistic regression
  - First predict detect/nondetect
  - Next predict concentration
- Preliminary results look promising
- Currently predicting NAICS sector/ subsectors with functional use models