United States Environmental Protection Agency

The Chemical Landscape of High-Throughput New Approach Methodologies for Exposure

Case Study Closeout

Kristin K. Isaacs,[1] Peter Egeghy,[1] Kathie Dionisio,[1] Katherine Phillips,[1] Angelika Zidek,[2] Caroline Ring,[1] Jon R. Sobus,[1] Elin M. Ulrich,[1] Barbara A. Wetmore,[1] Antony J. Williams,[1] and John Wambaugh[1]

[1]Center for Computational Toxicology and Exposure, Office of Research and Development, U.S. Environmental Protection Agency

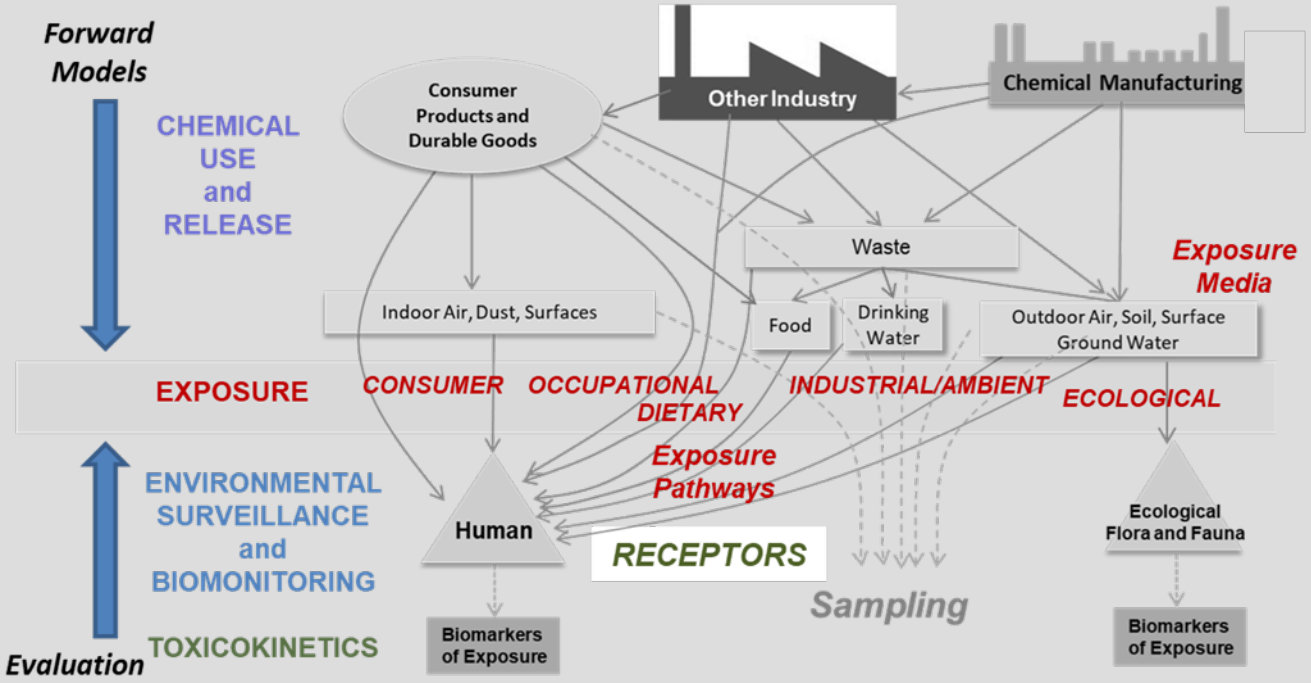
[2]Healthy Environments and Consumer Safety Branch, Health Canada

Accelerating the Pace of Chemical Risk Assessment
APCRA

Office of Research and Development
Center for Computational Toxicology and Exposure

APCRA Teleconference
November 10, 2022

Forecasting Exposure is a Systems Problem

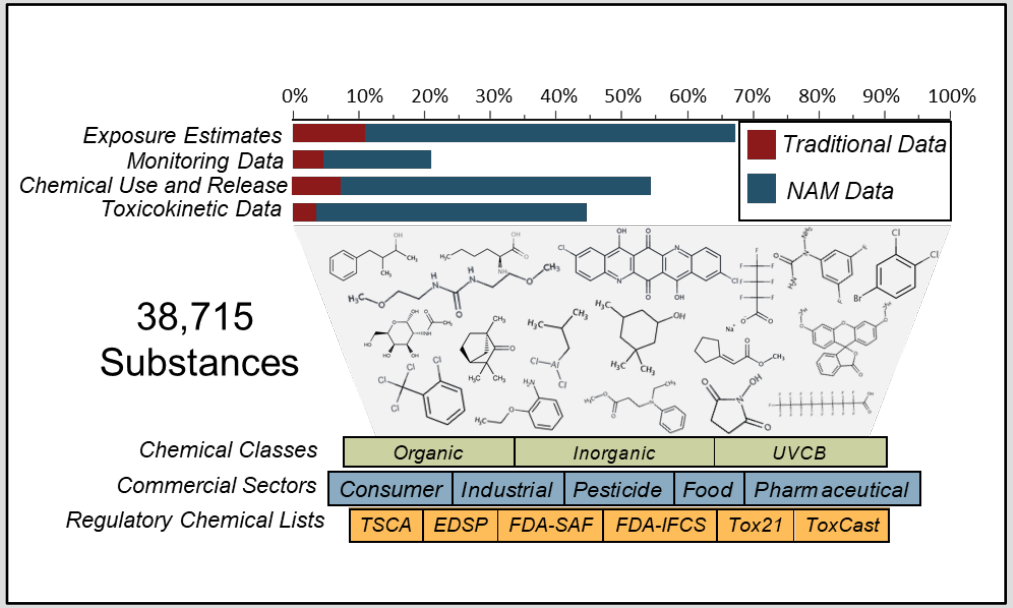


Critical Exposure-Relevant Domains

- ***Chemical use and release.*** Provides critical information for identifying chemical sources, exposure pathways, and relevant predictive models for a given chemical.
- ***Media occurrence, environmental surveillance, and biomonitoring***. Provides exposure data for evaluating predictive models.
- ***Exposure estimates***. Predictions of chemical intake in mg/kg/day that can be compared with hazard information to inform risk.
- ***Toxicokinetics***. Provides real-world exposure context to *in vitro* high-throughput screening data and biological receptor monitoring information.

Case Study History

- Proposed originally as case study ***Triaging Chemical Exposure Data Needs and Tools for Advancing Next-Generation Risk Assessment***
- First landscape analysis exercise (~6600 APCRA inventory chemicals) presented at APCRA 2 meeting
- Subsequent publication of multiple exposure NAMs papers, including formal definition of NAMs for exposure (Wambaugh et al. 2019), Chemicals and Products Database (Dionisio et al. 2018), ExpoCast SEEM3 exposure estimates (Ring et al. 2019), harmonized monitoring databases (Isaacs et al. 2022), *in silico* toxicokinetics (e.g., Dawson et al. 2021)
- Updated analysis presented at APCRA public webinar in March 2020
- **Final analysis examined updated published datasets for an inventory of 38,715 regulatory-relevant chemical substances**



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Eight Classes of NAMs for Exposure

- ***Chemical descriptors*** that provide information on chemicals in an exposure context (e.g., how chemicals are used)
- ***Machine-learning approaches*** that use these descriptors to fill gaps in existing data
- ***High-throughput exposure models*** for various pathways
- ***High-throughput measurements*** to fill gaps in monitoring data
- High-throughput approaches for measuring and predicting chemical ***toxicokinetics***
- New ***evaluation frameworks*** for integrating models and monitoring to provide consensus exposure predictions
- All these pieces together provide the tools for high-throughput ***chemical prioritization***


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New approach methodologies for exposure science

John F. Wambaugh [1], Jane C. Bare [2], Courtney C. Carignan [3], Kathie L. Dionisio [4], Robin E. Dodson [5], Olivier Jolliet [6], Xiaoyu Liu [7], David E. Meyer [2], Seth R. Newton [4], Katherine A. Phillips [4], Paul S. Price [4], Caroline L. Ring [8], Hyeong-Moo Shin [9], Jon R. Sobus [4], Tamara Tal [10], Elin M. Ulrich [4], Daniel A. Vallero [4], Barbara A. Wetmore [4], Kristin K. Isaacs [4]

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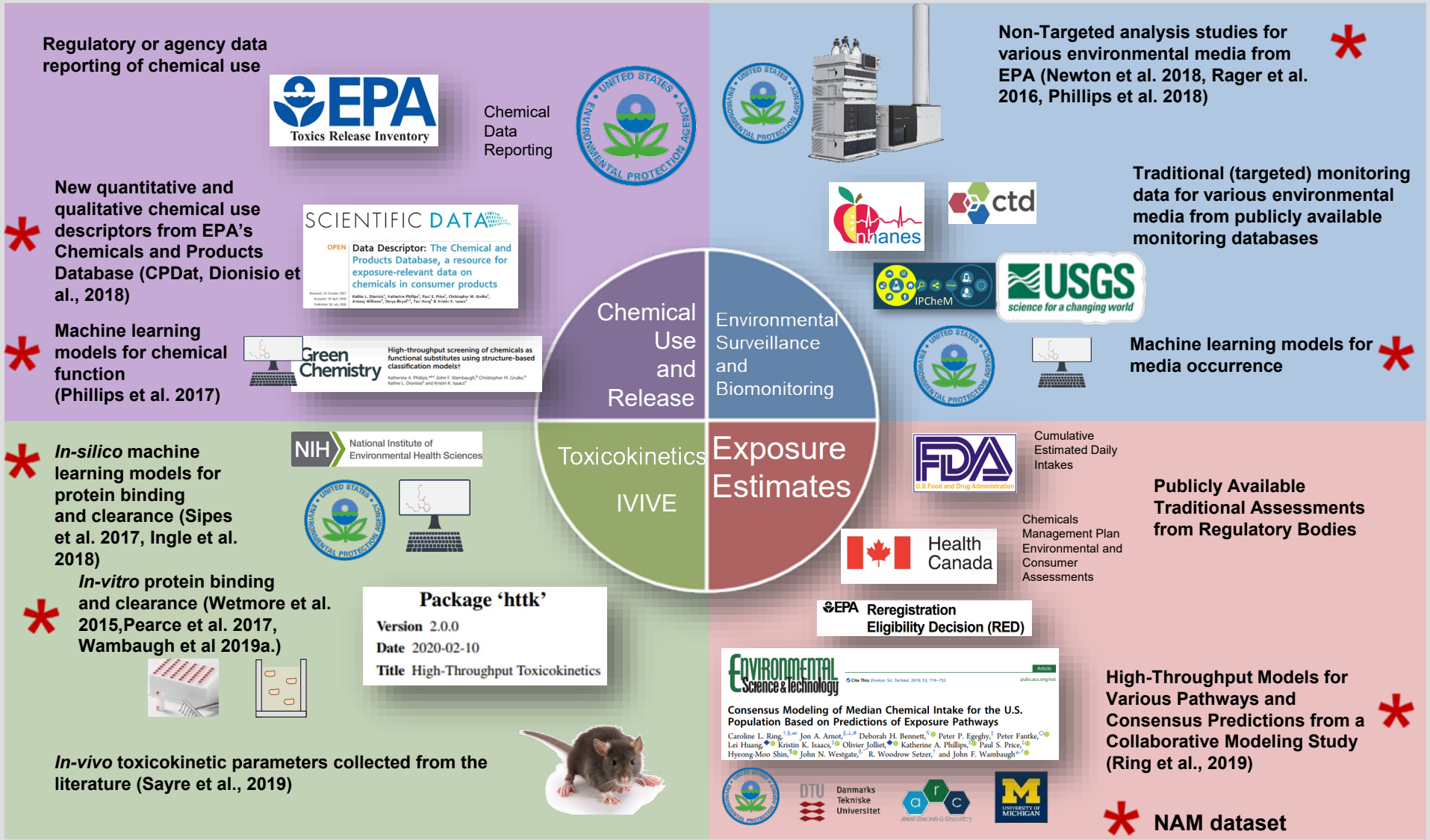
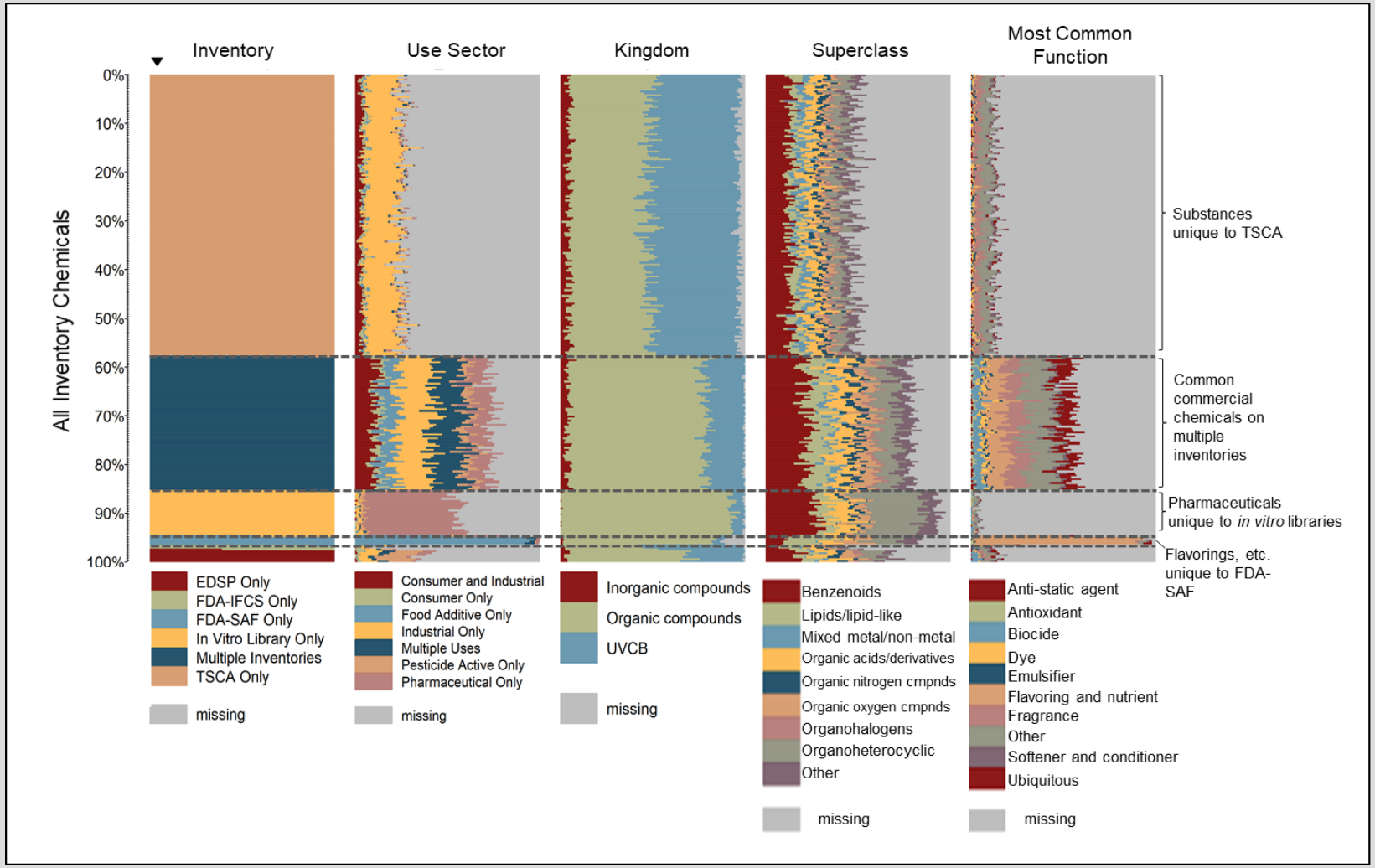
Traditional and NAM Exposure Datasets



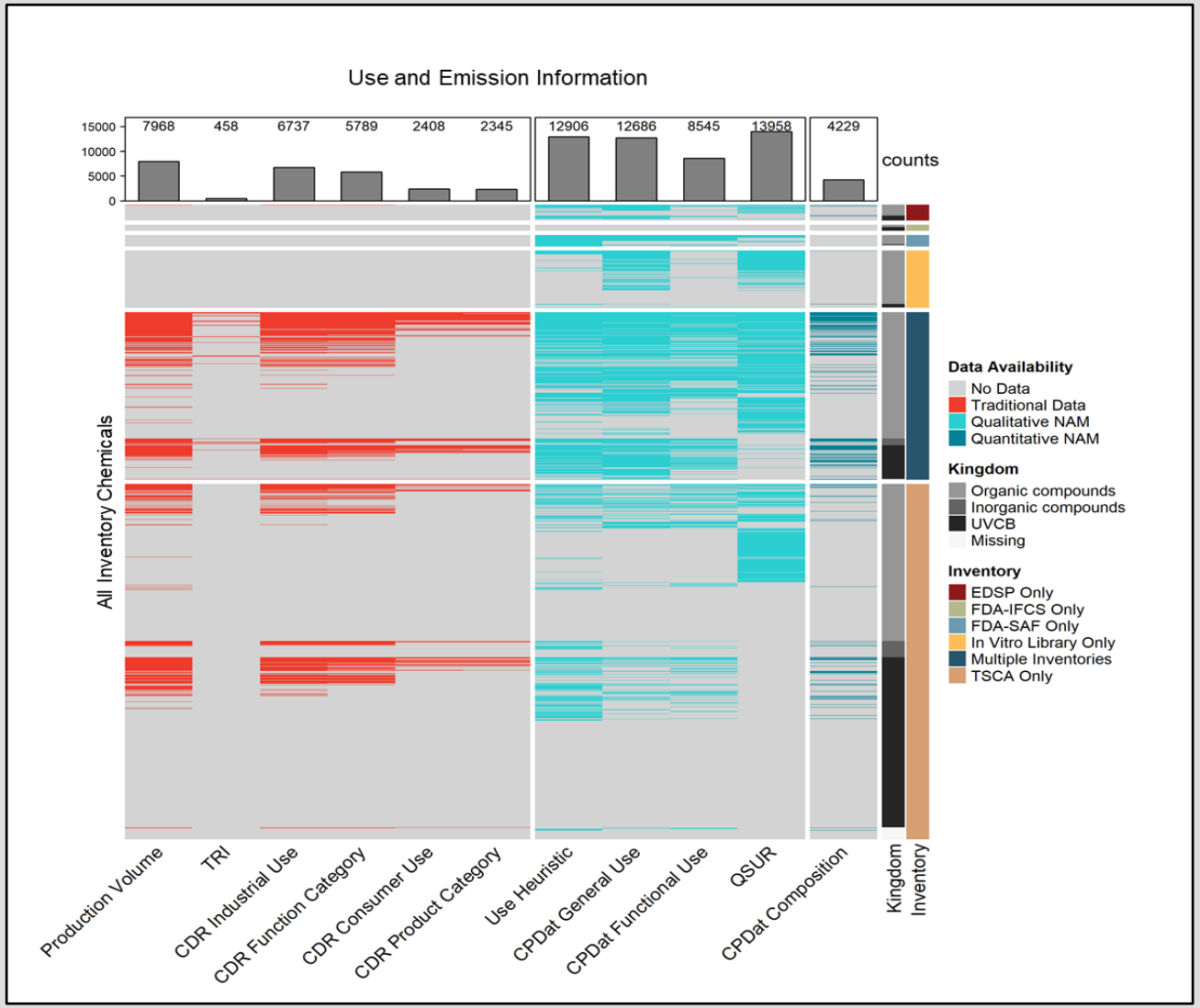
Chemical Inventory

- Combined list of 38,715 chemicals from several regulatory inventories from EPA (e.g., TSCA, EDSP), the U.S. Food and Drug Administration, ToxCast and Tox21 *in vitro* libraries
  - High degree of coverage of other lists (Canada DSL, pesticide actives/inerts, etc.)
- Inventory examined in terms of use sector and structural classes
- Aided in identification of data gaps



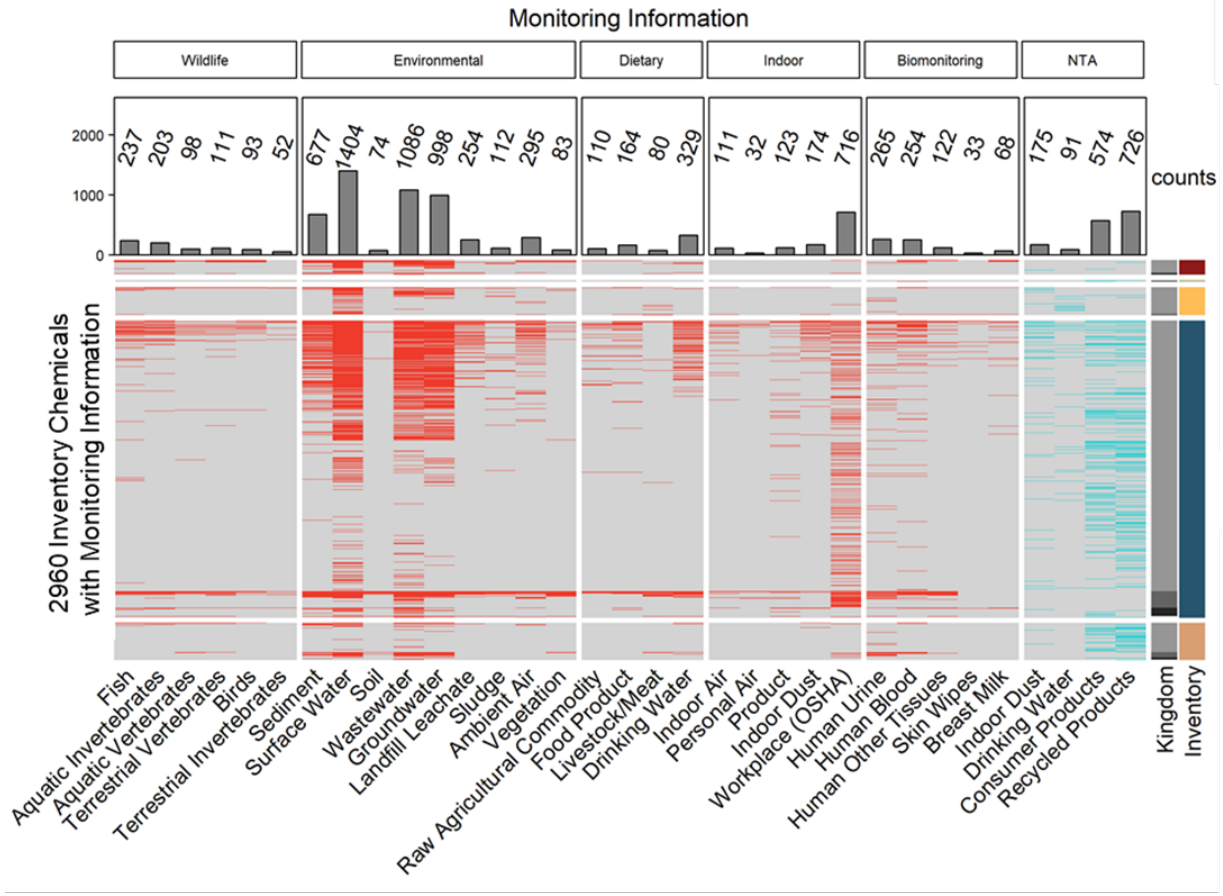
Use and Release Data

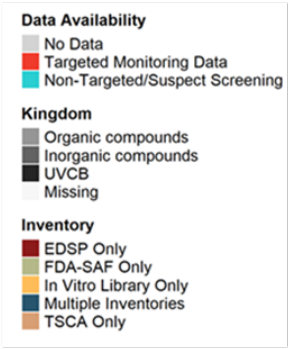
- Efforts to collect and curate publicly available information on how chemicals are used have greatly expanded reported use information
- Quantitative release information is still a bottleneck
- QSUR predictions have provided new information for many organic chemicals
- Data for UVCBs is still a critical gap



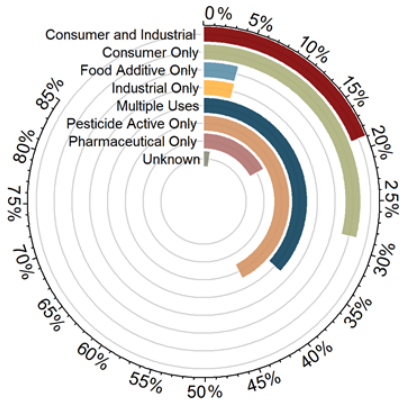
Monitoring Data

- Only 2960 chemicals with traditional monitoring data
  - Most coverage of water categories
  - Most data for pesticide actives
- NTA studies have provided new information for near-field sources

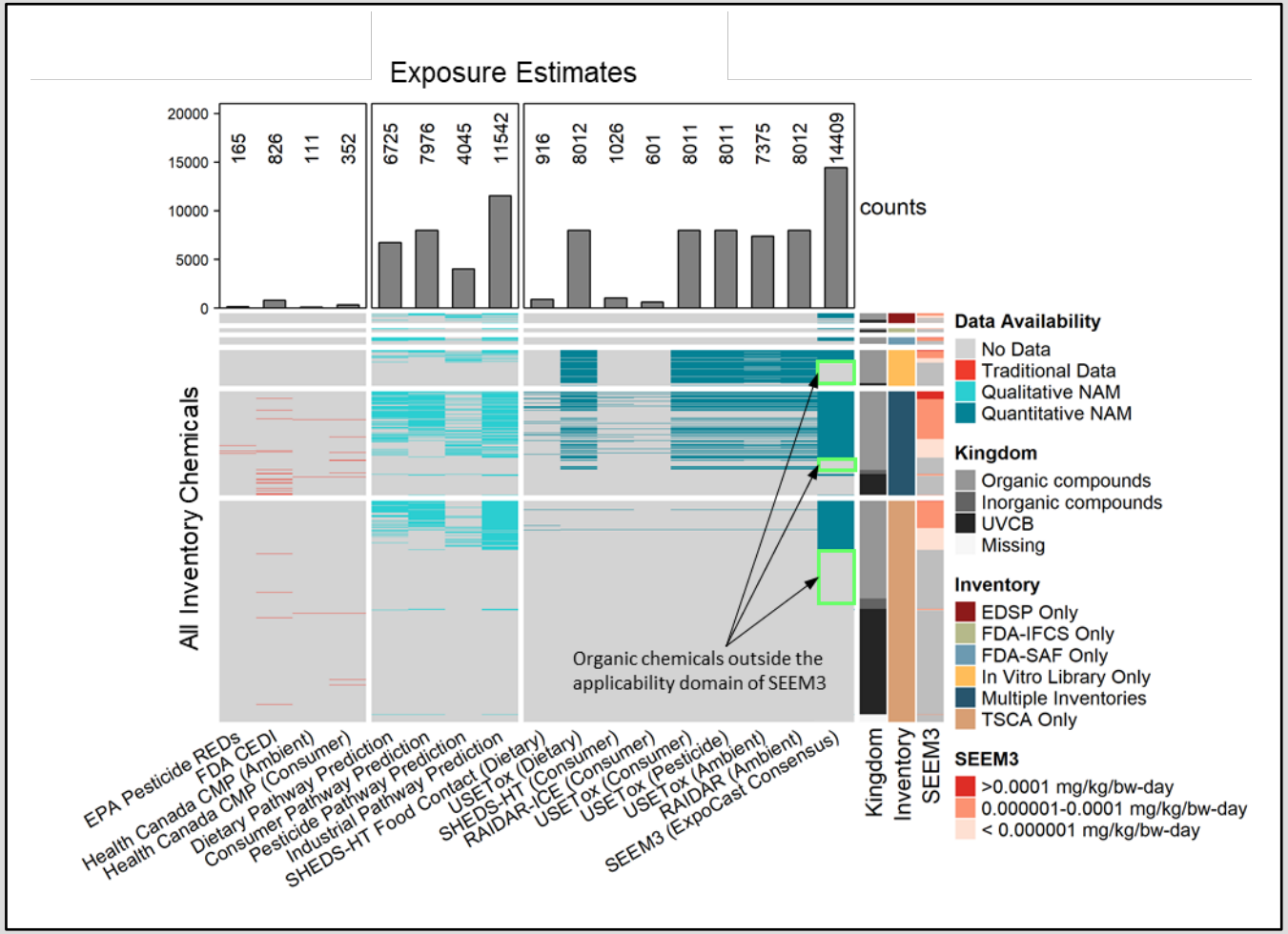




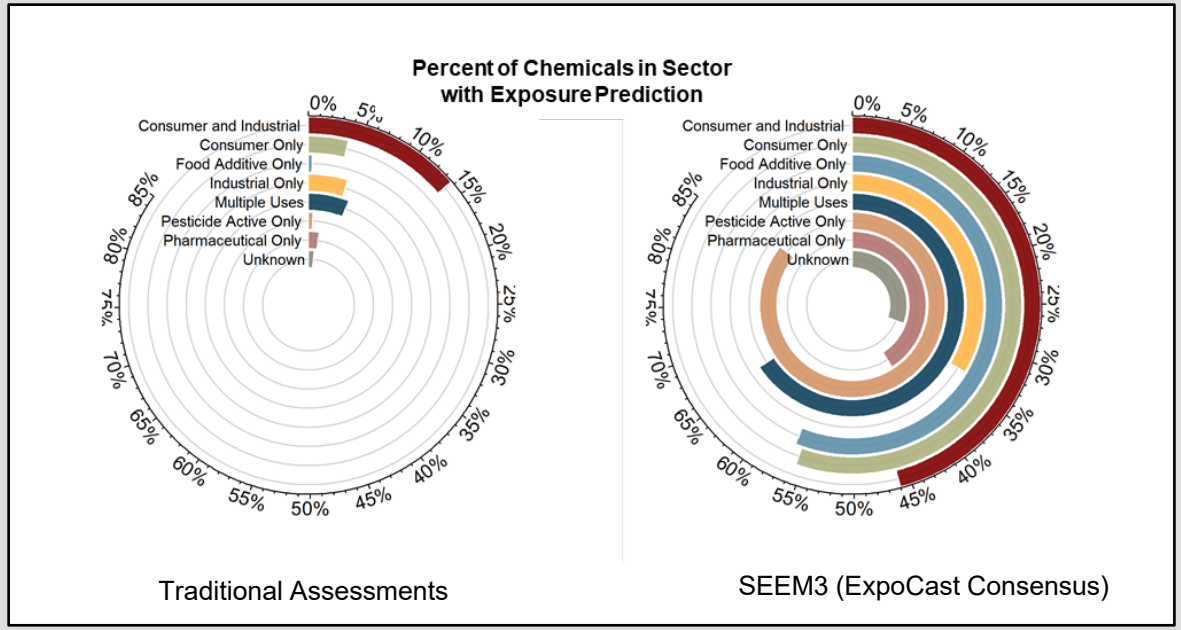
Percent of Chemicals in Sector with Traditional Monitoring Data



Exposure Estimates

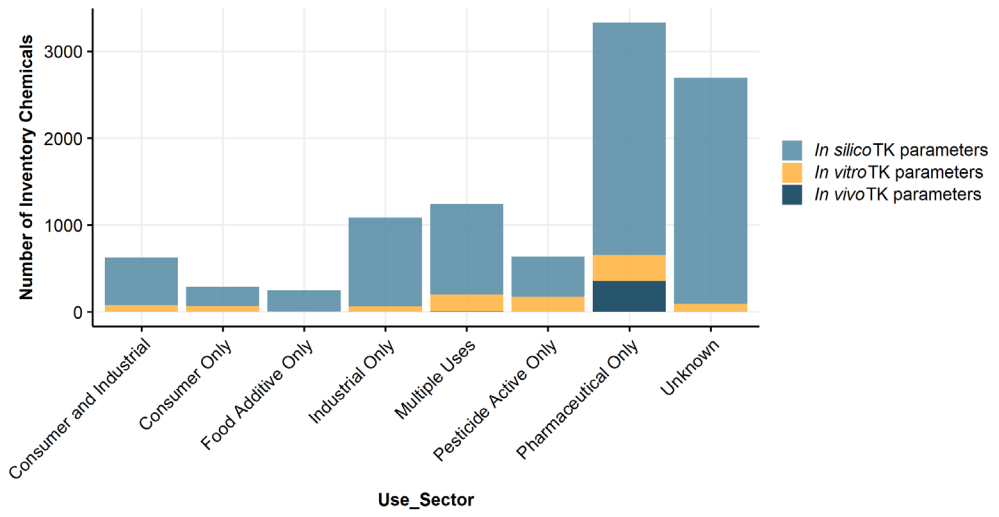


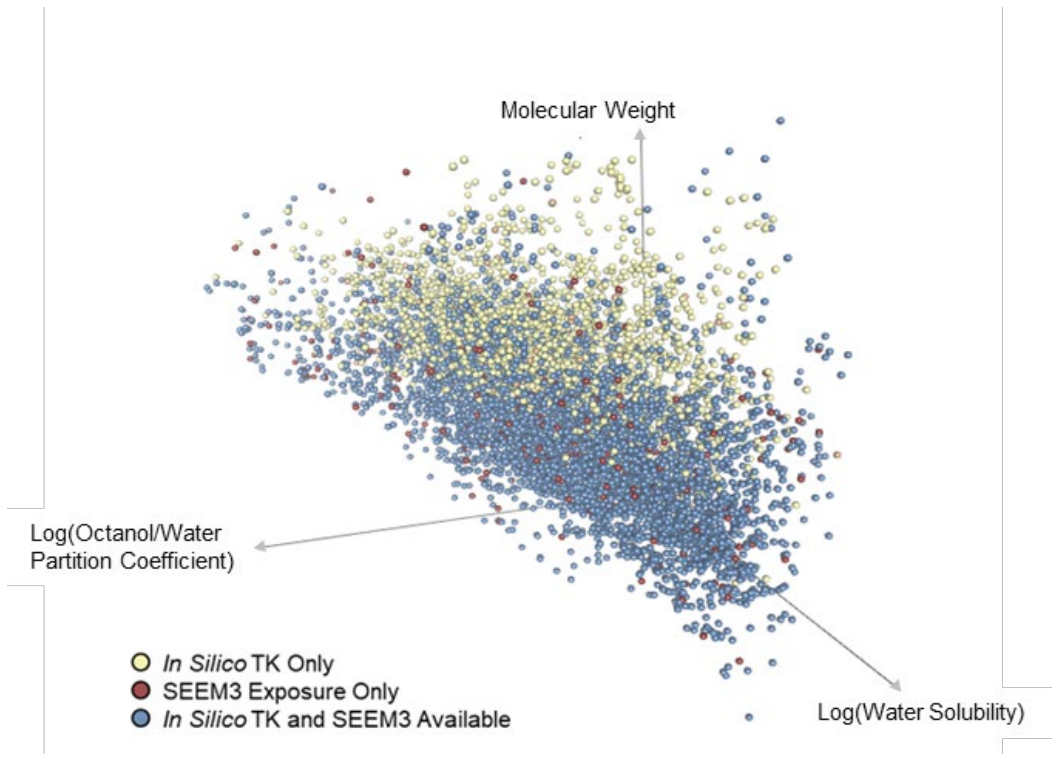
- Consensus HT models for exposure have improved availability of exposure estimates for common chemicals
- Still significant organic chemicals outside the domain of current models



HT Toxicokinetics and Risk Prioritization

- *In silico* parameters still have bias toward pharmaceutical domains
- There are some chemicals with bioactivity data for which we can't currently develop a SEEM exposure estimate





Recommendations for High-Value Activities in Developing Exposure NAMs

- Expansion of chemical use information or QSUR predictions to inadequately-covered product types and sectors
- Expansion of models for predicting chemical releases into ambient or near-field environments
- Expansion of NTA approaches to include quantitative methods
- Refinement of monitoring databases and development of quantitative machine-learning models for media occurrence and concentrations
- Use of available exposure NAM data in the design of monitoring studies
- Development of methods for characterizing, annotating, and modeling use and exposures for UVCBs
- Continued evaluation of the chemical domain of models for estimating physicochemical properties and toxicokinetic parameters
- Expansion of the SEEM framework to additional human and ecological receptor populations

ExpoCast Project (Exposure Forecasting)

Center for Computational Toxicology and Exposure

Linda Adams
Matthew Boyce*
Miyuki Breen*
Alex Chao
Ciara Dalton*
Sarah Davidson
Nikki DeLuca*
Mike Devito
Alex East*
Lindsay Eddy*
Christopher Eklund
Peter Egeghy
Marina Evans
Alex Fisher*
Mary Jacketti*
Richard Judson
Elaina Kenyon
Jen Korol-Bexell*
Paul Kruse *
Charles Lowe*
Annabel Meade*
Seth Newton
Katherine Phillips
Paul Price
Elin Ulrich
Dan Vallero
Taylor Wall
Barbara Wetmore
John Wambaugh
Antony Williams

CEMM
Hongwan Li*
Xiaoyu Liu
Zachary Robbins*
Mark Strynar

CESER
David Meyer
David Perez
Gerardo Ruiz Mercado

***Trainees**

Collaborators

Arnot Research and Consulting
Jon Arnot
Johnny Westgate
Integrated Laboratory Systems
Xiaoqing Chang
Shannon Bell
National Toxicology Program
Steve Ferguson
Kamel Mansouri
Ramboll
Harvey Clewell
Silent Spring Institute
Robin Dodson
Simulations Plus
Michael Lawless
Southwest Research Institute
Alice Yau
Kristin Favela
Summit Toxicology
Lesa Aylward
Technical University of Denmark
Peter Fantke
Unilever
Beate Nicol
Cecilie Rendal
Ian Sorrell
United States Air Force
Heather Pangburn
Matt Linakis
University of California, Davis
Deborah Bennett
University of Michigan
Olivier Jolliet
University of Texas, Arlington
Hyeong-Moo Shin
University of Nevada
Li Li
University of North Carolina, Chapel Hill
Julia Rager
Marc Serre