United States Environmental Protection Agency

International Society of Regulatory Toxicology and Pharmacology Annual Meeting
December 2, 2020

Paracelsus, Dose, and the Importance of Exposure in Translating Toxicology into Public Health Risk

John Wambaugh
Center for Computational Toxicology and Exposure
Office of Research and Development
U.S. Environmental Protection Agency

http://orcid.org/0000-0002-4024-534X

The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. EPA

US EPA Office of Research and Development

- The Office of Research and Development (ORD) is the scientific research arm of EPA
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- Research is conducted by ORD's four national centers, and three offices organized to address:
  - Public health and env. assessment; comp. tox. and exposure; env. measurement and modeling; and env. solutions and emergency response.

- 13 facilities across the United States

- Research conducted by a combination of Federal scientists (including uniformed members of the **Public Health Service**); contract researchers; and postdoctoral, graduate student, and post-baccalaureate trainees

ORD Facility in
Research Triangle Park, NC

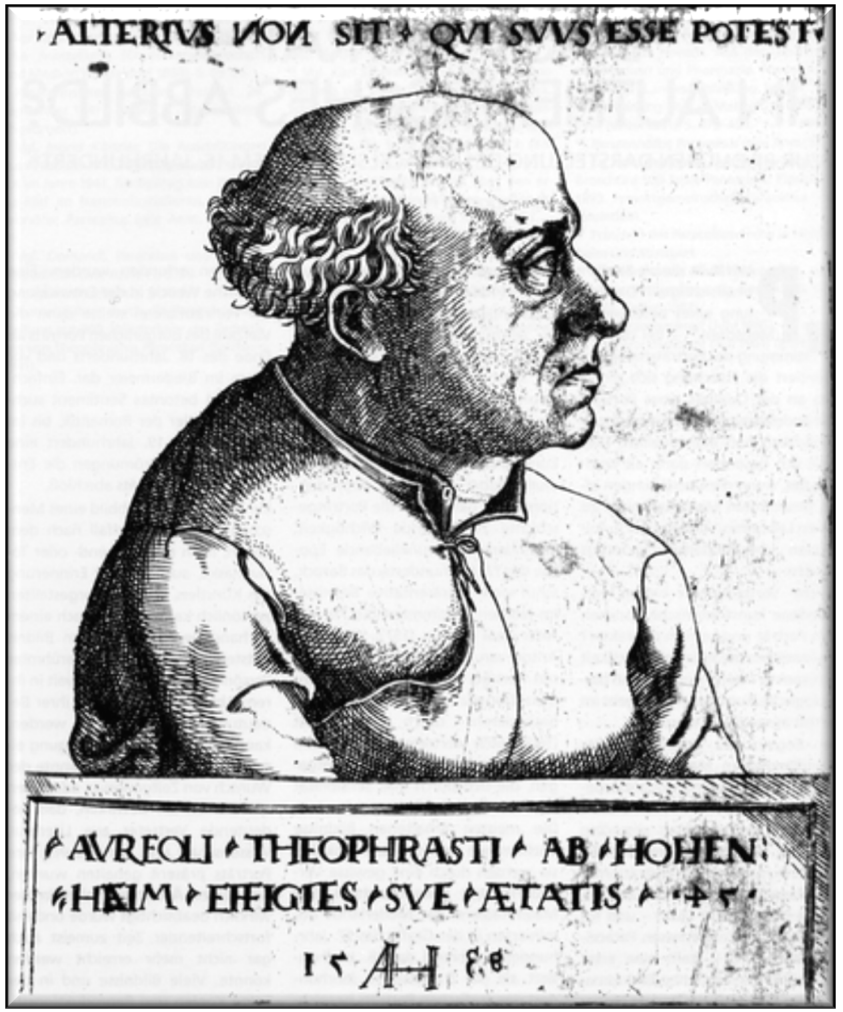
Paracelsus

"What is there that is not poison? All things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison" — Paracelsus (1493-1541)

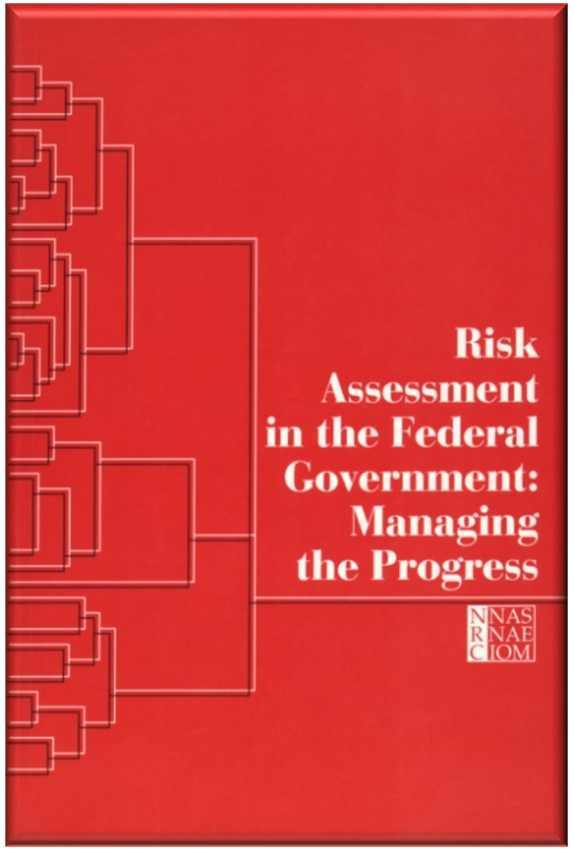
Complications (adapted from Grandjean, 2016):

- Many thousands of chemicals in the environment
- Developmental windows of susceptibility
- Confounding benefits (nutrition vs. toxicity)
- Genetic variability in susceptibility
- Variability in exposure (occupational, heavy users)

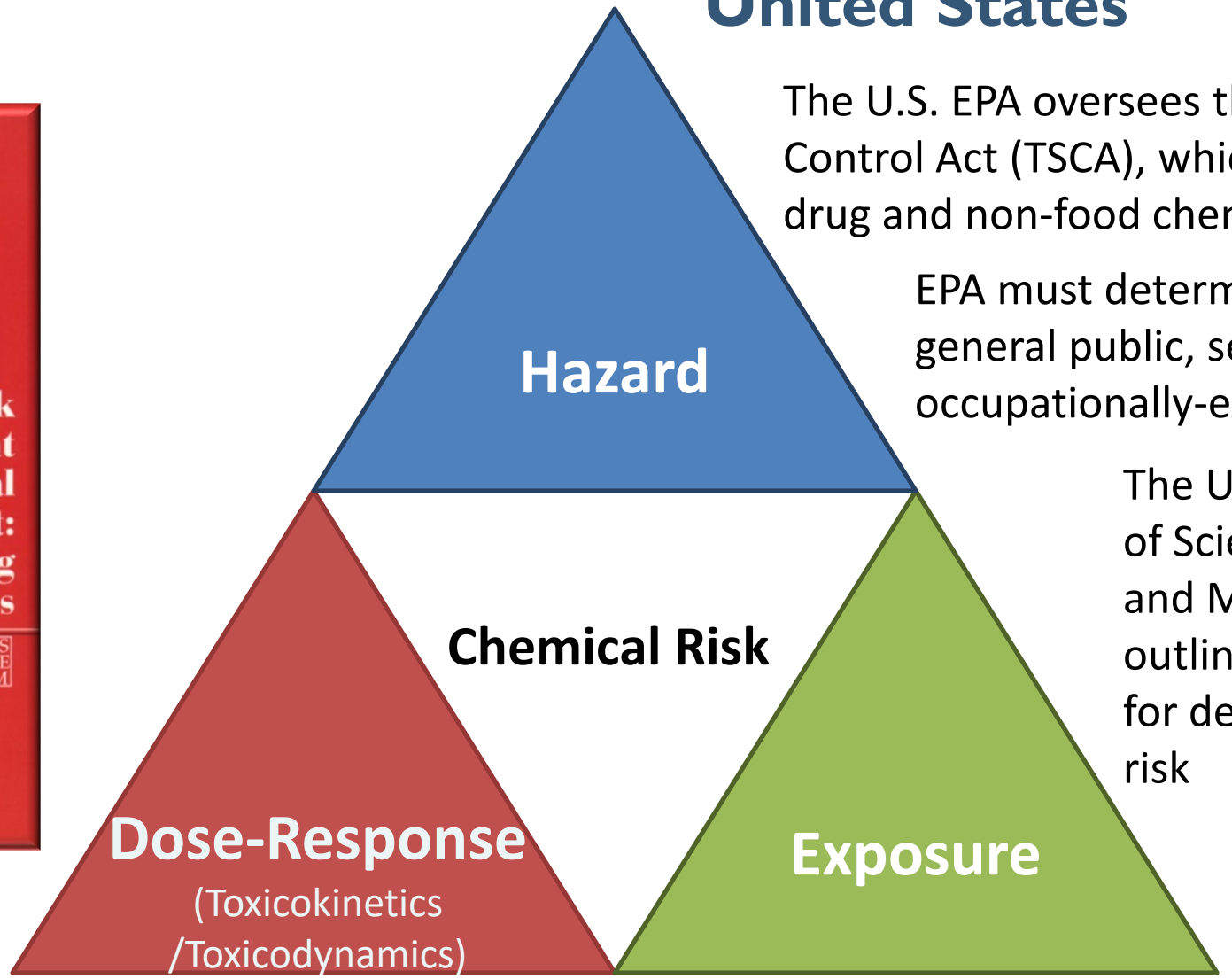
"From a public health viewpoint, toxicology needs to provide better guidance on decision-making under ever-present uncertainty" — *Grandjean (2016)*



Three Components for Chemical Risk in the United States



NRC (1983)



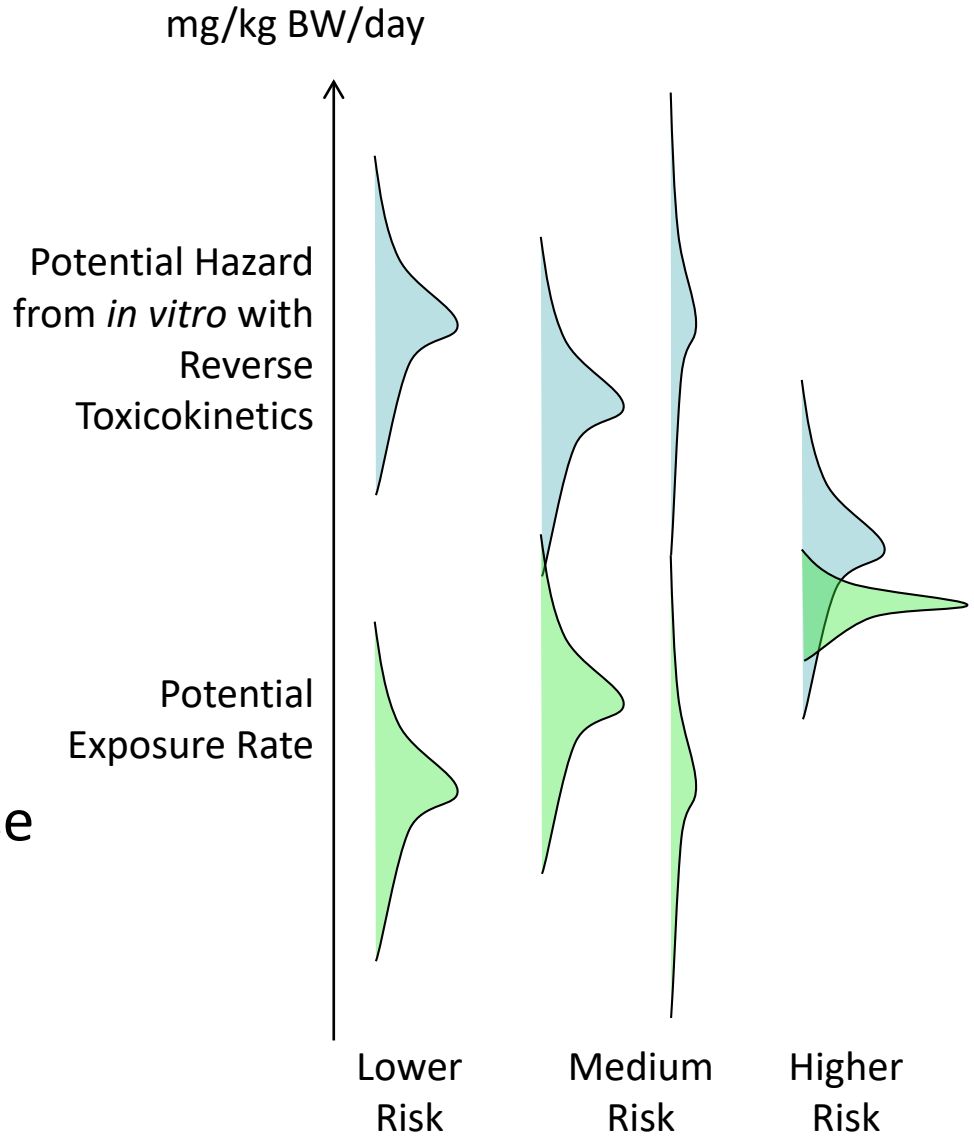
The U.S. EPA oversees the U.S. Toxic Substances Control Act (TSCA), which regulates most non-drug and non-food chemicals

EPA must determine risk to the general public, sensitive, and occupationally-exposed populations

The U.S. National Academy of Sciences, Engineering and Medicine (1983) outlined three components for determining chemical risk

Decision-Making Under Ever-Present Uncertainty

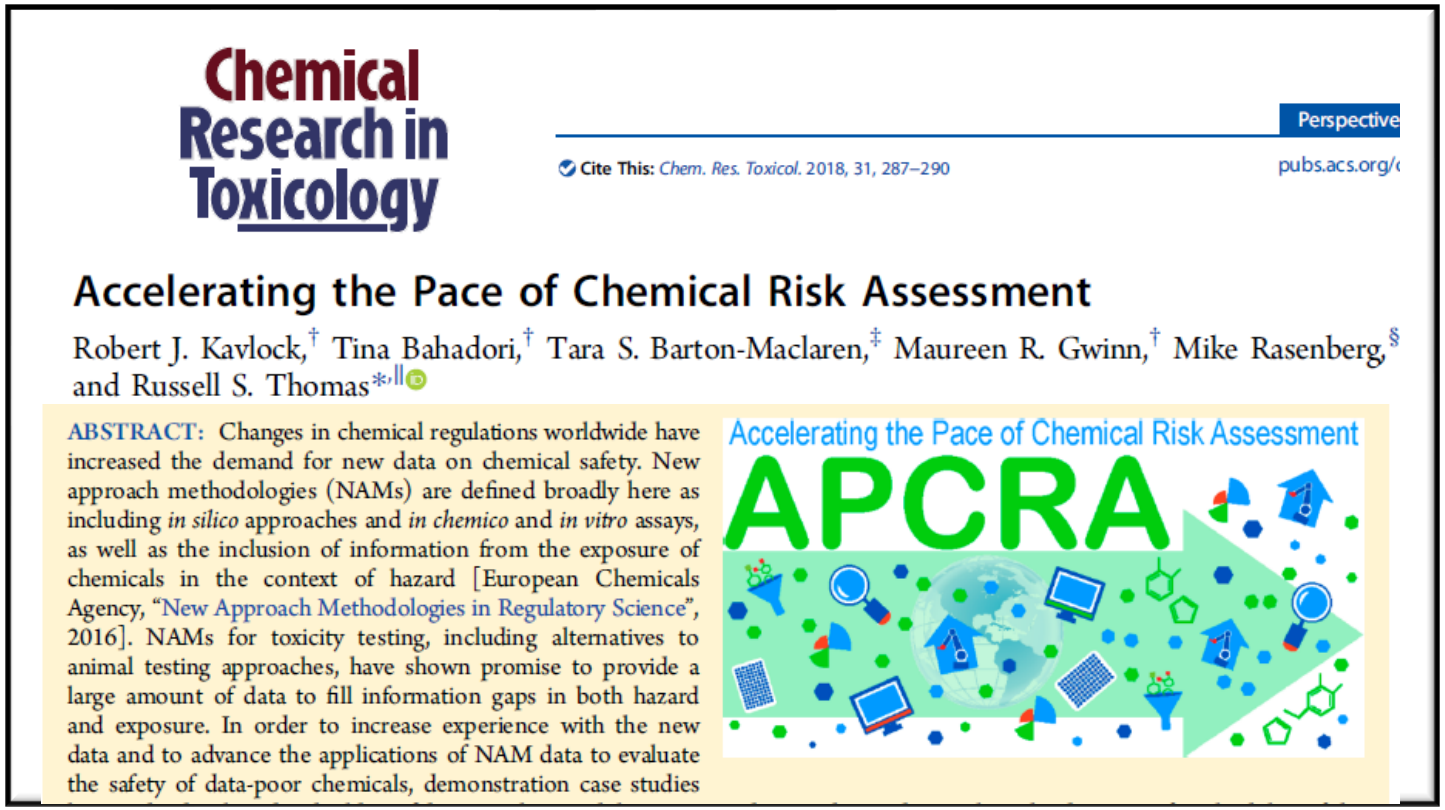
- There are roughly 10,000 TSCA-relevant chemicals in commerce
  - Traditional methods are too resource-intensive to address all of these
- Therefore, high throughput risk prioritization needs:
  1. High throughput hazard characterization (Dix et al., 2007, Collins et al., 2008)
  2. High throughput exposure forecasts (Wambaugh et al., 2013, 2014; Ring et al., 2019)
  3. High throughput toxicokinetics (i.e., dose-response relationship) linking hazard and exposure (Wetmore et al., 2012, 2015)



New Approach Methodologies (NAMs)

- NAMs include:
  - High throughput screening (ToxCast)
  - High throughput exposure estimates (ExpoCast)
  - High throughput toxicokinetics (HTTK)

- TSCA was updated in 2016 to allow more rapid evaluation of chemicals



Chemical Research in Toxicology

Perspective

Cite This: *Chem. Res. Toxicol.* 2018, 31, 287–290

pubs.acs.org/

Accelerating the Pace of Chemical Risk Assessment

Robert J. Kavlock,[†] Tina Bahadori,[†] Tara S. Barton-Maclaren,[‡] Maureen R. Gwinn,[†] Mike Rasenberg,[§] and Russell S. Thomas*[,∥]

ABSTRACT: Changes in chemical regulations worldwide have increased the demand for new data on chemical safety. New approach methodologies (NAMs) are defined broadly here as including *in silico* approaches and *in chemico* and *in vitro* assays, as well as the inclusion of information from the exposure of chemicals in the context of hazard [European Chemicals Agency, "New Approach Methodologies in Regulatory Science", 2016]. NAMs for toxicity testing, including alternatives to animal testing approaches, have shown promise to provide a large amount of data to fill information gaps in both hazard and exposure. In order to increase experience with the new data and to advance the applications of NAM data to evaluate the safety of data-poor chemicals, demonstration case studies

- TSCA Proof of concept: Examine ~200 chemicals with ToxCast, ExpoCast and HTTK
  - Toxicokinetics was rate limiting factor on number of chemicals in study
  - *"A Proof-of-Concept Case Study Integrating Publicly Available Information to Screen Candidates for Chemical Prioritization under TSCA"*

High-Throughput Bioactivity Screening Projects

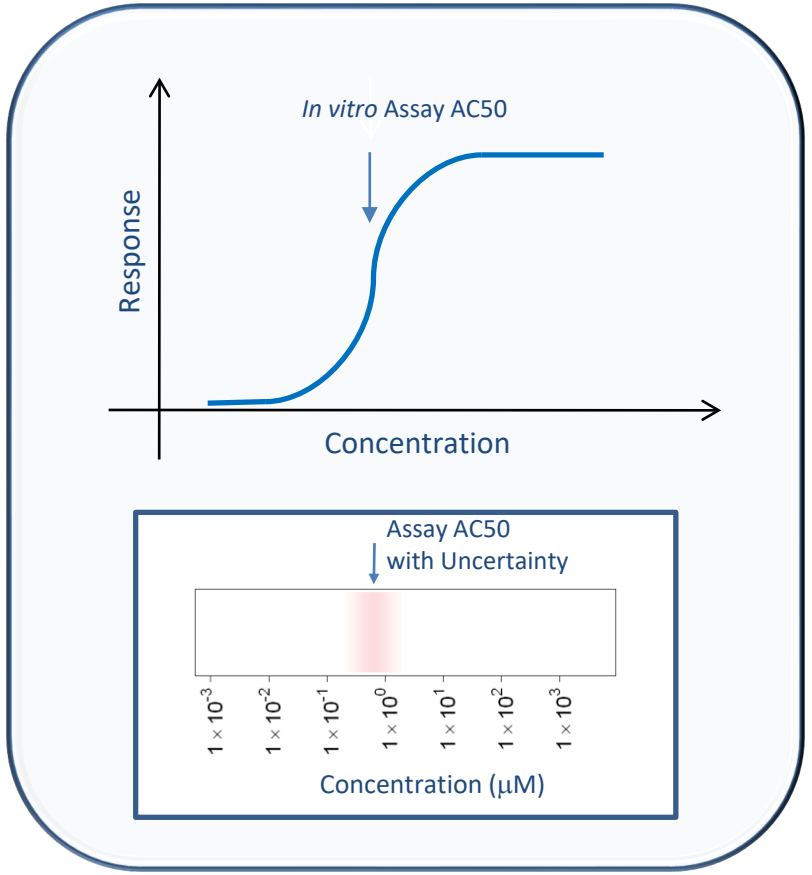
- High throughput screening (HTS) for *in vitro* bioactivity potentially allows characterization of thousands of chemicals for which no other testing has occurred

- **Tox21**: Examining >8,000 chemicals using ~50 assays intended to identify interactions with biological pathways (Schmidt, 2009)

- **ToxCast**: For a subset (>2000) of Tox21 chemicals ran >1100 additional assays (Kavlock *et al.*, 2012)

- Most assays conducted in dose-response format (identify 50% activity concentration – AC_{50} – and efficacy if data described by a Hill function, Filer *et al.*, 2016)

- All data are public: http://comptox.epa.gov/dashboard/



The Margin Between Exposure and Hazard

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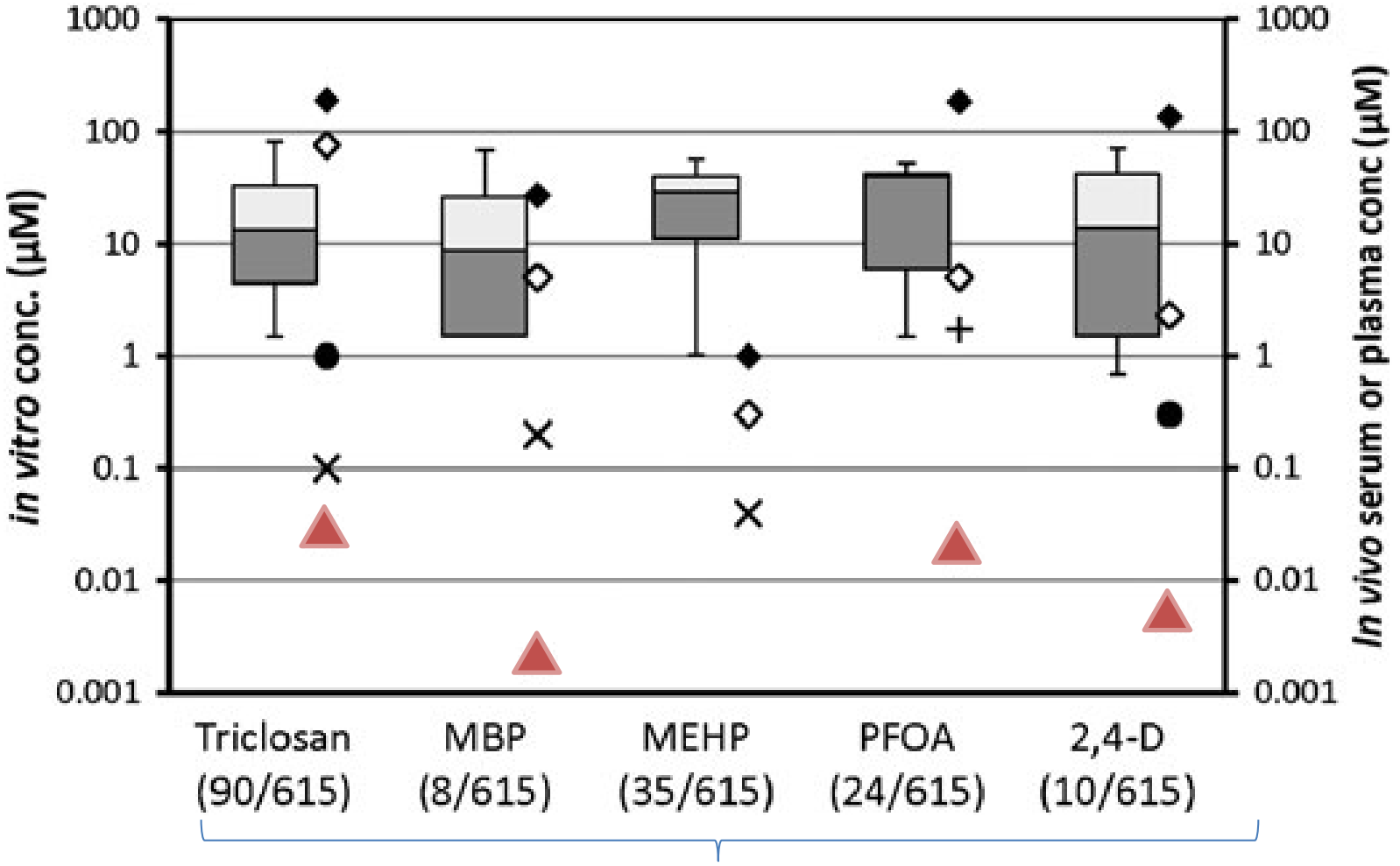
in vitro

Each "Box and whisker" plot indicates median and range of active concentrations across (then) 615 ToxCast assays



in vivo

- ◆ estimated or measured average concentrations associated with the LOAEL in animal studies
- ◇ NOAEL in animal studies
- ● Humans with chronic exposure reference values (solid circles)
- X Volunteers using products containing the chemical
- \+ Biomonitored occupational populations
- ▲ General populations

This study was limited to five chemicals by general population data on exposure

Aylward and Hays (2011)

New Approach Methodologies and Exposure

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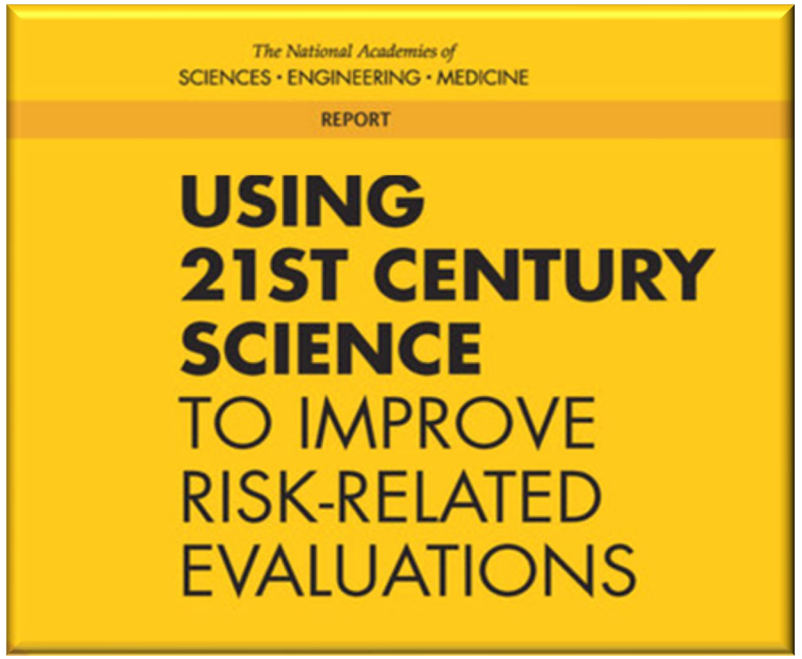
"NAMs were taken in a broad context to ***include*** **in silico** ***approaches,*** in chemico *and* in vitro *assays, as* ***well as the inclusion of information from the exposure of chemicals*** *in the context of hazard assessment"*



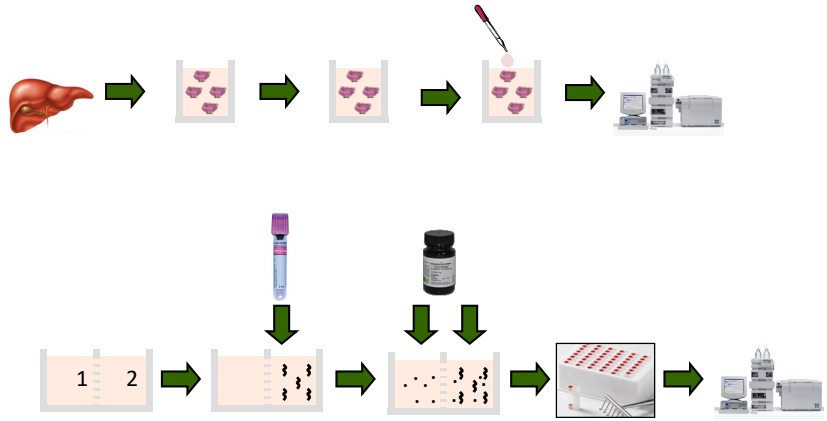
"…the committee sees the potential for the application of ***computational exposure science*** *to be highly valuable and credible for comparison and priority-setting among chemicals in a risk-based context."*

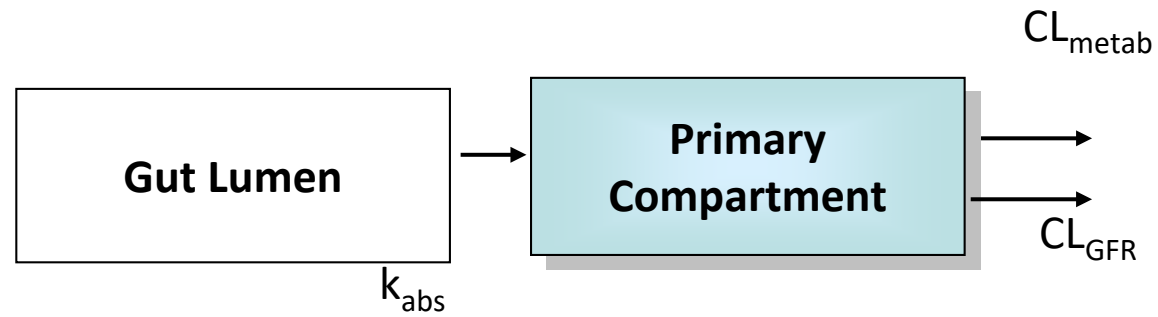
Slide from Kristin Isaacs

NAMs for Toxicokinetics: HTTK

In vitro **toxicokinetic data + generic toxicokinetic model**

= high(er) throughput toxicokinetics





= *httk*

Open-Source Tools and Data for HTTK

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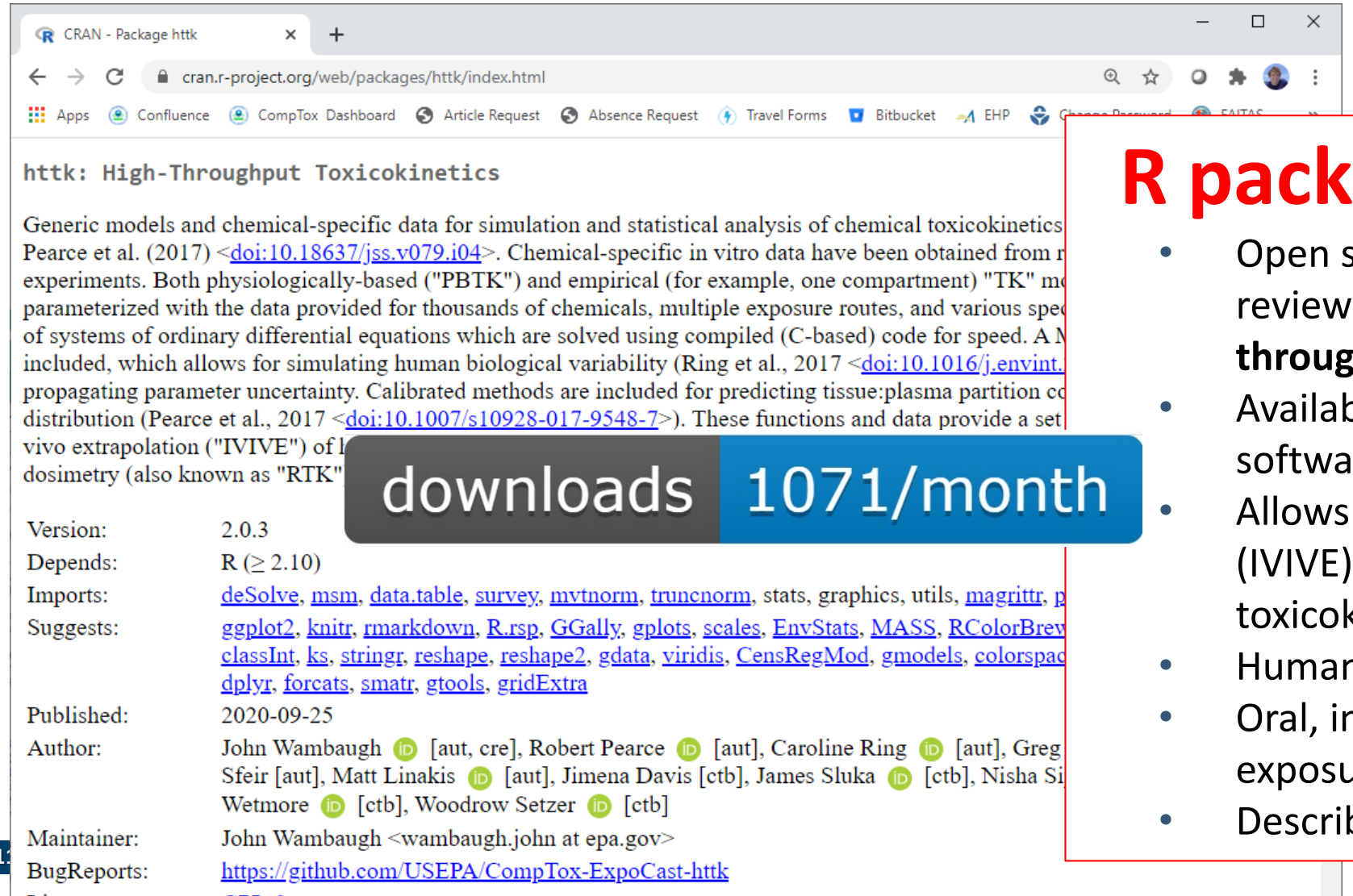
https://CRAN.R-project.org/package=httk



R package "httk"

- Open source, transparent, and peer-reviewed tools and data for **high throughput toxicokinetics (httk)**
- Available publicly for free statistical software R
- Allows *in vitro-in vivo* extrapolation (IVIVE) and physiologically-based toxicokinetics (PBTK)
- Human-specific data for >1000 chemicals
- Oral, intravenous, and inhalation exposure routes
- Described in Pearce et al. (2017)

NAMs for Exposure: High Throughput Models

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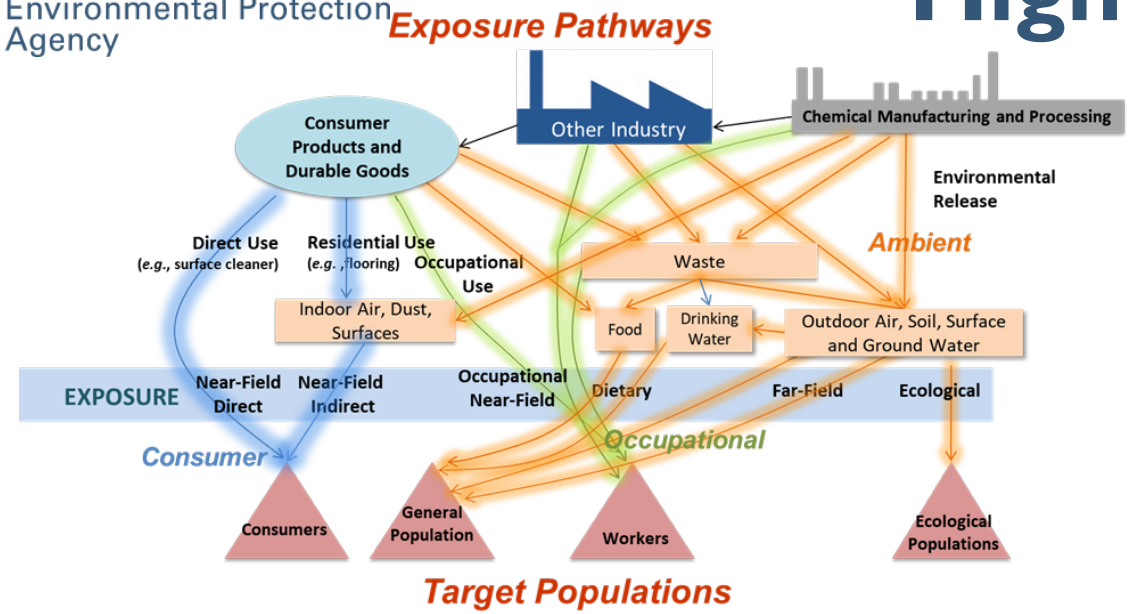
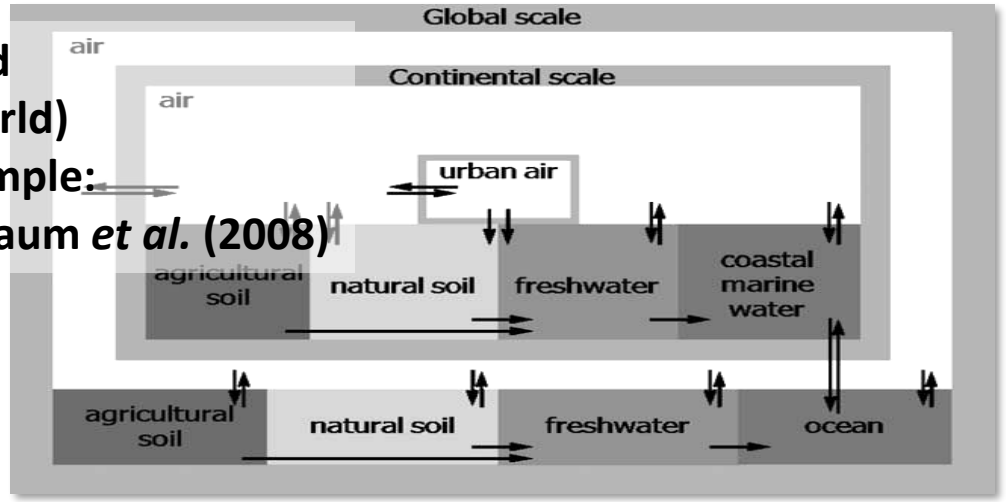
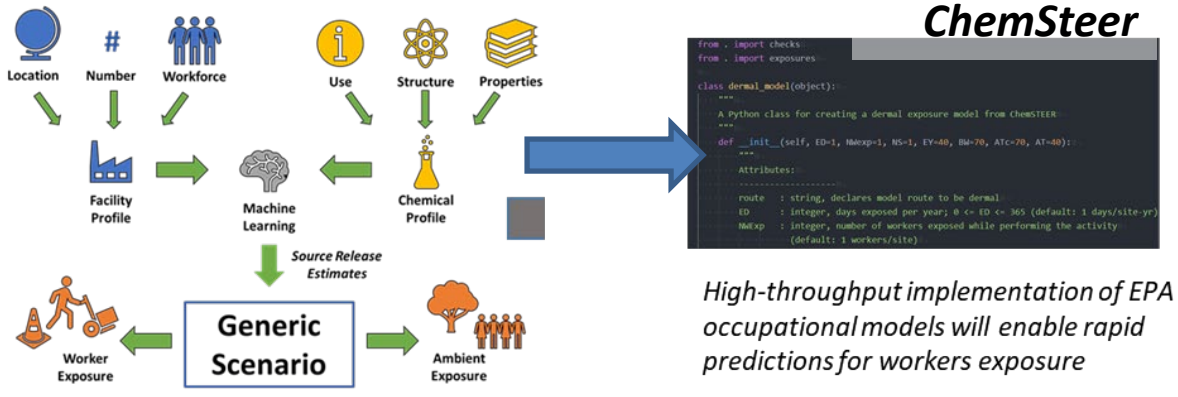


Far-field (the world) for example: Rosenbaum *et al.* (2008)



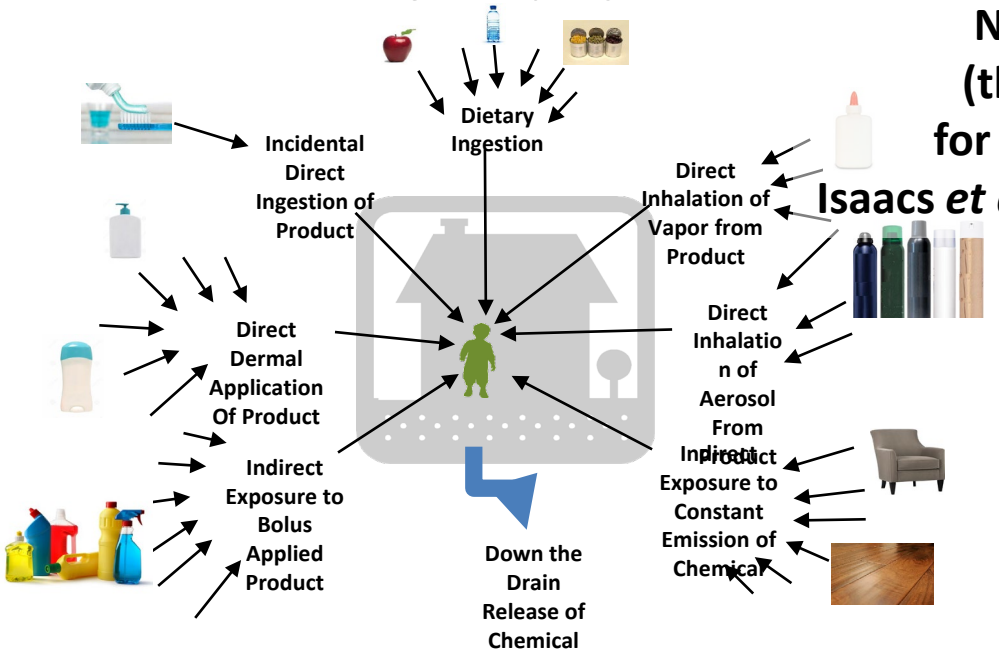
Occupational for example: ChemSteer



High-throughput implementation of EPA occupational models will enable rapid predictions for workers exposure

Meyer et al. (2018)

Near-field (the home) for example: Isaacs *et al.* (2014)



Slide from Kristin Isaacs

Selecting the Appropriate Model Depends on Chemical Use

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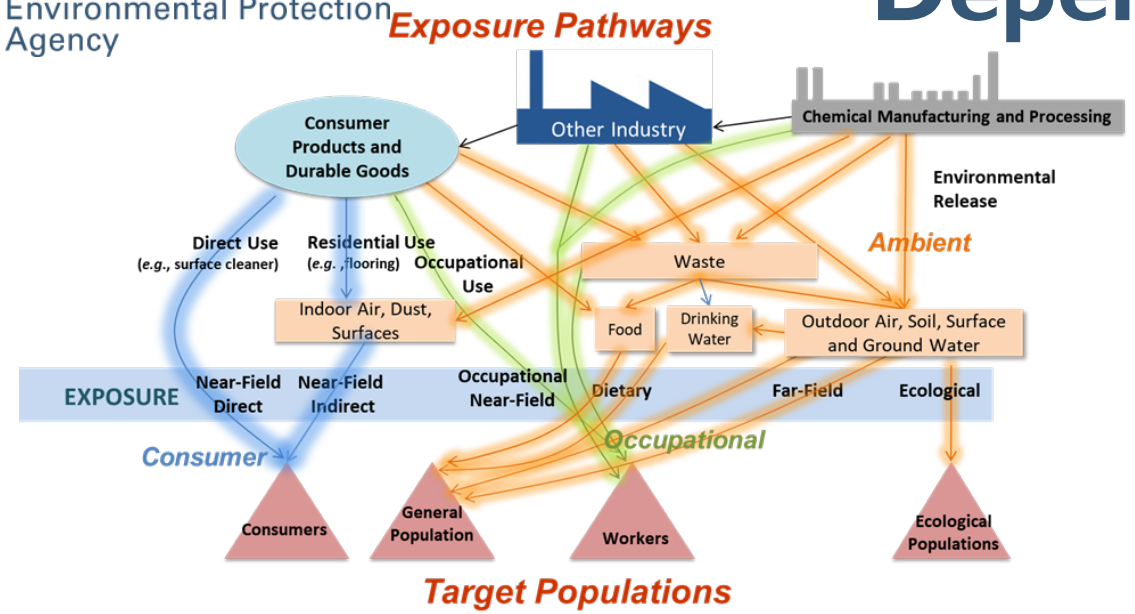
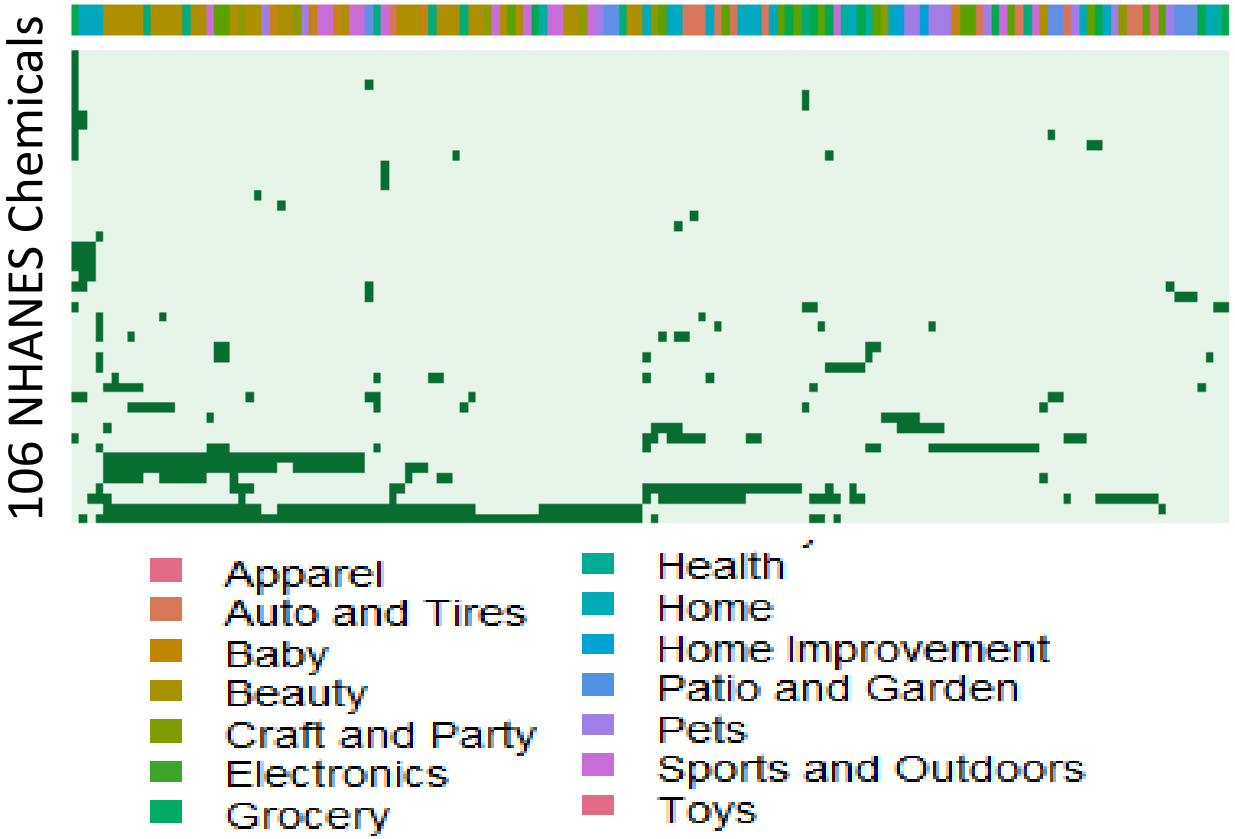


- Different chemicals are involved in different exposure pathways
- Some pathways have much higher average exposures!
- Near field sources have been known to be important at least since 1987 – see Wallace, *et al.*

Occurrence of Chemicals in Retail Products

>2000 chemicals with Material Safety Data Sheets

Goldsmith *et al.*, 2014



How Can we Know Chemical Use? Chemical Property NAMs

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Contents lists available at ScienceDirect

Food and Chemical Toxicology

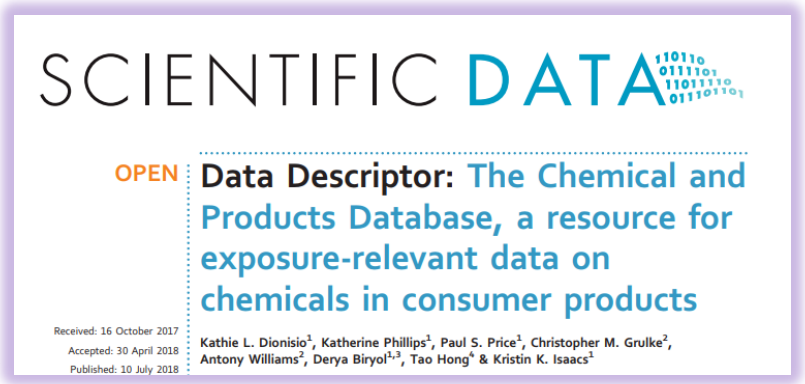
journal homepage: www.elsevier.com/locate/foodchemtox

Development of a consumer product ingredient database for chemical exposure screening and prioritization

M.-R. Goldsmith[a,*], C.M. Grulke[a], R.D. Brooks[b], T.R. Transue[c], Y.M. Tan[a], A. Frame[a,e], P.P. Egeghy[a], R. Edwards[d], D.T. Chang[a], R. Tornero-Velez[a], K. Isaacs[a], A. Wang[a,e], J. Johnson[a], K. Holm[a], M. Reich[f], J. Mitchell[g], D.A. Vallero[a], L. Phillips[a], M. Phillips[a], J.F. Wambaugh[a], R.S. Judson[a], T.J. Buckley[a], C.C. Dary[a]

MSDS Data

Occurrence and quantitative chemical composition


SCIENTIFIC DATA

OPEN

Data Descriptor: The Chemical and Products Database, a resource for exposure-relevant data on chemicals in consumer products

Received: 16 October 2017
Accepted: 30 April 2018
Published: 10 July 2018

Kathie L. Dionisio[1], Katherine Phillips[1], Paul S. Price[1], Christopher M. Grulke[2], Antony Williams[2], Derya Biryol[1,3], Tao Hong[4] & Kristin K. Isaacs[1]

Broad "index" of chemical uses


Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Exploring consumer exposure pathways and patterns of use for chemicals in the environment

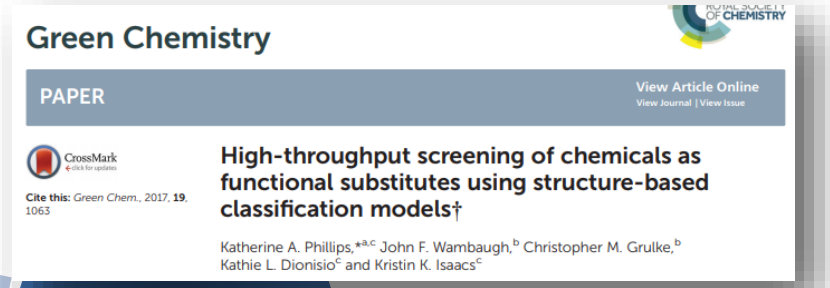
Kathie L. Dionisio[a], Alicia M. Frame[b,1], Michael-Rock Goldsmith[a,2], John F. Wambaugh[b], Alan Liddell[c,3], Tommy Cathey[d], Doris Smith[b], James Vail[b], Alexi S. Ernstoff[e], Peter Fantke[e], Olivier Jolliet[f],

CPCat

CPDat

EPA United States Environmental Protection Agency

Chemistry Dashboard


Green Chemistry

PAPER

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Cite this: Green Chem., 2017, 19, 1063

High-throughput screening of chemicals as functional substitutes using structure-based classification models†

Katherine A. Phillips,*[a,c] John F. Wambaugh,[b] Christopher M. Grulke,[b] Kathie L. Dionisio[c] and Kristin K. Isaacs[c]

Functional Use Data

The roles that chemicals serve in products


Journal of Exposure Science and Environmental Epidemiology (2018) 28, 216–222

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www.nature.com/jes

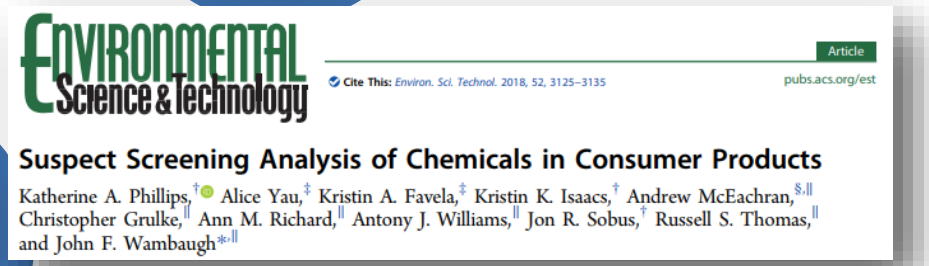
ORIGINAL ARTICLE

Consumer product chemical weight fractions from ingredient lists

Kristin K. Isaacs[1], Katherine A. Phillips[1], Derya Biryol[1,2], Kathie L. Dionisio[1] and Paul S. Price[1]

Ingredient Lists

Occurrence data


Environmental Science & Technology

Article

Cite This: Environ. Sci. Technol. 2018, 52, 3125−3135

pubs.acs.org/est

Suspect Screening Analysis of Chemicals in Consumer Products

Katherine A. Phillips,[†] Alice Yau,[‡] Kristin A. Favela,[‡] Kristin K. Isaacs,[†] Andrew McEachran,[§,∥] Christopher Grulke,[∥] Ann M. Richard,[∥] Antony J. Williams,[∥] Jon R. Sobus,[†] Russell S. Thomas,[∥] and John F. Wambaugh*[,∥]

Measured Data

Measurement of chemicals in consumer products

https://comptox.epa.gov/dashboard

Slide from Kristin Isaacs

Machine Learning NAMs for Exposure

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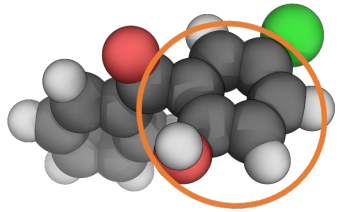
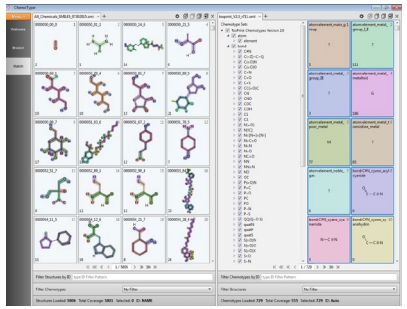
Use Database (FUSE)

"…**machine learning** can be thought of as inferring plausible models to explain observed data." Gharamani (2015)



Chemical Structure and Property Descriptors



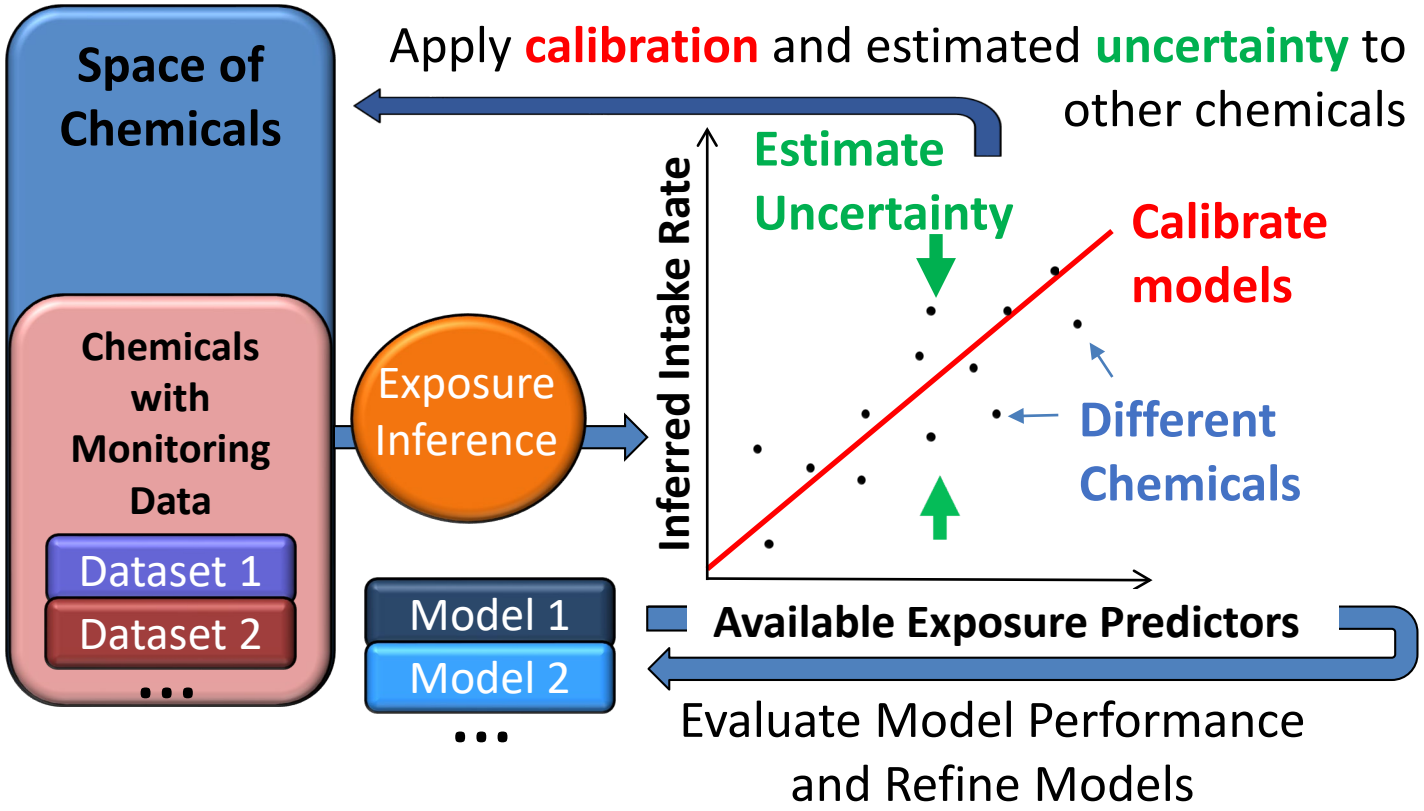
Machine Learning Based Classification Models
(Random Forest, Breiman, 2001)

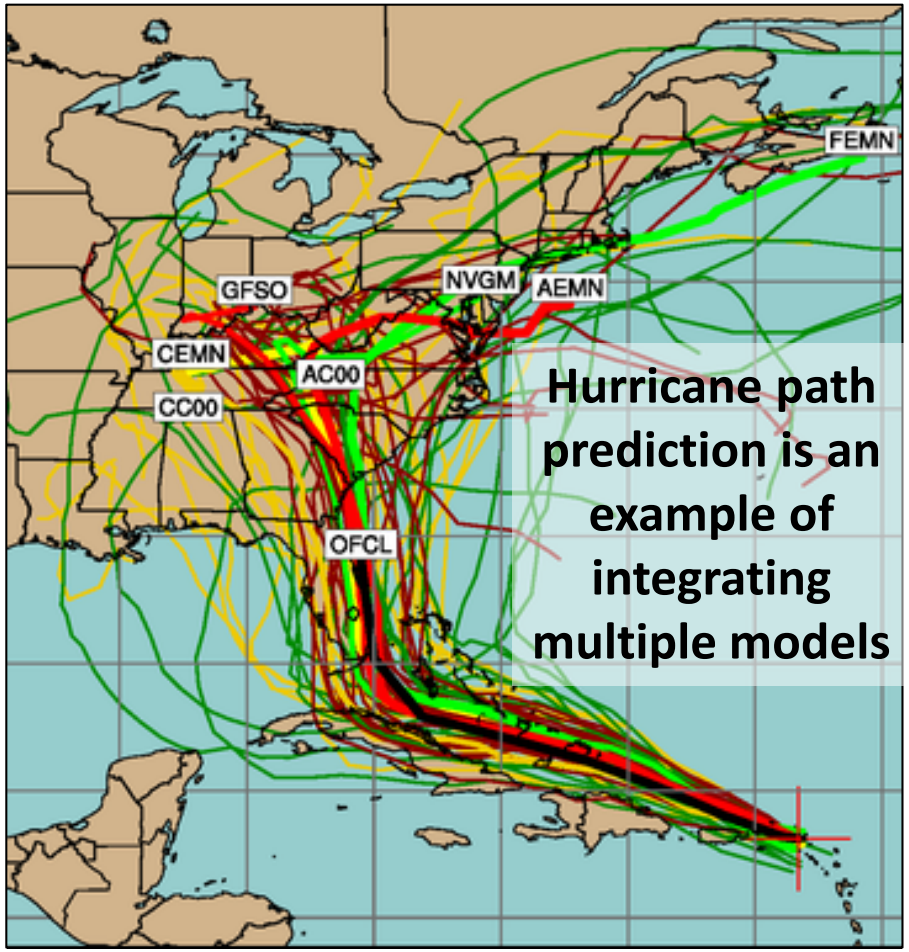
Prediction of Of Potential Alternatives from Chemical Libraries

Phillips *et al.* (2017)

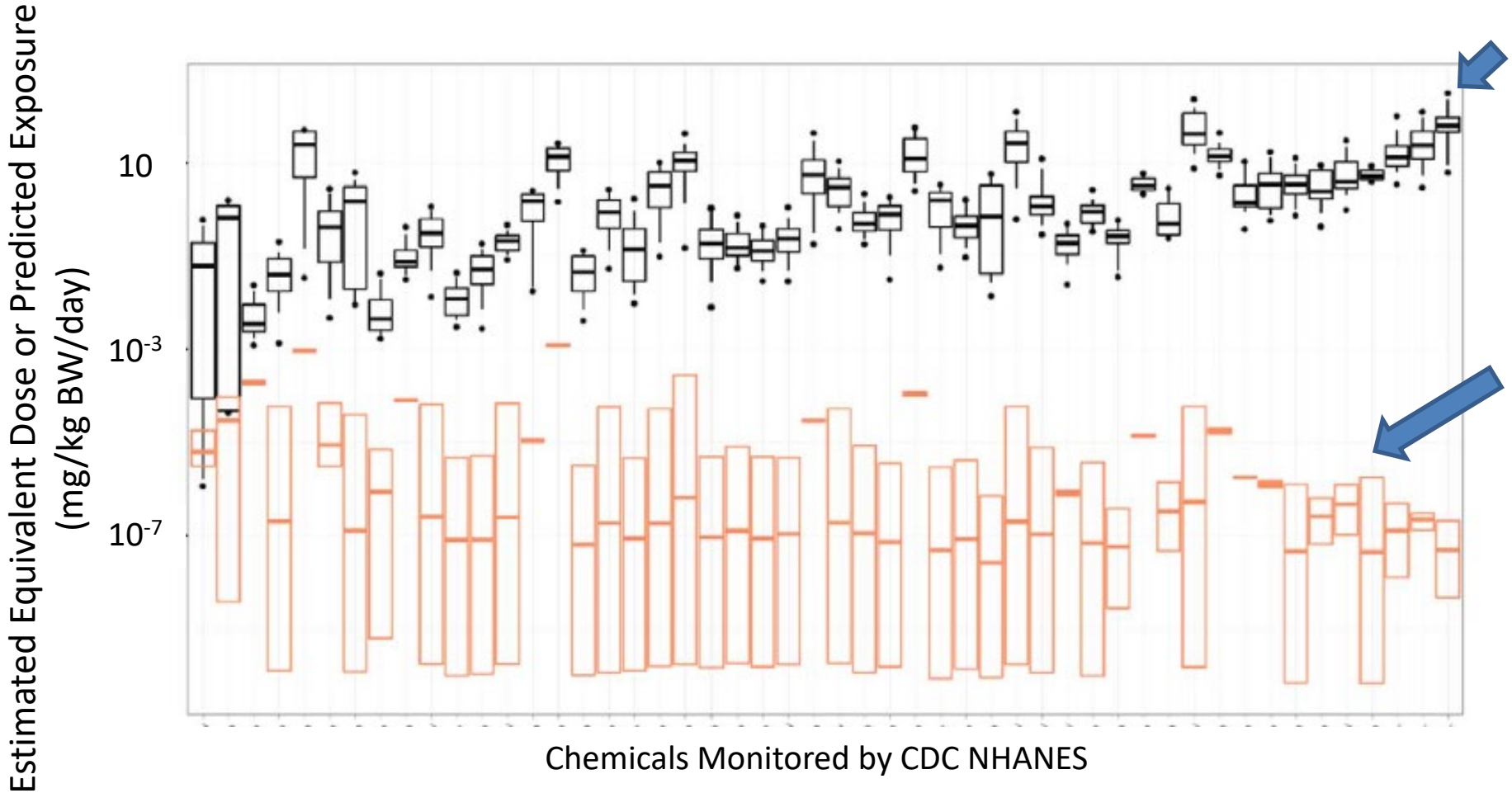
Evaluation NAMs for Exposure: The SEEM Framework

- We use Bayesian methods to incorporate multiple models into consensus predictions for 1000s of chemicals within the **Systematic Empirical Evaluation of Models (SEEM)** (Wambaugh et al., 2013, 2014; Ring et al., 2018)



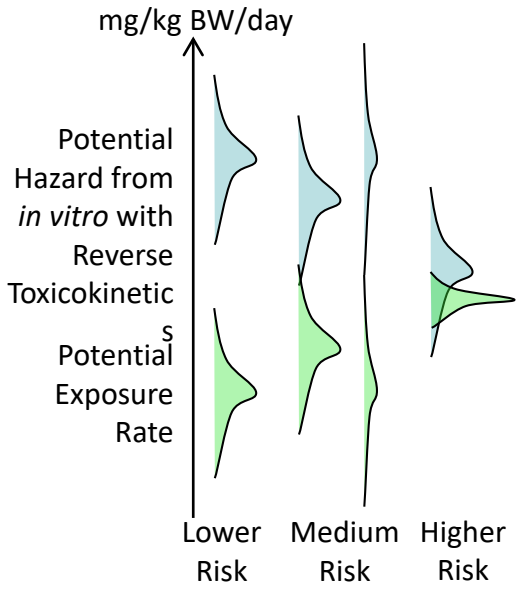


Chemical Prioritization NAMs



High throughput *in vitro* screening can estimate doses needed to cause bioactivity (for example, Wetmore et al., 2015)

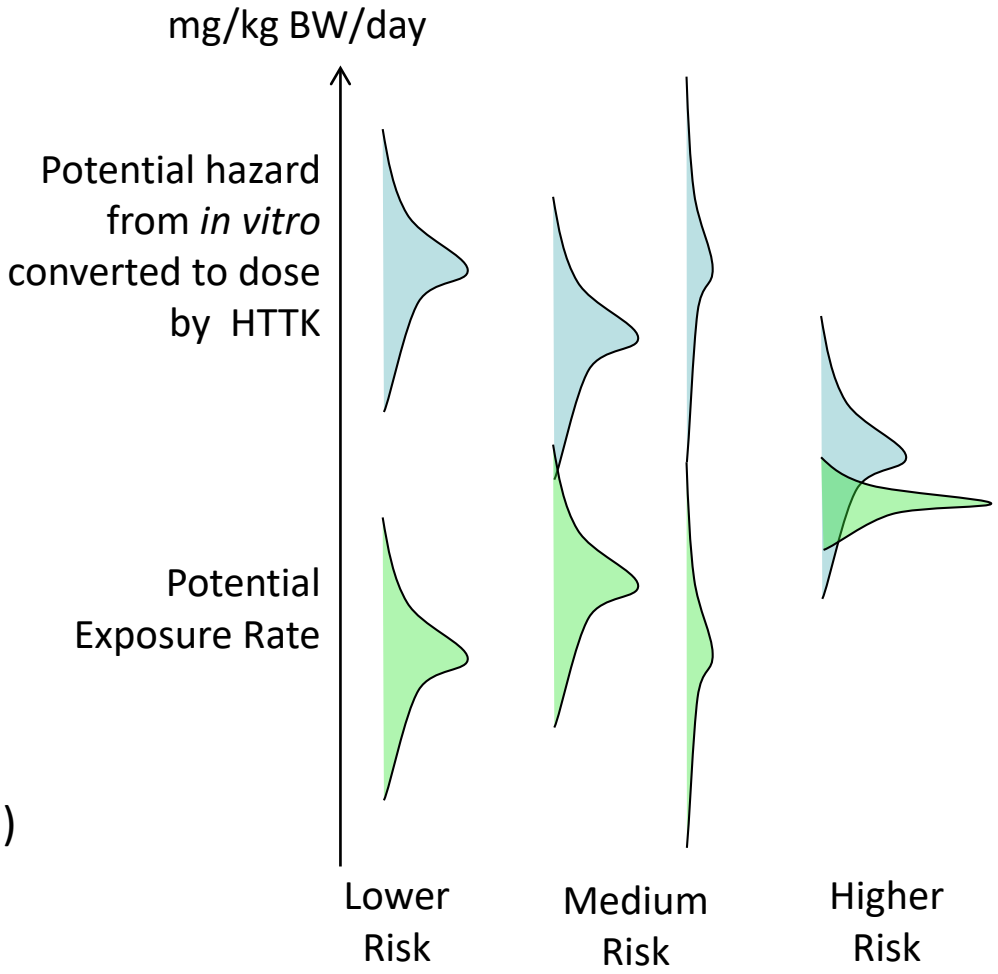
Exposure intake rates can be inferred from biomarkers (for example, Ring et al., 2018)



Ring *et al*. (2017)

Summary

- We must consider **exposure** to identify chemical risk – for example, windows of developmental susceptibility and occupational exposure
- In the U.S. **both** the toxic potency (**hazard**) and the magnitude of the **exposure** is needed to calculate risk
  - There are thousands of chemicals in commerce and the environment without these data
- **New approach methodologies (NAMs)** are being developed to prioritize these existing and new chemicals for testing
  - These NAMs include TK and exposure (Wambaugh et al., 2019)
- If the **uncertainty** in these tools is **properly evaluated and quantified**, we can inform public health decision making



The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. EPA

ExpoCast Project (Exposure Forecasting)

Center for Computational Toxicology and Exposure

Linda Adams
Lucas Albrecht
Matthew Boyce*
Miyuki Breen*
Alex Chao
Daniel Dawson*
Mike Devito
Christopher Eklund
Peter Egeghy
Marina Evans
Alex Fisher*
Rocky Goldsmith
Louis Groff*
Chris Grulke
Colin Guider*
Mike Hughes
Victoria Hull*
Kristin Isaacs
Richard Judson
Jen Korol-Bexell*
Anna Kreutz*
Charles Lowe*
Katherine Phillips
Paul Price
Tom Purucker
Ann Richard
Caroline Ring
Risa Sayre*
Mark Sfeir*
Marci Smeltz*
Jon Sobus
Zach Stanfield*
Mike Tornero-Velez
Rusty Thomas
Elin Ulrich
Dan Vallero
Barbara Wetmore
John Wambaugh
Antony Williams

*Trainees

CEMM

Hongwan Li
Xiaoyu Liu
Seth Newton
Mark Strynar

Collaborators

Arnot Research and Consulting
Jon Arnot
Johnny Westgate
Integrated Laboratory Systems
Kamel Mansouri
Xiaoqing Chang
Shannon Bell
National Toxicology Program
Steve Ferguson
Nisha Sipes
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

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