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Environmental Protection
Agency

EPA Exposure Forecasting (ExpoCast)

John Wambaugh
Center for Computational Toxicology and Exposure
Office of Research and Development
U.S. Environmental Protection Agency
wambaugh.john@epa.gov https://orcid.org/0000-0002-4024-534X

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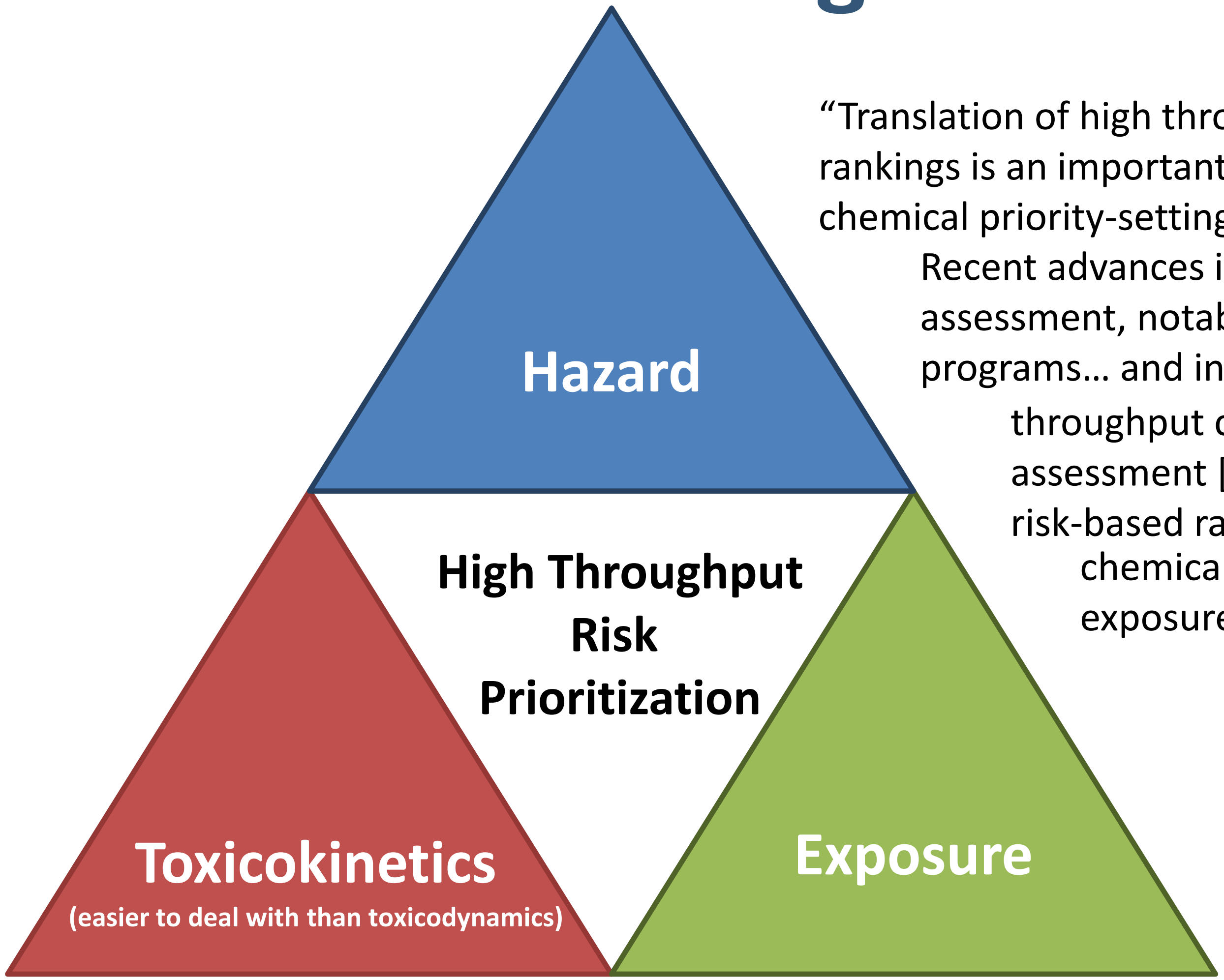
Calculating Chemical Risk

NASEM (2017)



"Translation of high throughput data into risk-based rankings is an important application of exposure data for chemical priority-setting. Recent advances in high throughput toxicity assessment, notably the ToxCast and Tox21 programs… and in high throughput computational exposure assessment [ExpoCast] have enabled first-tier risk-based rankings of chemicals on the basis of margins of exposure" - National Academies of Sciences, Engineering, and Medicine (NASEM)

New approach methodologies (NAMs) enable risk assessors to more rapidly address public health challenges and chemical regulation

United States Environmental Protection Agency

NAMs for Exposure Science

Exposure NAM Class	Description	Traditional Approach	NAM Makes Use of: Measurement	Toxicokinetics	Models	Descriptors	Evaluation	Machine Learning
Measurements	New techniques including screening analyses capable of detecting hundreds of chemicals present in a sample	Targeted (chemical-specific) analyses	-	●	●	●		●
Toxicokinetics	High throughput methods using *in vitro* data to generate chemical-specific models	Analyses based on *in vivo* animal studies	●	-		●		●
HTE Models	Models capable of making predictions for thousands of chemicals	Models requiring detailed, chemical- and scenario-specific information	●	●	-	●		
Chemical Descriptors	Informatic approaches for organizing chemical information in a machine-readable format	Tools targeted at single chemical analyses by humans				-		●
Evaluation	Statistical approaches that use the data from many chemicals to estimate the uncertainty in a prediction for a new chemical	Comparison of model predictions to data on a per chemical basis	●	●	●	●	-	●
Machine Learning	Computer algorithms to identify patterns	Manual Inspection of the Data	●	●		●		-
Prioritization	Integration of exposure and other NAMs to identify chemicals for follow-up study	Expert decision making	●	●	●	●	●	●

Wambaugh et al., (2019)

EPA United States Environmental Protection Agency

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Wambaugh et al., (2019)

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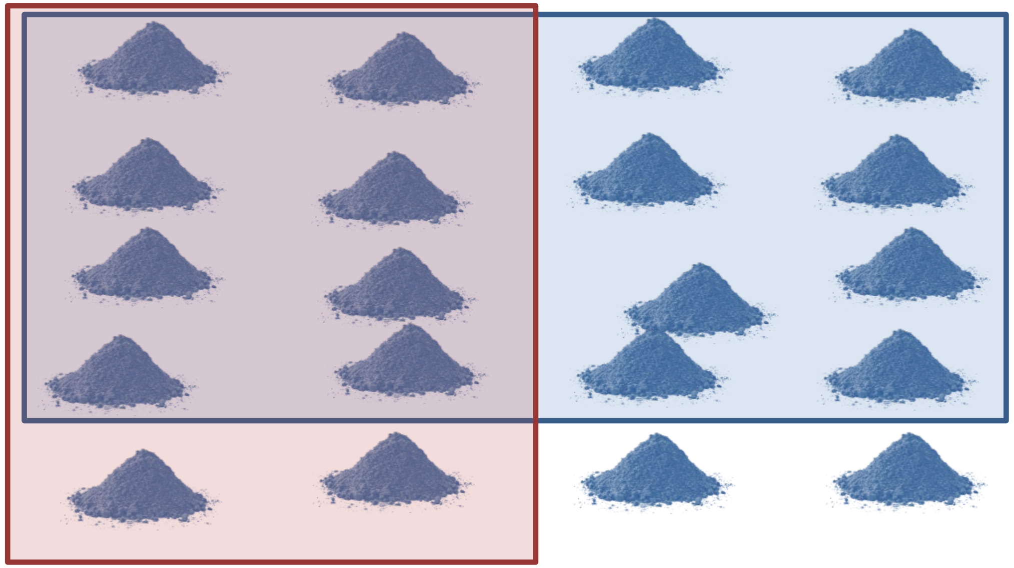
EPA's Non-Targeted Analysis Collaborative Trial (ENTACT)

- Suspect screening / Non-targeted analyses (SSA/NTA) present opportunities for new exposure data

- What NTA methods are available? What is the coverage of chemical universe and matrices? How do methods differ in their coverage?

The Chemical Universe

Method 1



Method 2

Led by Jon Sobus,
Seth Newton and Elin Ulrich

- Phase 1:
  - Collaborators provided 10 mixtures of 100-400 ToxCast chemicals each
  - Mass spectrometry equipment vendors provided with individual chemical standards

- Phase 2: Fortified reference house dust, human serum, and silicone wristbands

Ulrich et al. (2019)
Sobus et al. (2019)

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Wambaugh et al., (2019)

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Chemical Property NAMs

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]

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

Broad "index" of chemical uses

CPCat

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],

CPDat

EPA United States Environmental Protection Agency — Chemistry Dashboard

Green Chemistry

PAPER

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
© 2018 Nature America, Inc., part of Springer Nature. All rights reserved 1559-0631/18
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

Measured 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[*,∥]

Measurement of chemicals in consumer products

https://comptox.epa.gov/dashboard

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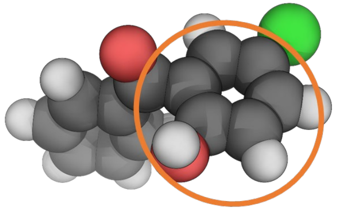
Wambaugh et al., (2019)

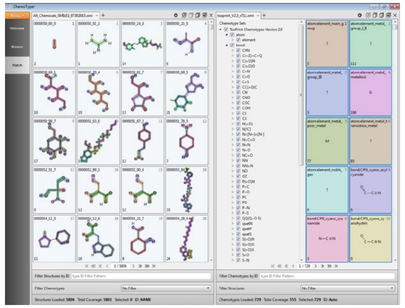
Machine Learning NAMS

Chemical Functional Use Database (FUSE)

Positive Examples Negative Examples

Chemical Structure and Property Descriptors





Random Forest Classification Models
(Breiman, 2001)
with five-fold cross validation

Successful Model

Failed Model

Probabilistic Predictions of Potential Chemical Uses

Phillips *et al.* (2017)

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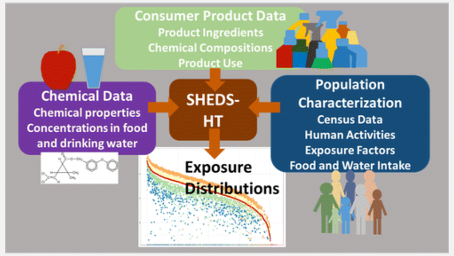
Wambaugh et al., (2019)

United States Environmental Protection Agency

High Throughput Exposure (HTE) Models for Key Pathways

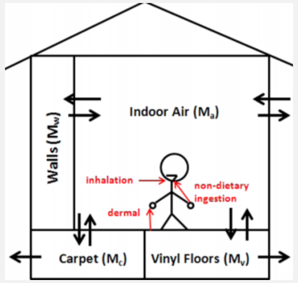
Consumer (Near-Field) Pathways

SHEDS-HT *(Isaacs et al., 2014)*



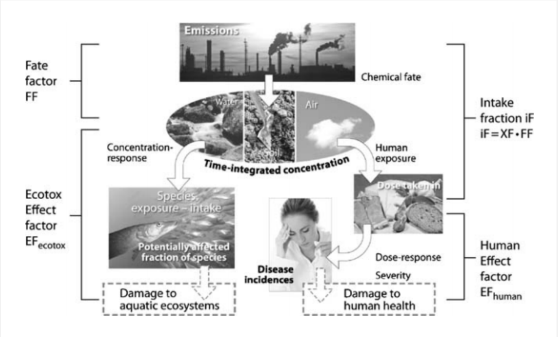
RAIDAR-ICE *(Li et al., 2018)*

FINE *(Shin et al., 2015)*

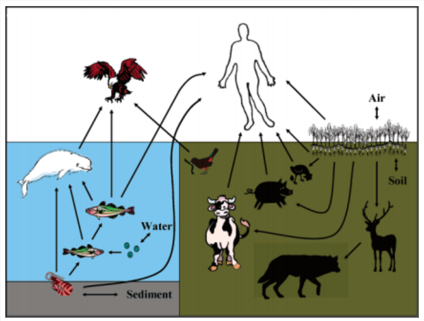


Ambient (Far-Field) Pathways

UseTox *(Rosenbaum et al., 2008)*

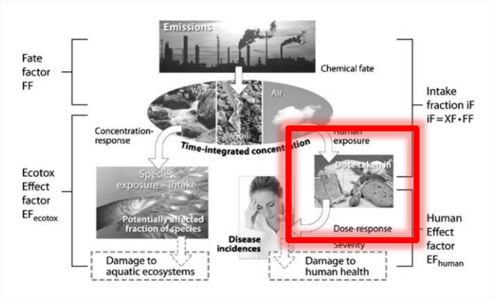


RAIDAR *(Arnot et al., 2006, 2008)*

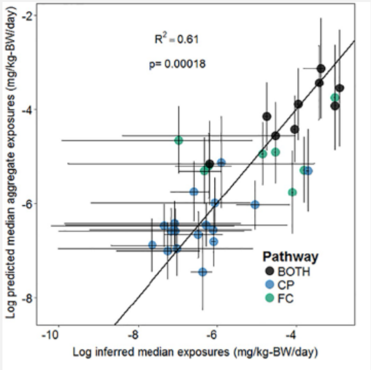


Dietary Pathways

UseTox *(Rosenbaum et al. (2008)*



SHEDS-HT *(Biryol et al., 2017)*



 Office of Research and Development

Slide from Kristin Isaacs

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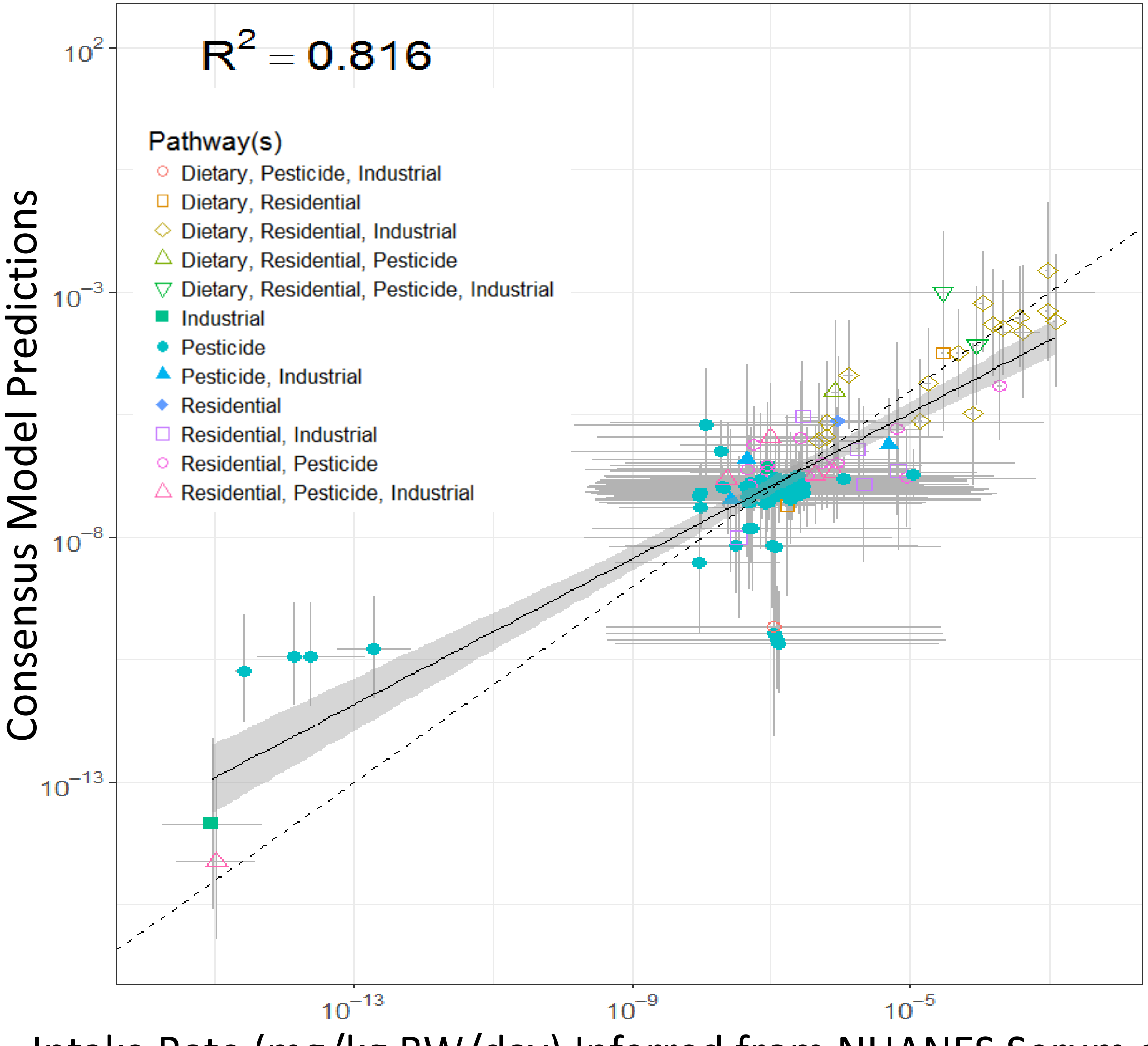
Wambaugh et al., (2019)

SEEM3: Pathway-Based Consensus Modeling



- SEEM3 consensus model provides estimates of human median intake rate (mg/kg/day) for nearly 500,000 chemicals via the CompTox Chemicals Dashboard (http://comptox.epa.gov/dashboard)
- SEEM3 first predicts relevant exposure pathways from chemical structure – model predictions are then weighted according to the models' abilities to explain NHANES data
- We rely on pathway determinations from CPDat
- We rely on NHANES biomonitoring data
  - 2014 FIFRA Scientific Advisory Panel identified need for broader sets of evaluation data

Ring et al., 2018

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Wambaugh et al., (2019)

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Open-Source Tools and Data for HTTK

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

CRAN - Package httk

cran.r-project.org/web/packages/httk/index.html

Apps Confluence CompTox Dashboard Article Request Absence Request Travel Forms Bitbucket EHP Change Password FAITAS

httk: High-Throughput Toxicokinetics

Generic models and chemical-specific data for simulation and statistical analysis of chemical toxicokinetics Pearce et al. (2017) <doi:10.18637/jss.v079.i04>. Chemical-specific in vitro data have been obtained from r experiments. Both physiologically-based ("PBTK") and empirical (for example, one compartment) "TK" mo parameterized with the data provided for thousands of chemicals, multiple exposure routes, and various spec of systems of ordinary differential equations which are solved using compiled (C-based) code for speed. A M included, which allows for simulating human biological variability (Ring et al., 2017 <doi:10.1016/j.envint. propagating parameter uncertainty. Calibrated methods are included for predicting tissue:plasma partition co distribution (Pearce et al., 2017 <doi:10.1007/s10928-017-9548-7>). These functions and data provide a set vivo extrapolation ("IVIVE") of high throughput screening data (for example, Tox21, ToxCast) to real-worl dosimetry (also known as "RTK")

downloads 1071/month

Version:	2.0.3
Depends:	R (≥ 2.10)
Imports:	deSolve, msm, data.table, survey, mvtnorm, truncnorm, stats, graphics, utils, magrittr, p
Suggests:	ggplot2, knitr, rmarkdown, R.rsp, GGally, gplots, scales, EnvStats, MASS, RColorBrew classInt, ks, stringr, reshape, reshape2, gdata, viridis, CensRegMod, gmodels, colorspac dplyr, forcats, smatr, gtools, gridExtra
Published:	2020-09-25
Author:	John Wambaugh [aut, cre], Robert Pearce [aut], Caroline Ring [aut], Greg Sfeir [aut], Matt Linakis [aut], Jimena Davis [ctb], James Sluka [ctb], Nisha Si Wetmore [ctb], Woodrow Setzer [ctb]
Maintainer:	John Wambaugh <wambaugh.john at epa.gov>
BugReports:	https://github.com/USEPA/CompTox-ExpoCast-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 987 chemicals
- Described in Pearce et al. (2017)

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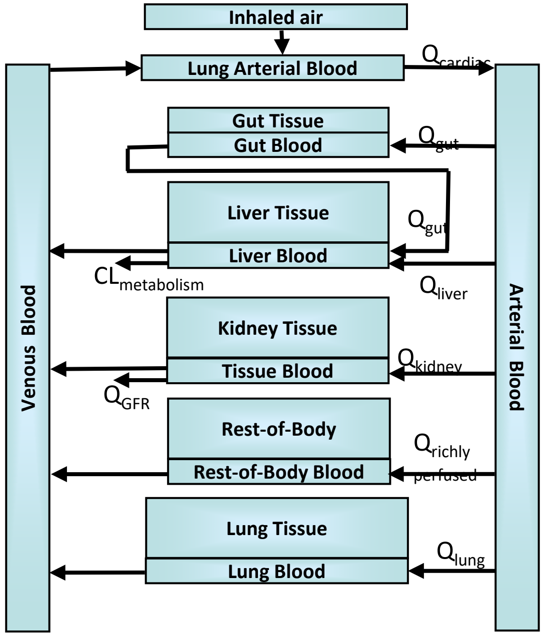
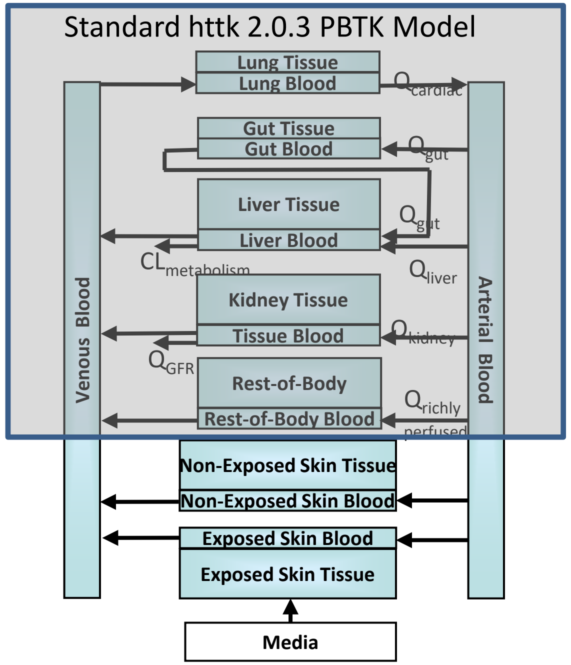
Toxicokinetics NAMs: *In Vitro* Measurements and Generic PBTK Models

Gas and Aerosol Inhalation Exposure Route

EPA, USAF, Linakis et al. (2020)

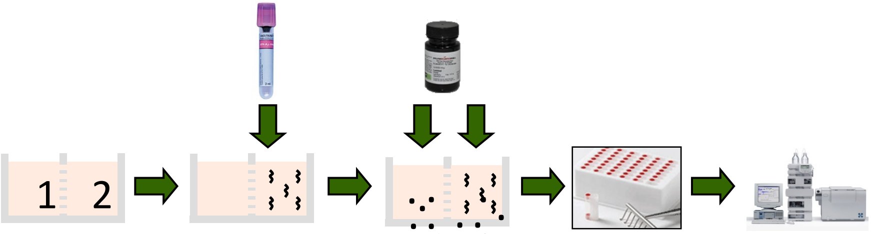




Dermal Exposure Route

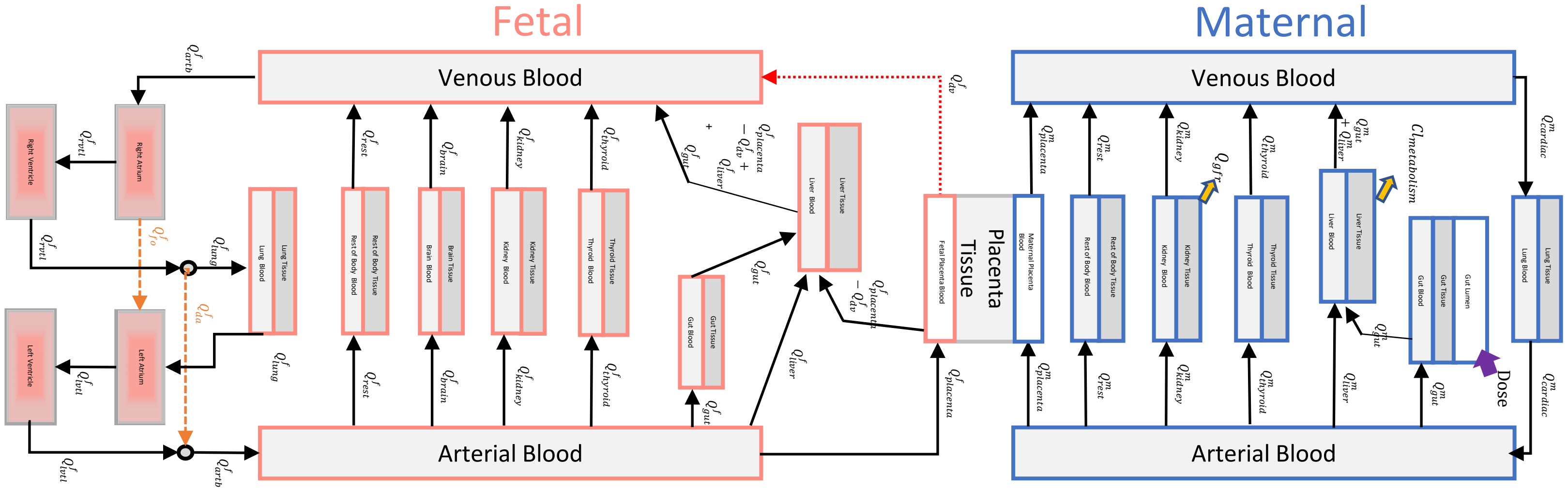
EPA, Unilever, INERIS

Wetmore et al. (2012, 2013, 2015), Wambaugh et al. (2019)



Human Gestational Model

EPA, FDA, Kapraun et al., (2020)



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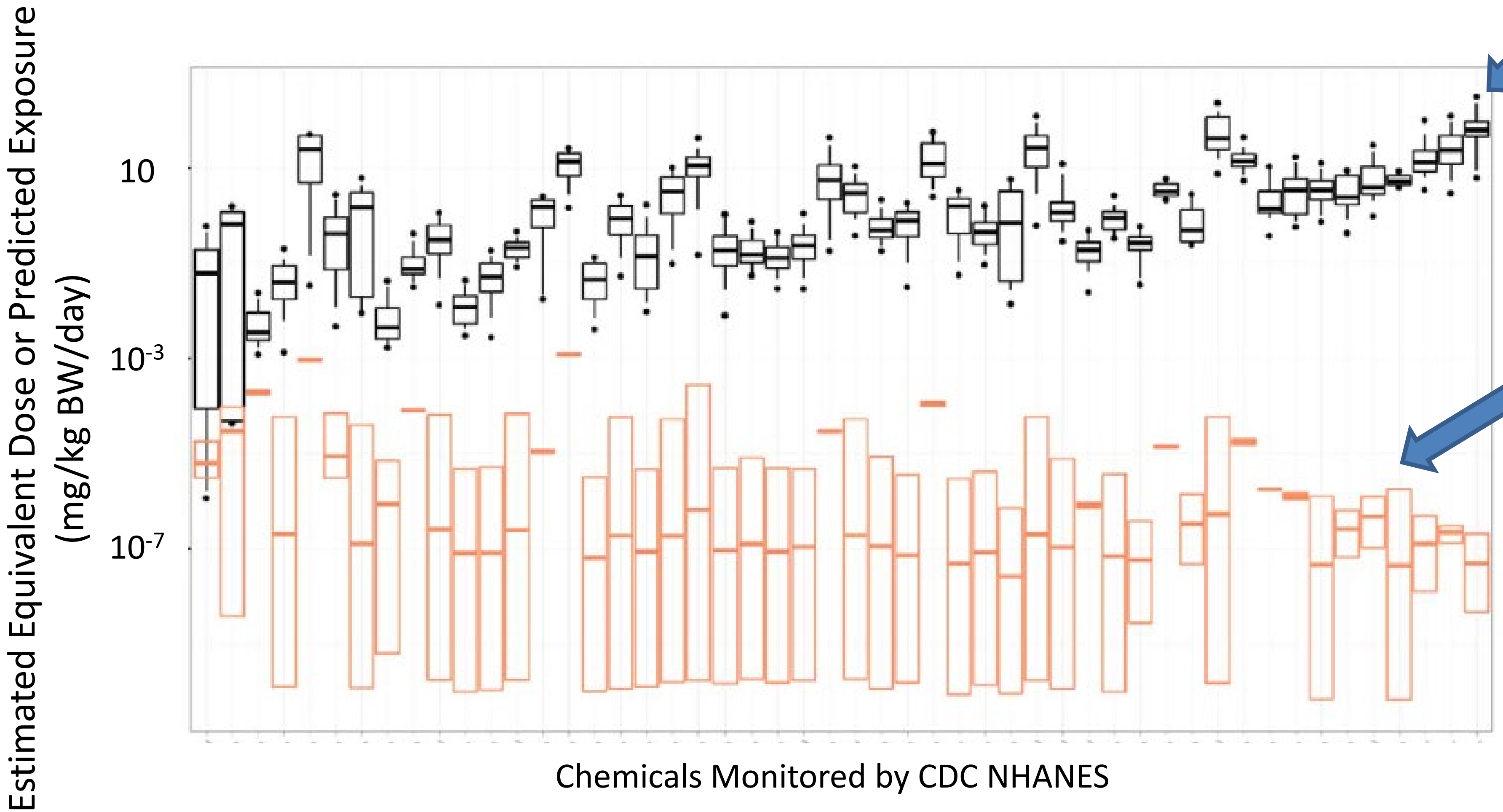
Wambaugh et al., (2019)

United States Environmental Protection Agency

Chemical Prioritization NAMs

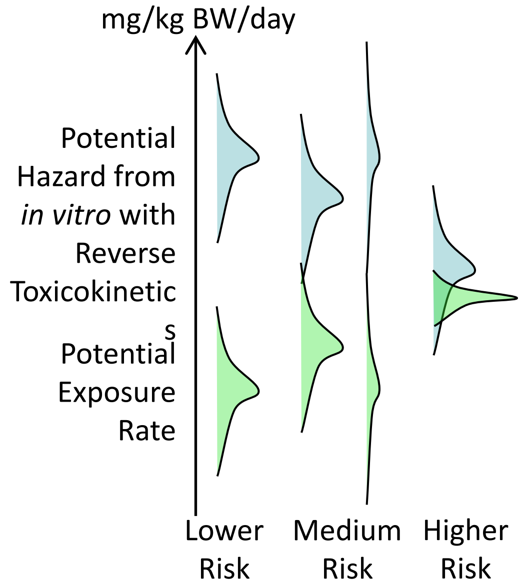


High throughput *in vitro* screening can estimate doses needed to cause bioactivity

(for example, Wetmore et al., 2015)

Exposure intake rates can be inferred from biomarkers

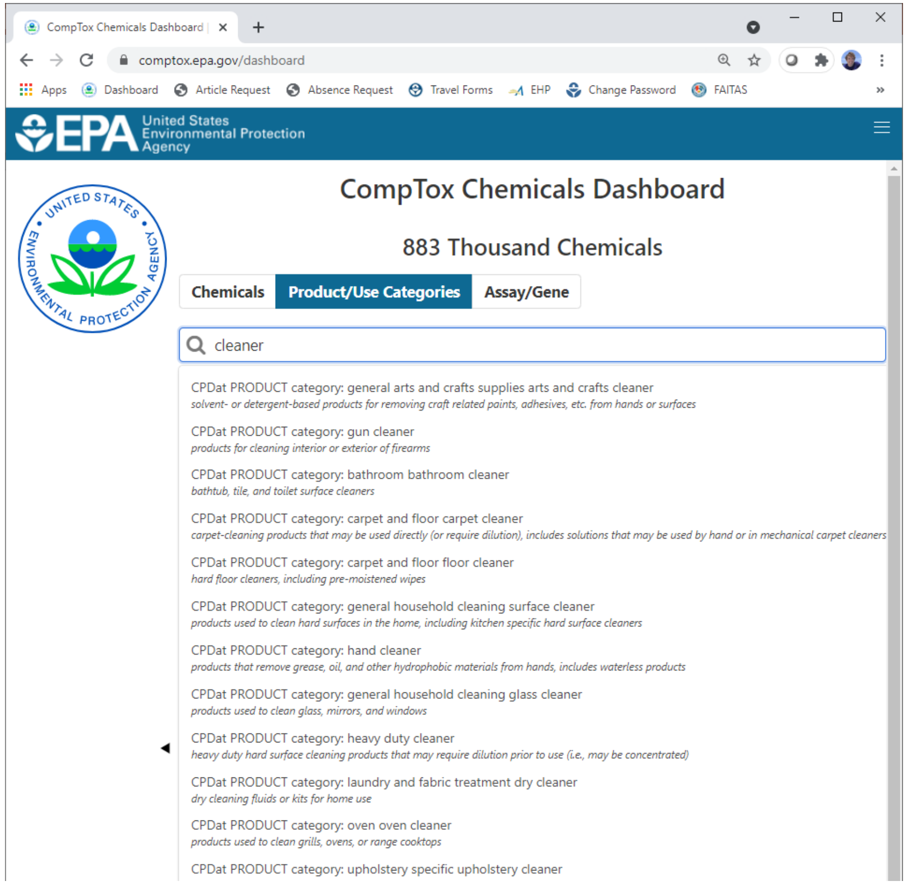
(for example, Ring et al., 2018)



Ring *et al.* (2017)

Dashboard Information

https://comptox.epa.gov/dashboard



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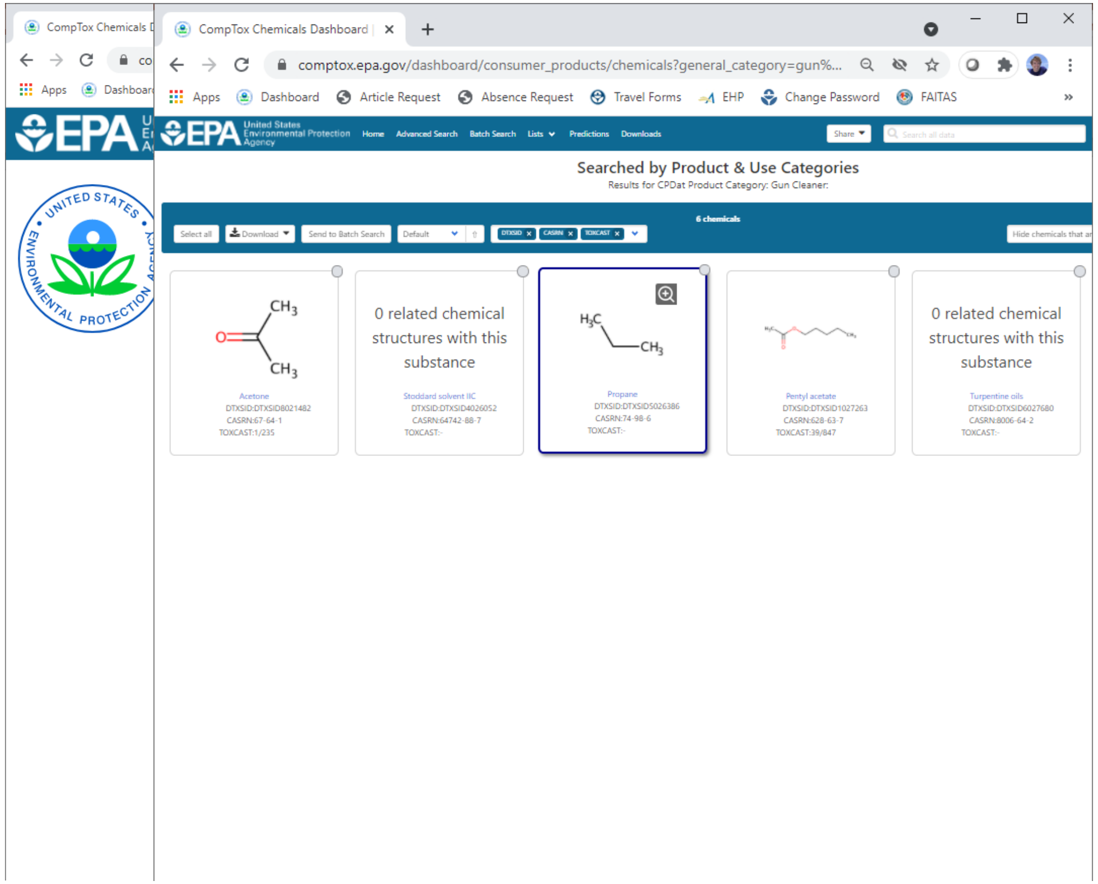

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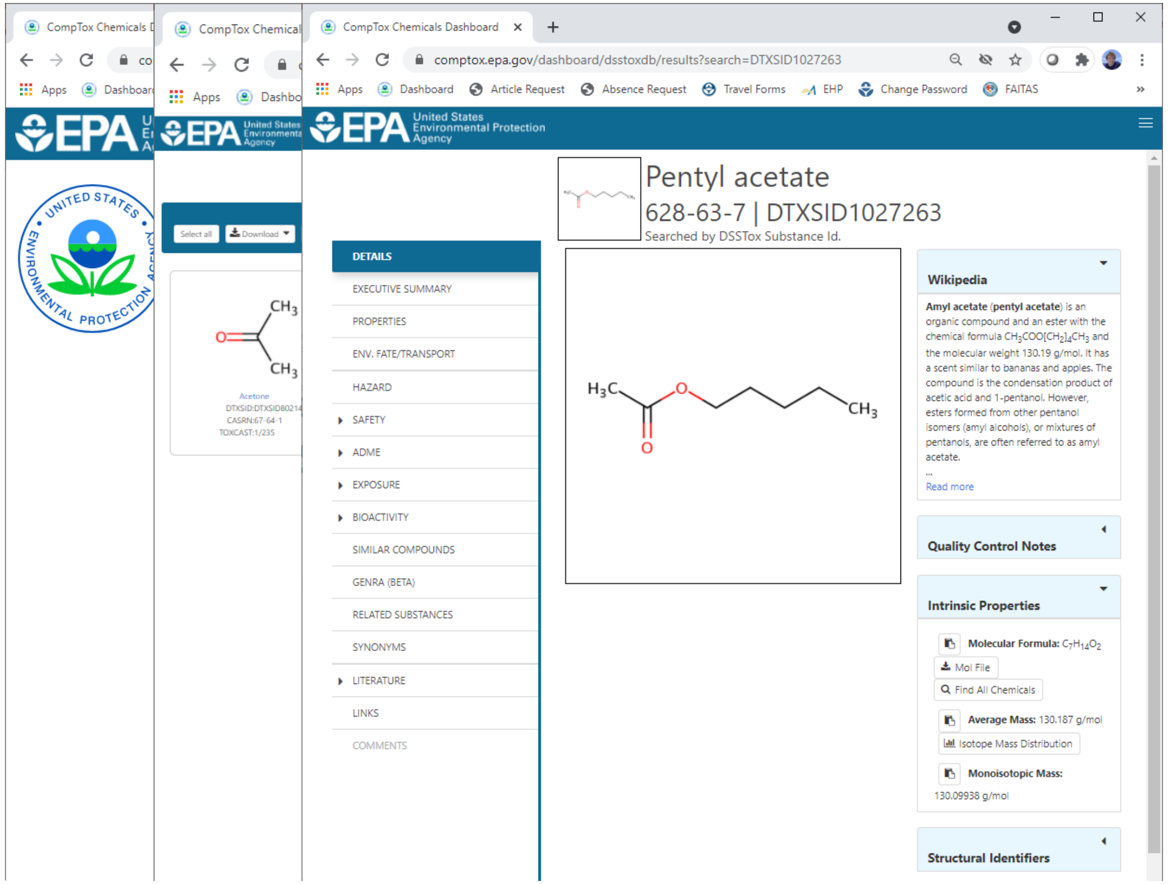

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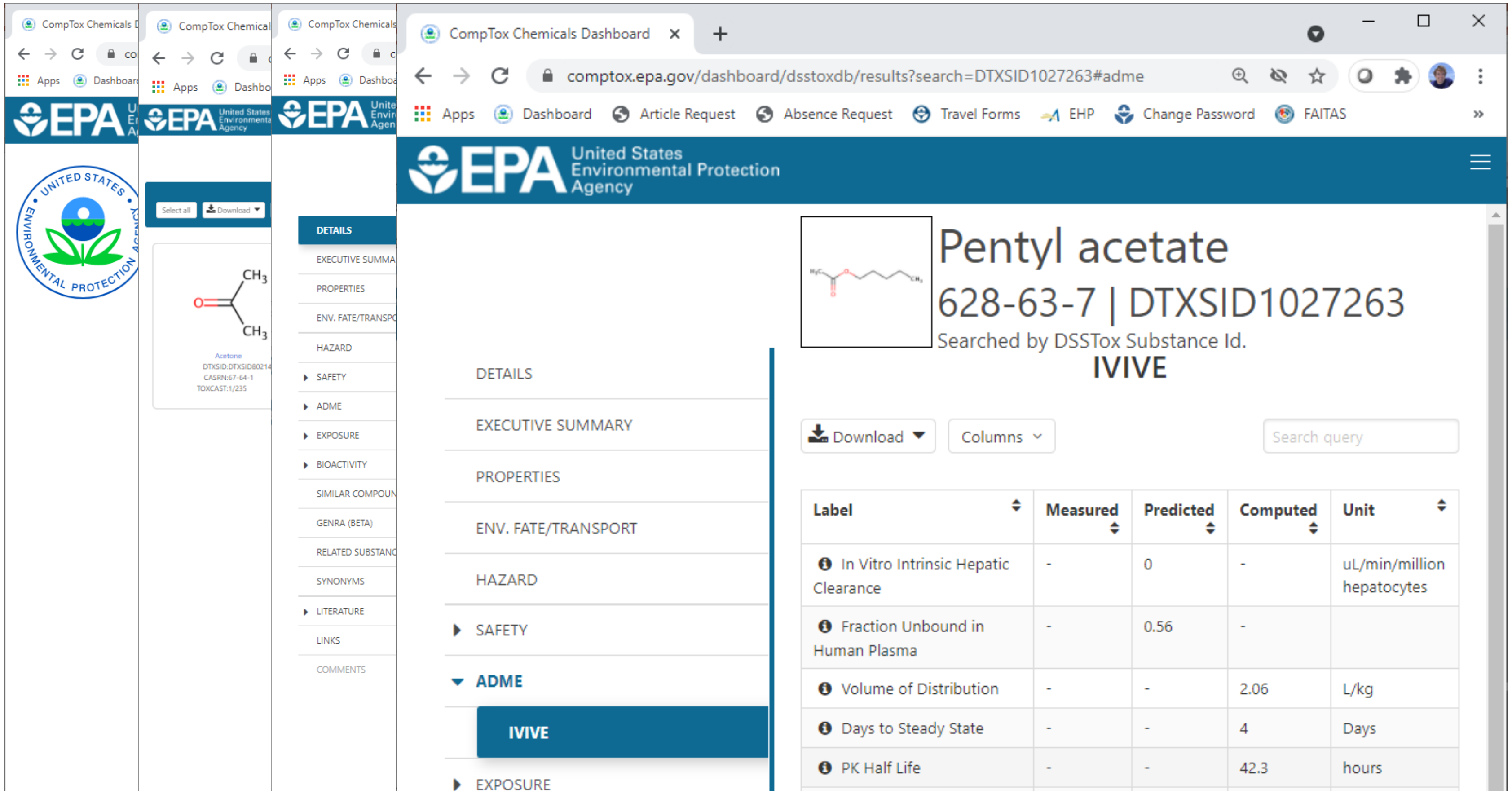

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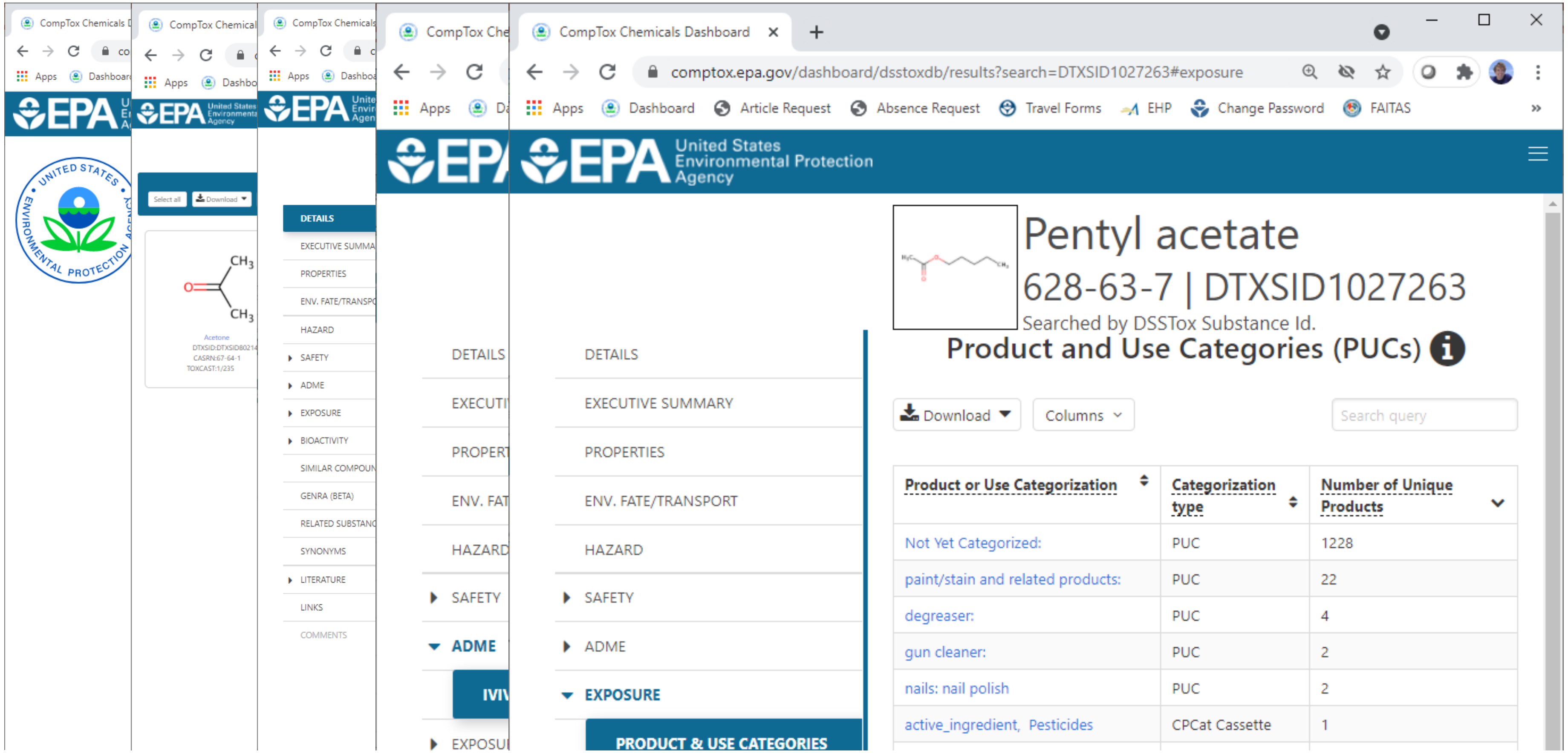

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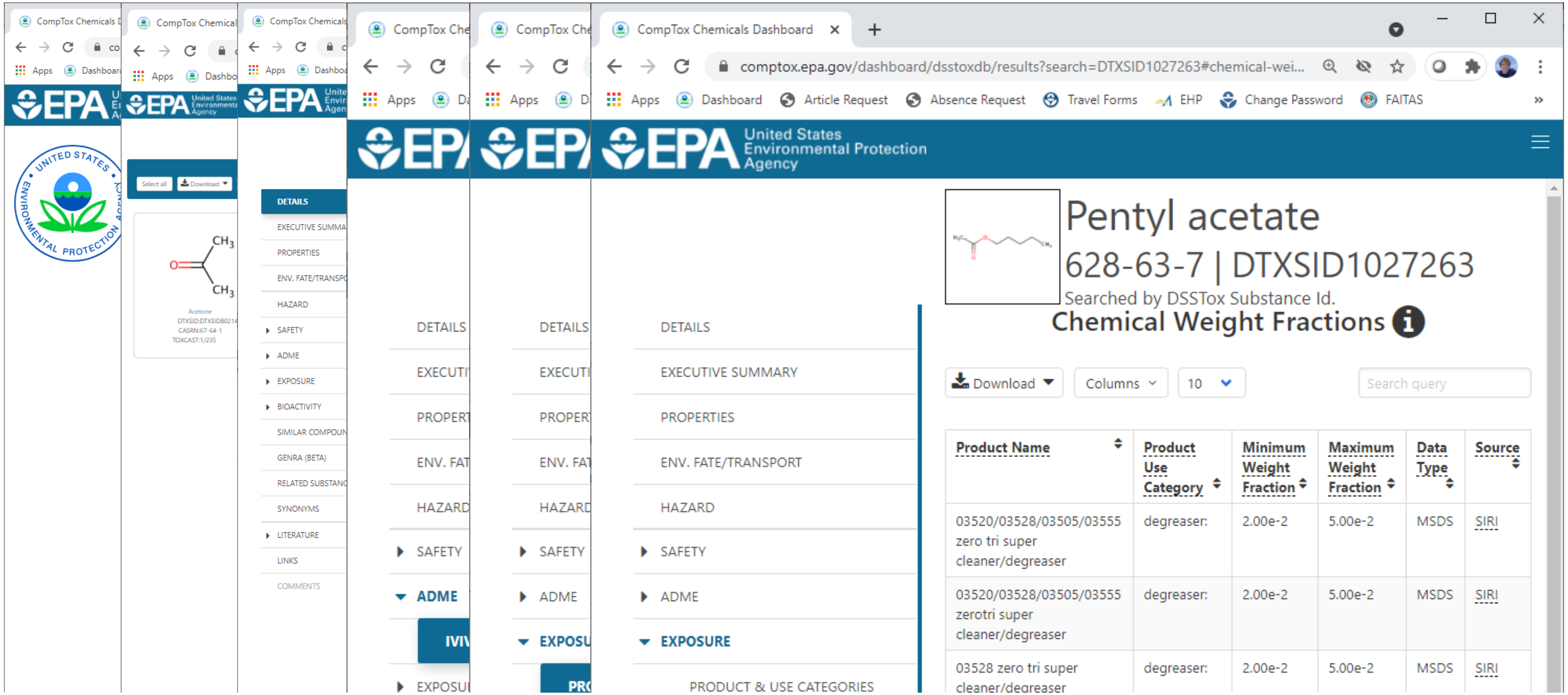

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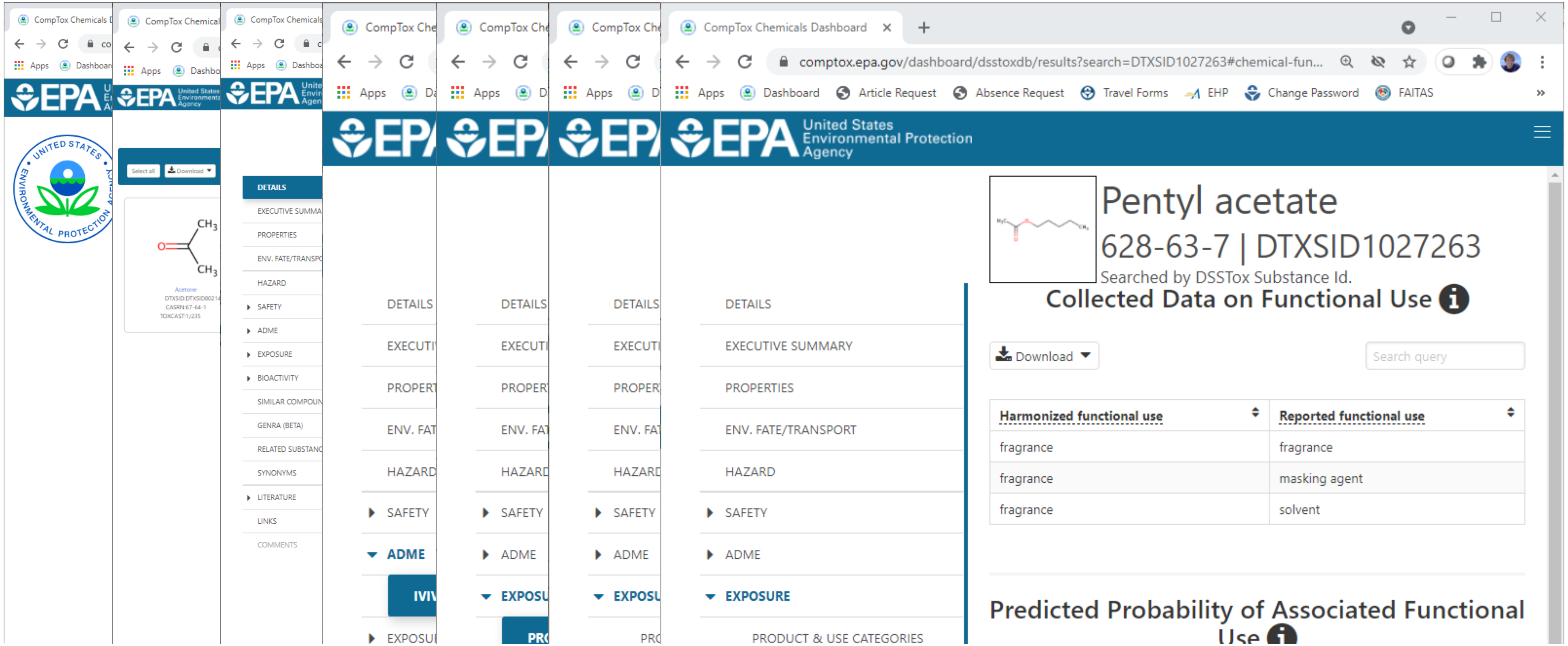
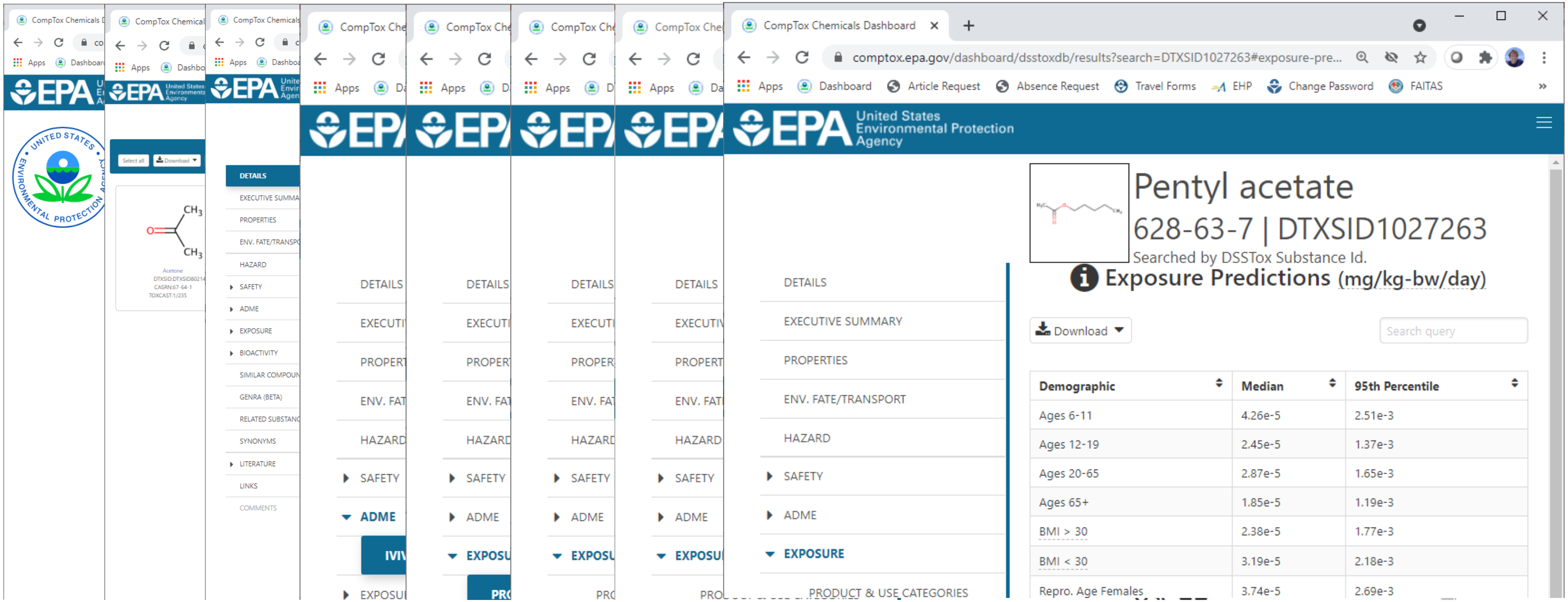


Dashboard Information

https://comptox.epa.gov/dashboard



US EPA's ExpoCast Project:

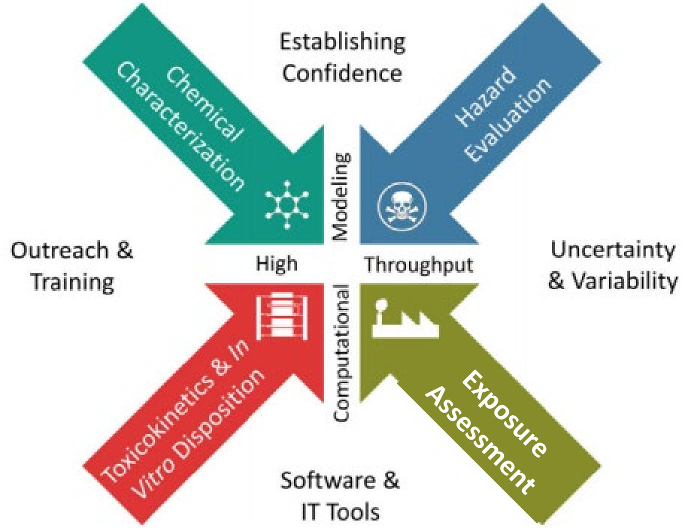
New Approach Methodologies for Exposure Forecasting

United States Environmental Protection Agency

*"**Investment in 21st century exposure science is now required** to fully realize the potential of the NRC vision for toxicity testing."*
Cohen Hubal (2009)

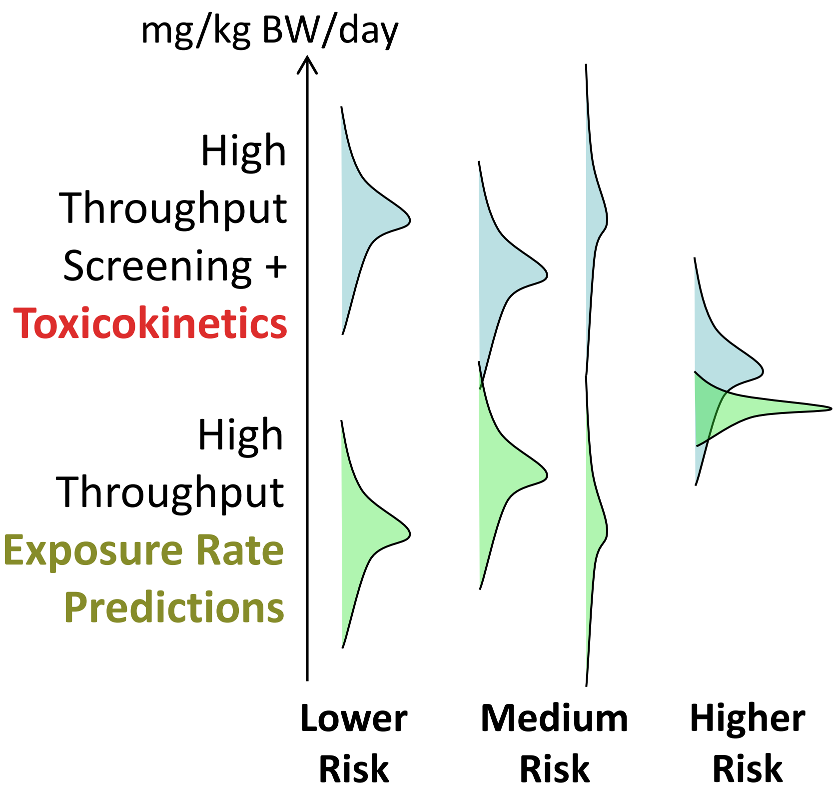
Lovell and Hegstad (2009): "Obama's FY10 Budget Includes Increased Toxicology":

- Funding allows for complementary exposure predictions from ExpoCast, which is slated to be **launched in FY10**
- Predict the impact of chemicals on the human body using data from ToxCast



Since 2010:

- 65 peer-reviewed publications
- 5 STAR grants awarded
- 3 Federal research contracts (SWRI and Battelle)



ExpoCast is

Models	Machine Learning	Measurements	Databases	Applied Statistics

Consumer	Ambient	Occupational	Ecological

ExpoCast Project (Exposure Forecasting)

Center for Computational Toxicology and Exposure

Linda Adams
Lucas Albrecht*
Matthew Boyce*
Miyuki Breen*
Alex Chao
Chris Cook*
Sarah Davidson
Daniel Dawson*
Mike Devito
Alex East*
Lindsay Eddy*
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*
Paui Kruse *
Charles Lowe*
Seth Newton
Katherine Phillips
Paul Price

Tom Purucker
Ann Richard
Caroline Ring
Risa Sayre
Marci Smeltz*
Jon Sobus
Zach Stanfield*
Mike Tornero-Velez
Rusty Thomas
Elin Ulrich
Dan Vallero
Taylor Wall
Barbara Wetmore
John Wambaugh
Antony Williams

CEMM

Hongwan Li*
Xiaoyu Liu
Zachary Robbins*
Mark Strynar

CESER

David Meyer
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

ExpoCast was initiated in 2009 by Elaine Cohen-Hubal

United States Environmental Protection Agency

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