

EPA Exposure Forecasting (ExpoCast)

John Wambaugh

Center for Computational Toxicology and Exposure

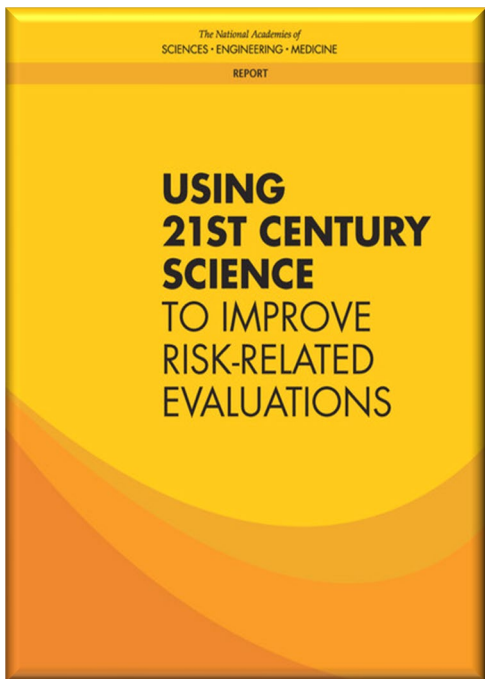
Office of Research and Development

U.S. Environmental Protection Agency

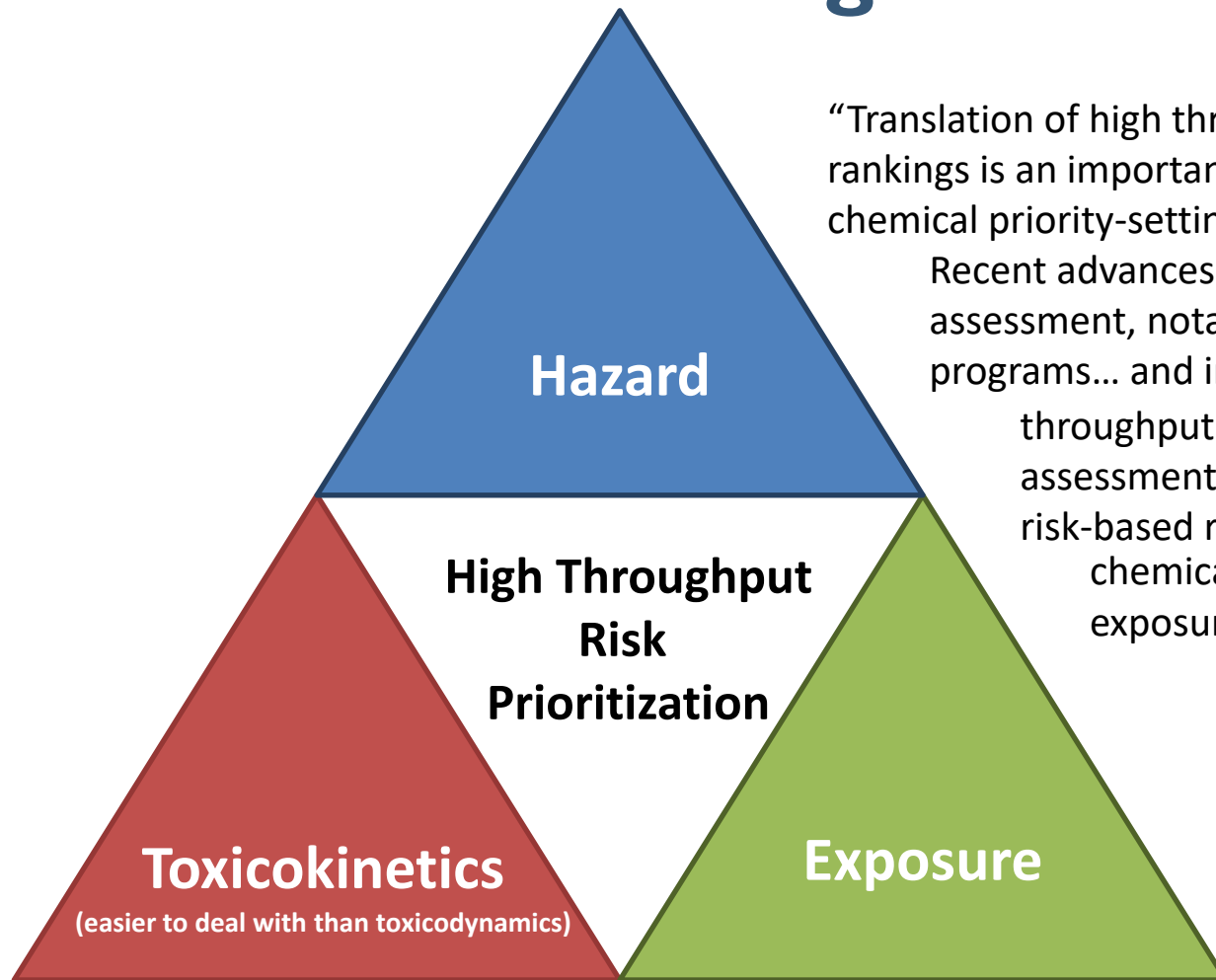
wambaugh.john@epa.gov *<https://orcid.org/0000-0002-4024-534X>*

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

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

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 <i>in vitro</i> data to generate chemical-specific models	Analyses based on <i>in vivo</i> 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)

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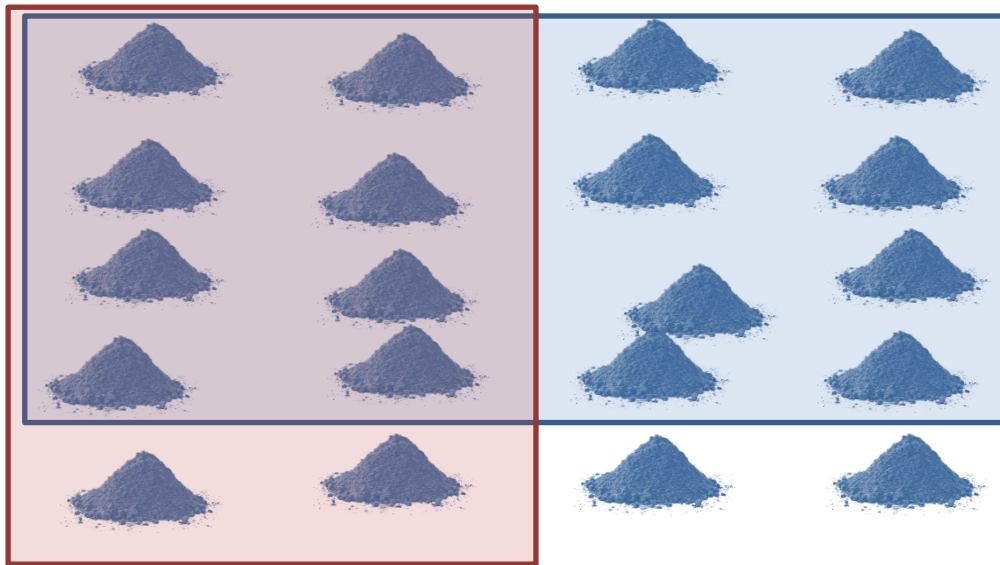
Wambaugh et al., (2019)

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)

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. Dionisio¹, Katherine Phillips¹, Paul S. Price¹, Christopher M. Grulke², Anthony Williams², Derya Biryol^{1,3}, Tao Hong⁴ & Kristin K. Isaacs¹



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,c}, P.P. Egeghy^a, R. Edwards^d, D.T. Chang^a, R. Tornero-Velez^a, K. Isaacs^a, A. Wang^{a,c}, 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

Green Chemistry

PAPER

View Article Online
View Journal | View Issue



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

CPCat

CPDat



Functional Use Data

The roles that chemicals serve in products

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



Ingredient Lists

Measured Data

Occurrence data

Environmental Science & Technology

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

ORIGINAL ARTICLE

Consumer product chemical weight fractions from ingredient lists

Kristin K. Isaacs¹, Katherine A. Phillips¹, Derya Biryol^{1,2}, Kathie L. Dionisio¹ and Paul S. Price¹

<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



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

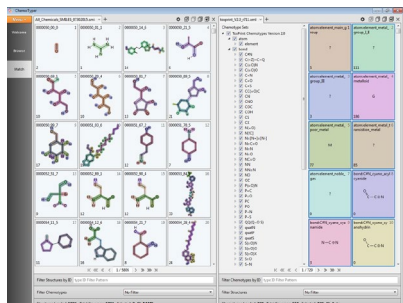
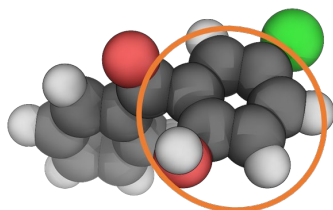
Successful
Model

Failed
Model

Probabilistic
Predictions of
Potential Chemical
Uses

Phillips *et al.* (2017)

Chemical Structure
and Property Descriptors



NAMs for Exposure Science

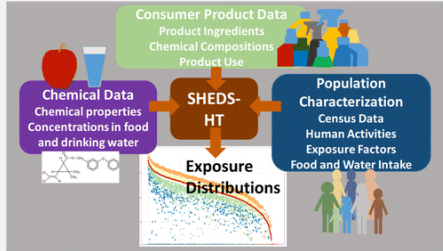
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Wambaugh et al., (2019)

High Throughput Exposure (HTE) Models for Key Pathways

Consumer (Near-Field) Pathways

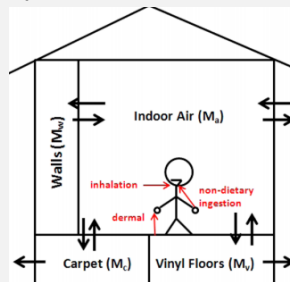
SHEDS-HT (Isaacs et al., 2014)



RAIDAR-ICE (Li et al., 2018)

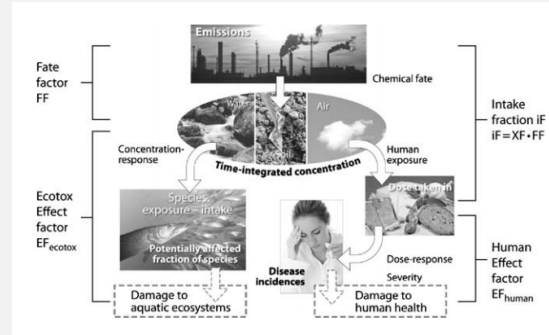


FINE (Shin et al., 2015)

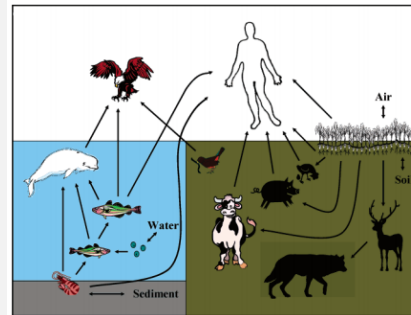


Ambient (Far-Field) Pathways

UseTox (Rosenbaum et al., 2008)

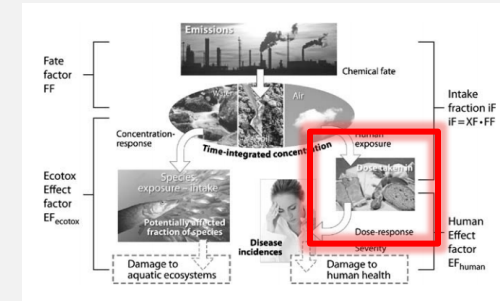


RAIDAR (Arnot et al., 2006, 2008)

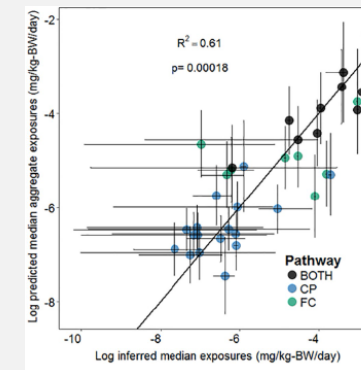


Dietary Pathways

UseTox (Rosenbaum et al. (2008)



SHEDS-HT (Biryol et al., 2017)

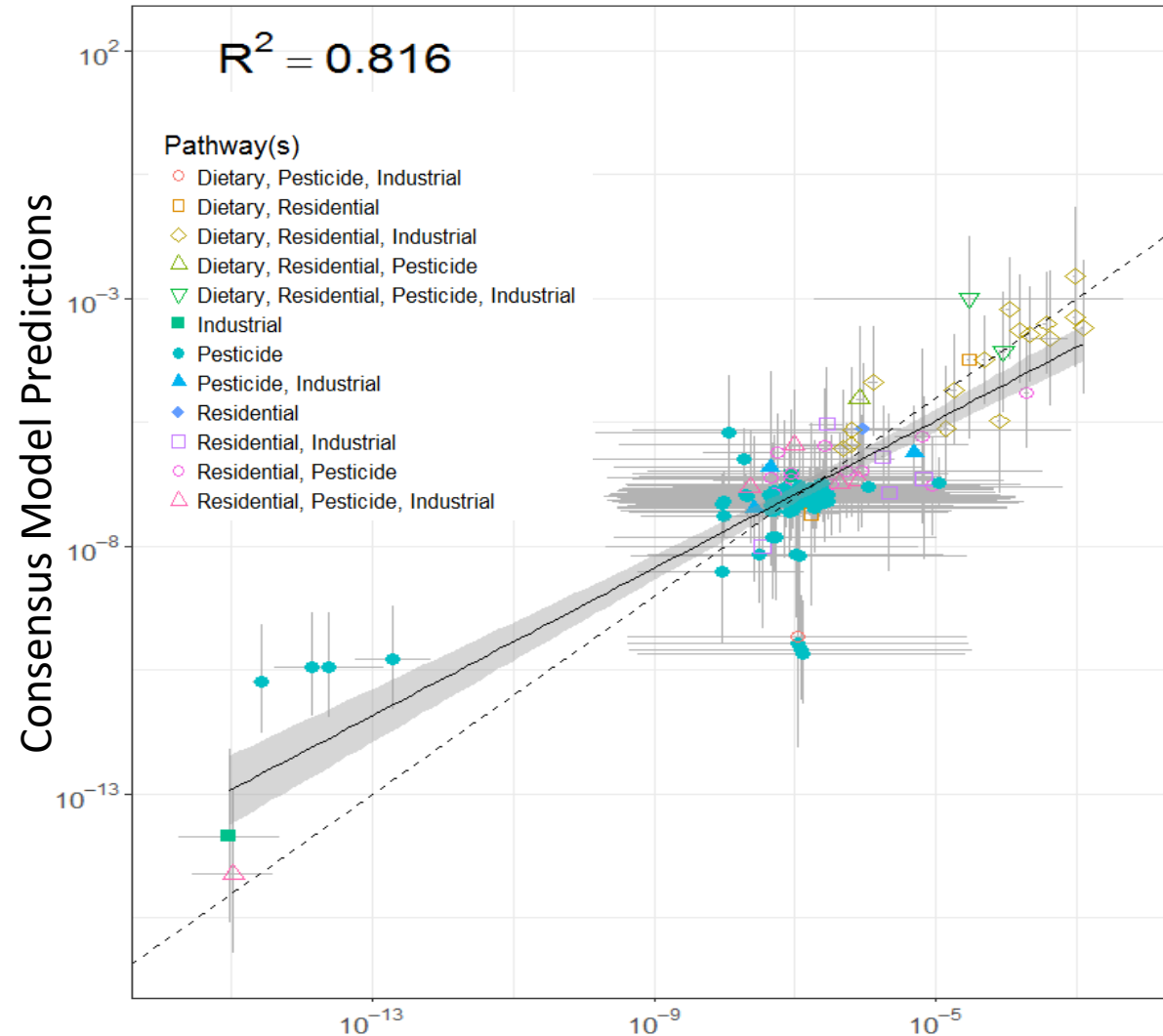


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Wambaugh et al., (2019)

SEEM3: Pathway-Based Consensus Modeling



Intake Rate (mg/kg BW/day) Inferred from NHANES Serum and Urine

- 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

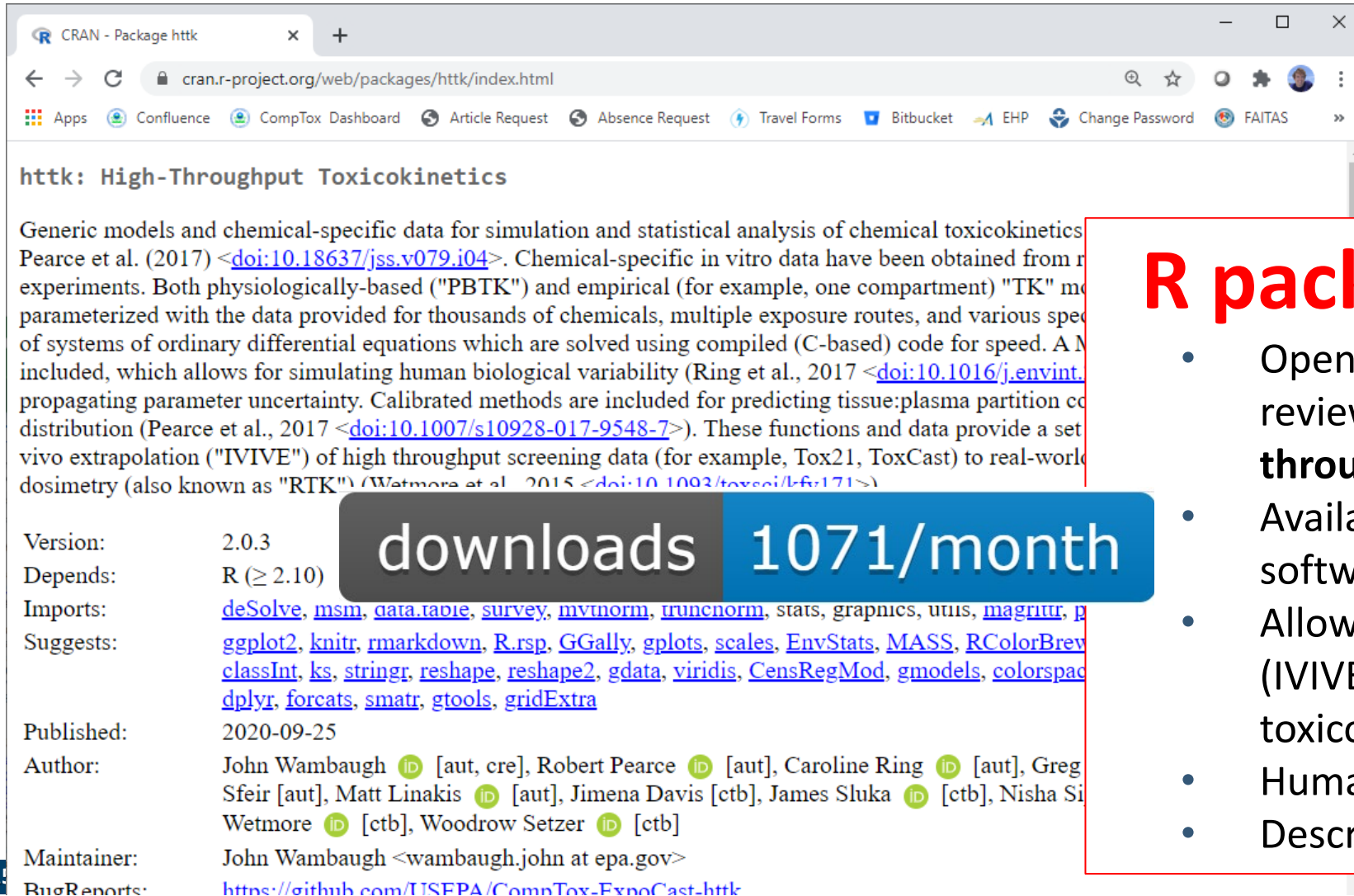
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Wambaugh et al., (2019)

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](https://doi.org/10.18637/jss.v079.i04)>). Chemical-specific in vitro data have been obtained from experiments. Both physiologically-based ("PBTK") and empirical (for example, one compartment) "TK" models are parameterized with the data provided for thousands of chemicals, multiple exposure routes, and various species of systems of ordinary differential equations which are solved using compiled (C-based) code for speed. A Monte Carlo approach is included, which allows for simulating human biological variability (Ring et al., 2017 <[doi:10.1016/j.envint.2017.05.011](https://doi.org/10.1016/j.envint.2017.05.011)>), propagating parameter uncertainty. Calibrated methods are included for predicting tissue:plasma partition coefficients and distribution (Pearce et al., 2017 <[doi:10.1007/s10928-017-9548-7](https://doi.org/10.1007/s10928-017-9548-7)>). These functions and data provide a set of tools for *in vivo* extrapolation ("IVIVE") of high throughput screening data (for example, Tox21, ToxCast) to real-world dosimetry (also known as "RTK") (Wetmore et al., 2015 <[doi:10.1093/toxsci/bfv171](https://doi.org/10.1093/toxsci/bfv171)>).

Version: 2.0.3
Depends: R (≥ 2.10)
Imports: [deSolve](#), [msm](#), [data.table](#), [survey](#), [mvtnorm](#), [runcnorm](#), stats, graphics, utils, [magrittr](#), [ggplot2](#), [knitr](#), [rmarkdown](#), [R.ssp](#), [GGally](#), [gplots](#), [scales](#), [EnvStats](#), [MASS](#), [RColorBrewer](#), [classInt](#), [ks](#), [stringr](#), [reshape](#), [reshape2](#), [gdata](#), [viridis](#), [CensRegMod](#), [gmodels](#), [colorspace](#), [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 Siwetmore  [ctb], Woodrow Setzer  [ctb]
Maintainer: John Wambaugh <wambaugh.john@epa.gov>
BugReports: <https://github.com/USEPA/CompTox-ExpoCast-httk>

downloads 1071/month

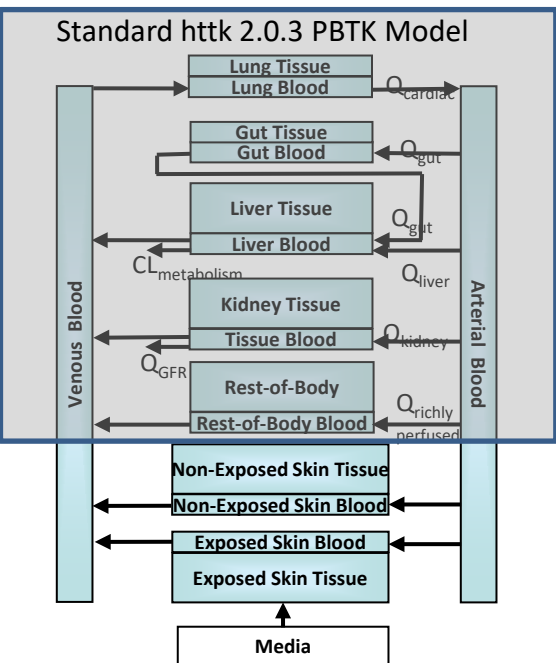
R package "httk"

- 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)

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

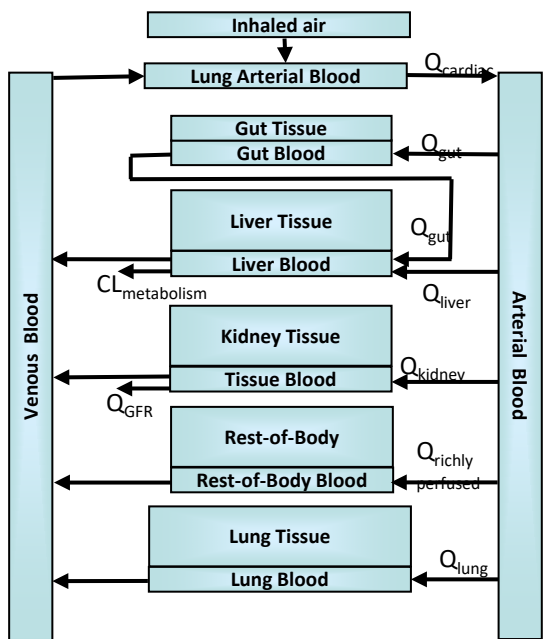
Gas and Aerosol Inhalation Exposure Route

EPA, USAF, Linakis et al. (2020)

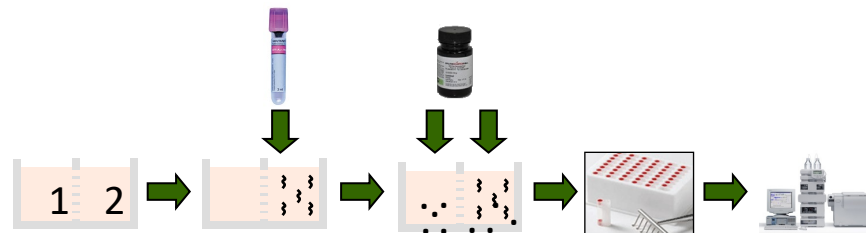


Dermal Exposure Route

EPA, Unilever, INERIS

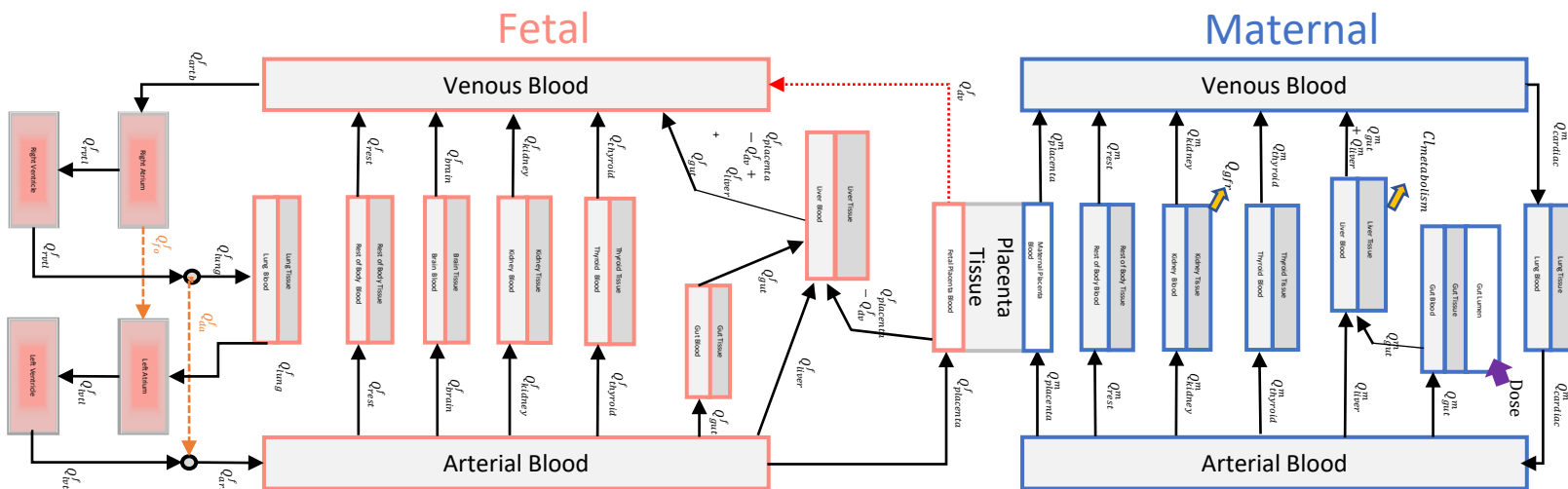


Wetmore et al. (2012, 2013, 2015), Wambaugh et al. (2019)



Human Gestational Model

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



NAMs for Exposure Science

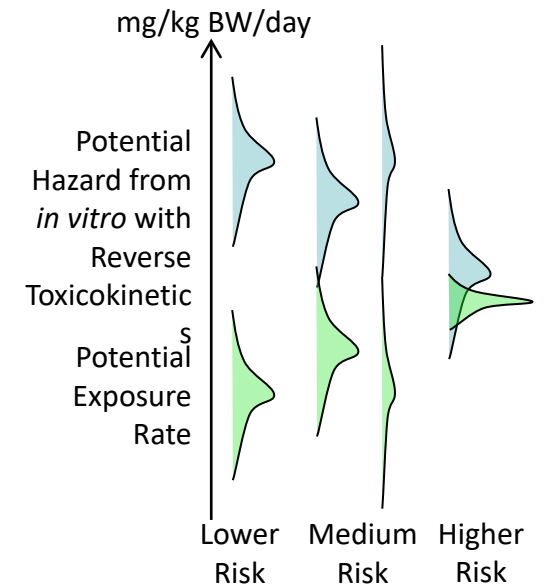
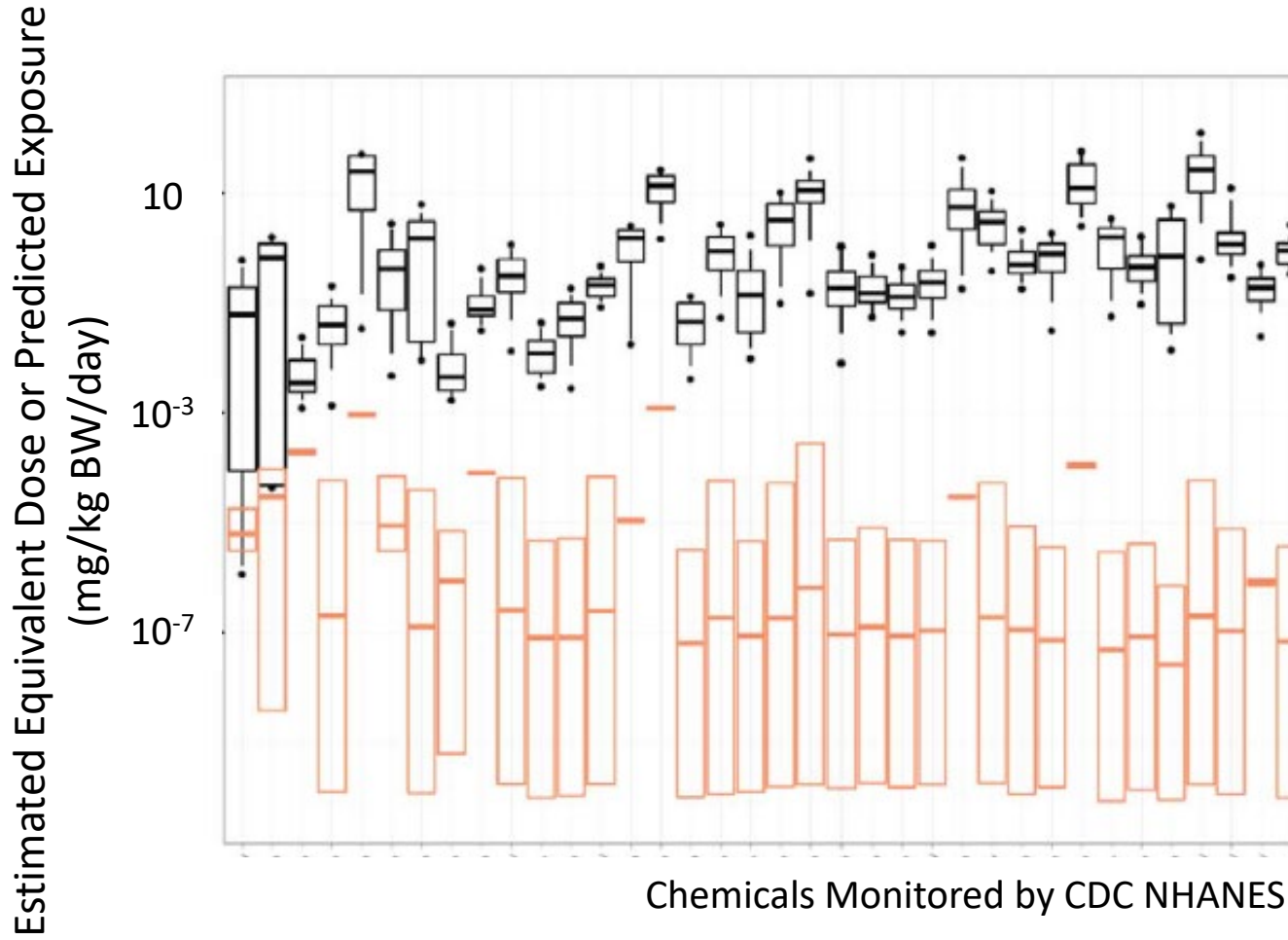
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Wambaugh et al., (2019)

Chemical Prioritization NAMs

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

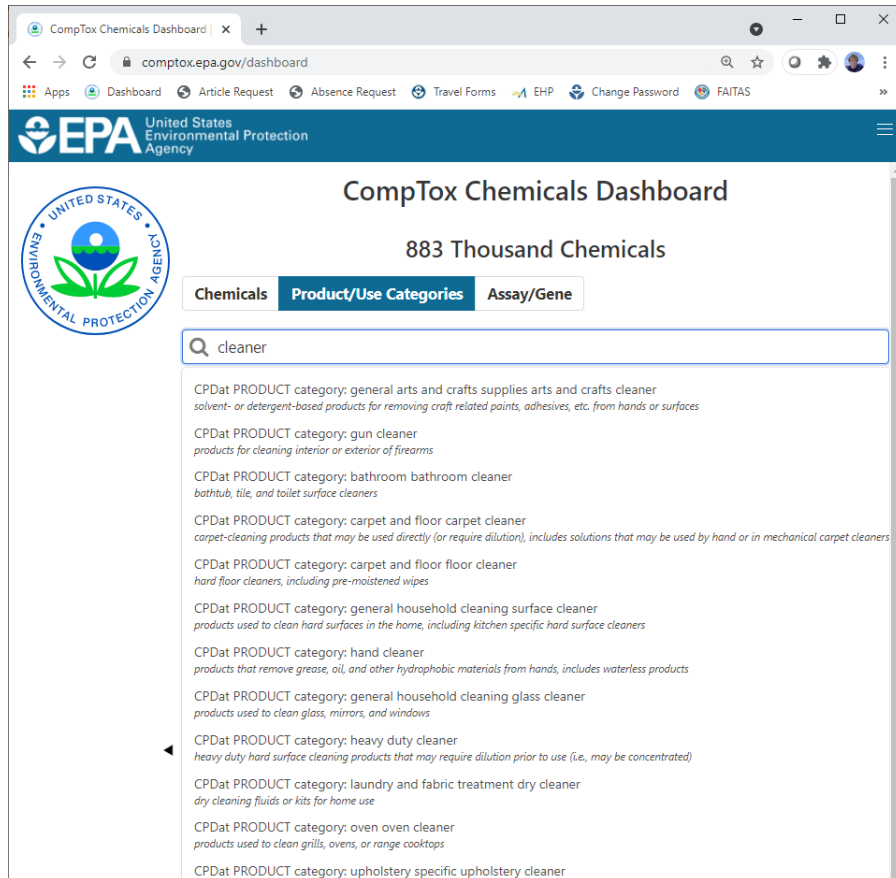
Exposure intake rates can be inferred from biomarkers (for example, Ring et al., 2018)



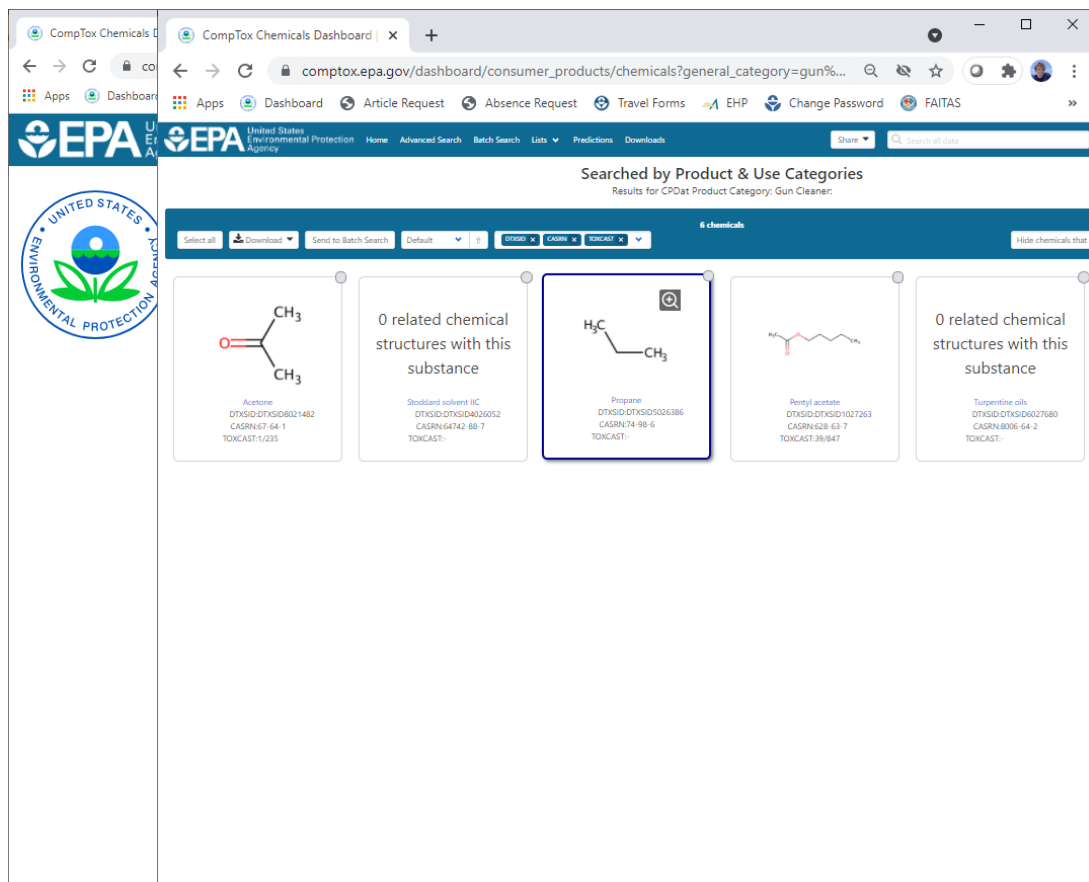
Ring et al. (2017)

Dashboard Information

<https://comptox.epa.gov/dashboard>

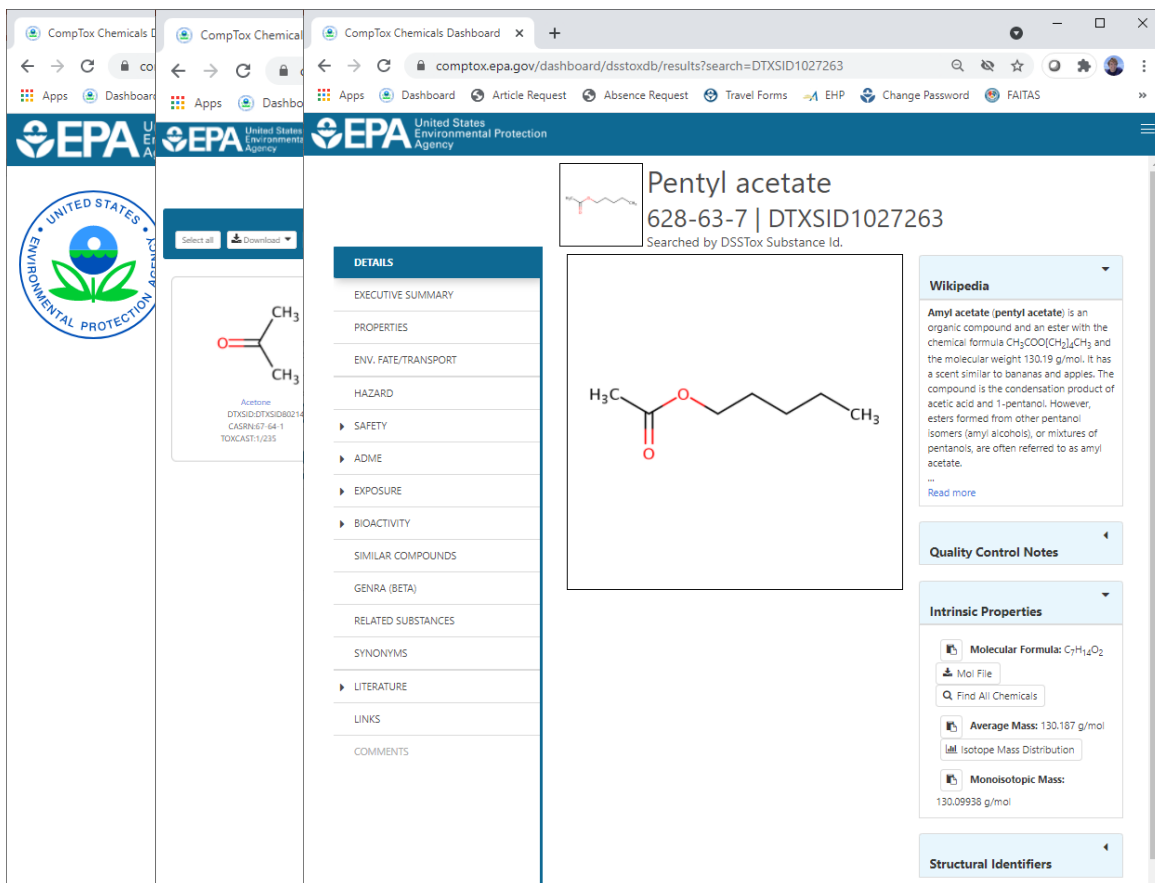


The screenshot shows the CompTox Chemicals Dashboard in a web browser. The browser's address bar displays "comptox.epa.gov/dashboard". The dashboard header includes the EPA logo and the text "United States Environmental Protection Agency". The main title is "CompTox Chemicals Dashboard". Below the title, it states "883 Thousand Chemicals". There are three tabs: "Chemicals", "Product/Use Categories" (which is selected), and "Assay/Gene". A search bar contains the text "cleaner". Below the search bar, a list of product categories is displayed, each starting with "CPDat PRODUCT category:" followed by a description. The categories listed are: general arts and crafts supplies arts and crafts cleaner, gun cleaner, bathroom bathroom cleaner, carpet and floor carpet cleaner, carpet and floor floor cleaner, general household cleaning surface cleaner, hand cleaner, general household cleaning glass cleaner, heavy duty cleaner, laundry and fabric treatment dry cleaner, oven oven cleaner, and upholstery specific upholstery cleaner.



Dashboard Information

<https://comptox.epa.gov/dashboard>



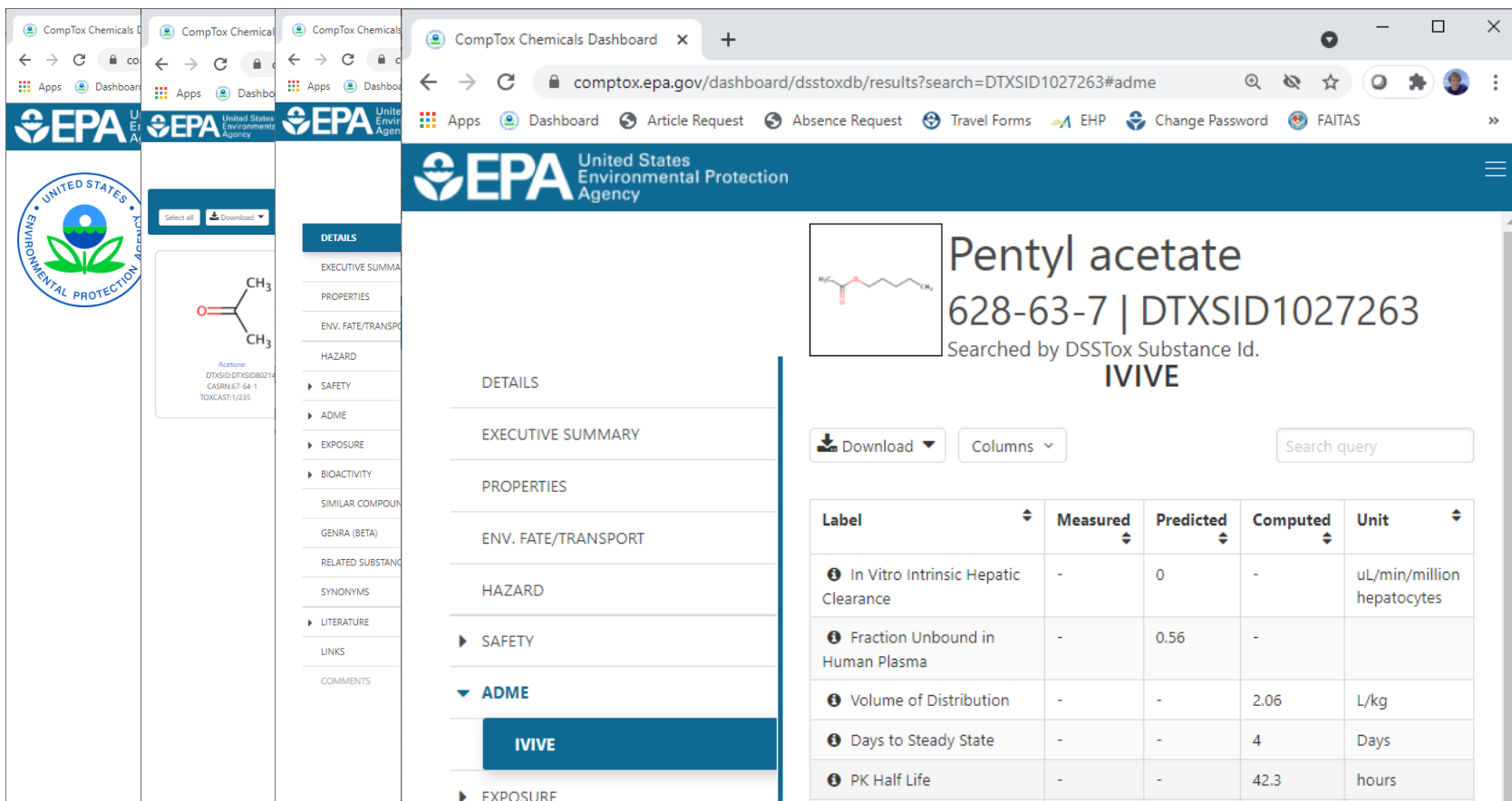
The screenshot displays the EPA Comptox Chemicals Dashboard interface. The browser address bar shows the URL: comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID1027263. The dashboard header includes the EPA logo and navigation links such as Apps, Dashboard, Article Request, Absence Request, Travel Forms, EHP, Change Password, and FAITAS.

The main content area displays the profile for **Pentyl acetate** (DTXSID1027263), identified by its DSSTox Substance Id. The chemical structure is shown as CCCCCOC(=O)C. A sidebar on the left provides a list of details including EXECUTIVE SUMMARY, PROPERTIES, ENV. FATE/TRANSPORT, HAZARD, SAFETY, ADME, EXPOSURE, BIOACTIVITY, SIMILAR COMPOUNDS, GENRA (BETA), RELATED SUBSTANCES, SYNONYMS, LITERATURE, LINKS, and COMMENTS. A small inset shows the chemical structure of Acetone (DTXSID10214) with its CASRN (67-64-1) and TOXCAST (1/235).

On the right, the **Wikipedia** section provides a brief description of Amyl acetate (pentyl acetate) as an organic compound and ester with the chemical formula $\text{CH}_3\text{COO}(\text{CH}_2)_4\text{CH}_3$ and a molecular weight of 130.19 g/mol. It notes its scent is similar to bananas and apples. The **Quality Control Notes** and **Intrinsic Properties** sections are also visible, with the latter showing the Molecular Formula ($\text{C}_7\text{H}_{14}\text{O}_2$), Average Mass (130.187 g/mol), and Monoisotopic Mass (130.09938 g/mol).

Dashboard Information

<https://comptox.epa.gov/dashboard>



The screenshot displays the EPA CompTox Chemicals Dashboard interface. The top navigation bar includes links for Apps, Dashboard, Article Request, Absence Request, Travel Forms, EHP, Change Password, and FAITAS. The main header features the EPA logo and the text "United States Environmental Protection Agency".

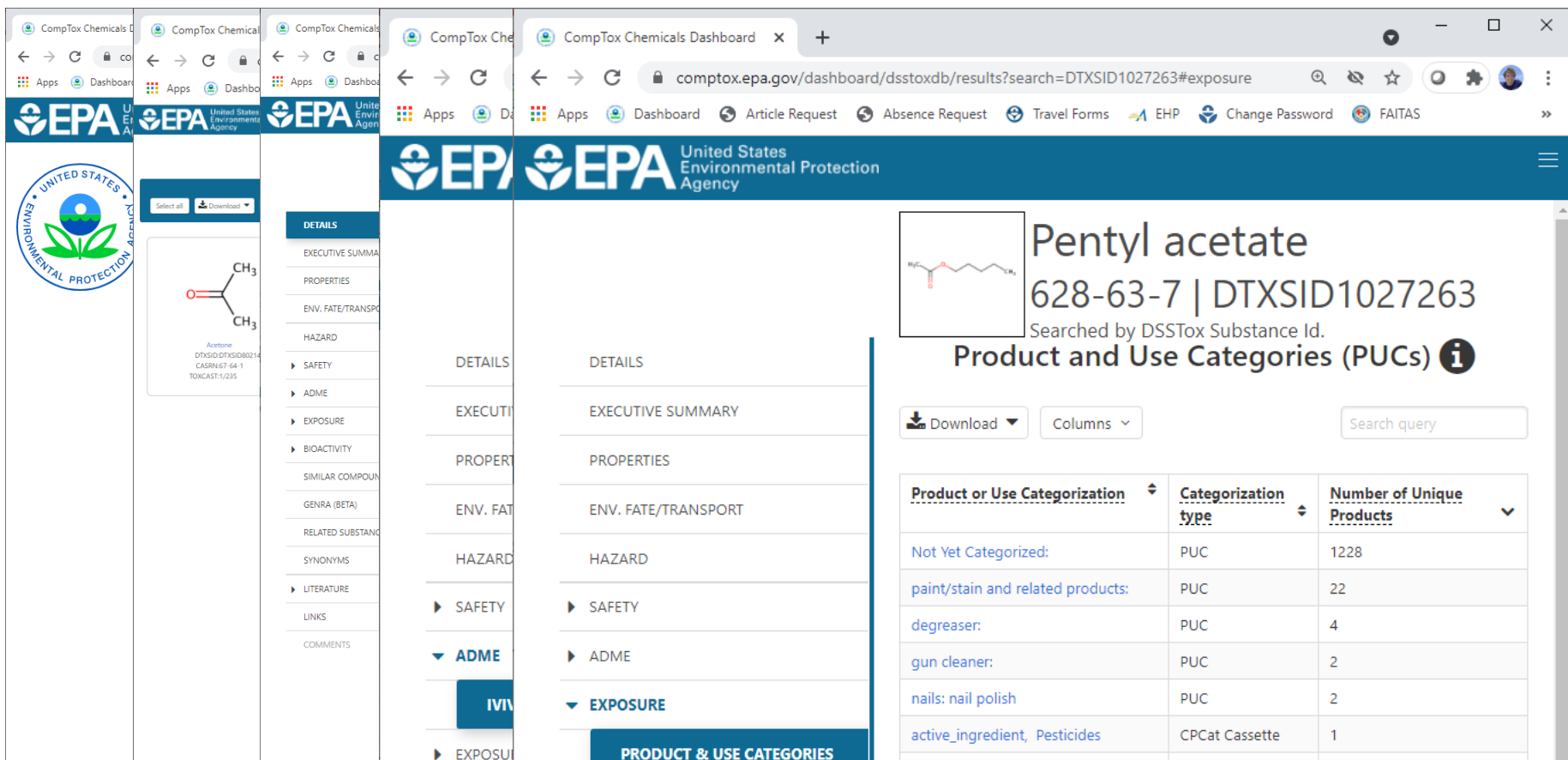
The dashboard is divided into several sections:

- Left Sidebar:** Contains a search bar, a chemical structure viewer (showing Acetone), and a list of navigation options including DETAILS, EXECUTIVE SUMMARY, PROPERTIES, ENV. FATE/TRANSPORT, HAZARD, SAFETY, ADME, EXPOSURE, BIOACTIVITY, SIMILAR COMPOUNDS, GENRA (BETA), RELATED SUBSTANCES, SYNONYMS, LITERATURE, LINKS, and COMMENTS.
- Main Content Area:** Displays the chemical name "Pentyl acetate" with its DTXSID (1027263) and CASRN (67-64-1). It also shows the search query "Searched by DSSTox Substance Id. IVIVE".
- Table:** A table with 5 columns: Label, Measured, Predicted, Computed, and Unit. It lists various pharmacokinetic parameters for Pentyl acetate.

Label	Measured	Predicted	Computed	Unit
In Vitro Intrinsic Hepatic Clearance	-	0	-	uL/min/million hepatocytes
Fraction Unbound in Human Plasma	-	0.56	-	
Volume of Distribution	-	-	2.06	L/kg
Days to Steady State	-	-	4	Days
PK Half Life	-	-	42.3	hours

Dashboard Information

<https://comptox.epa.gov/dashboard>



The screenshot displays the EPA Comptox Chemicals Dashboard. The browser address bar shows the URL: comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID1027263#exposure. The dashboard header includes the EPA logo and navigation links: Apps, Dashboard, Article Request, Absence Request, Travel Forms, EHP, Change Password, and FAITAS.

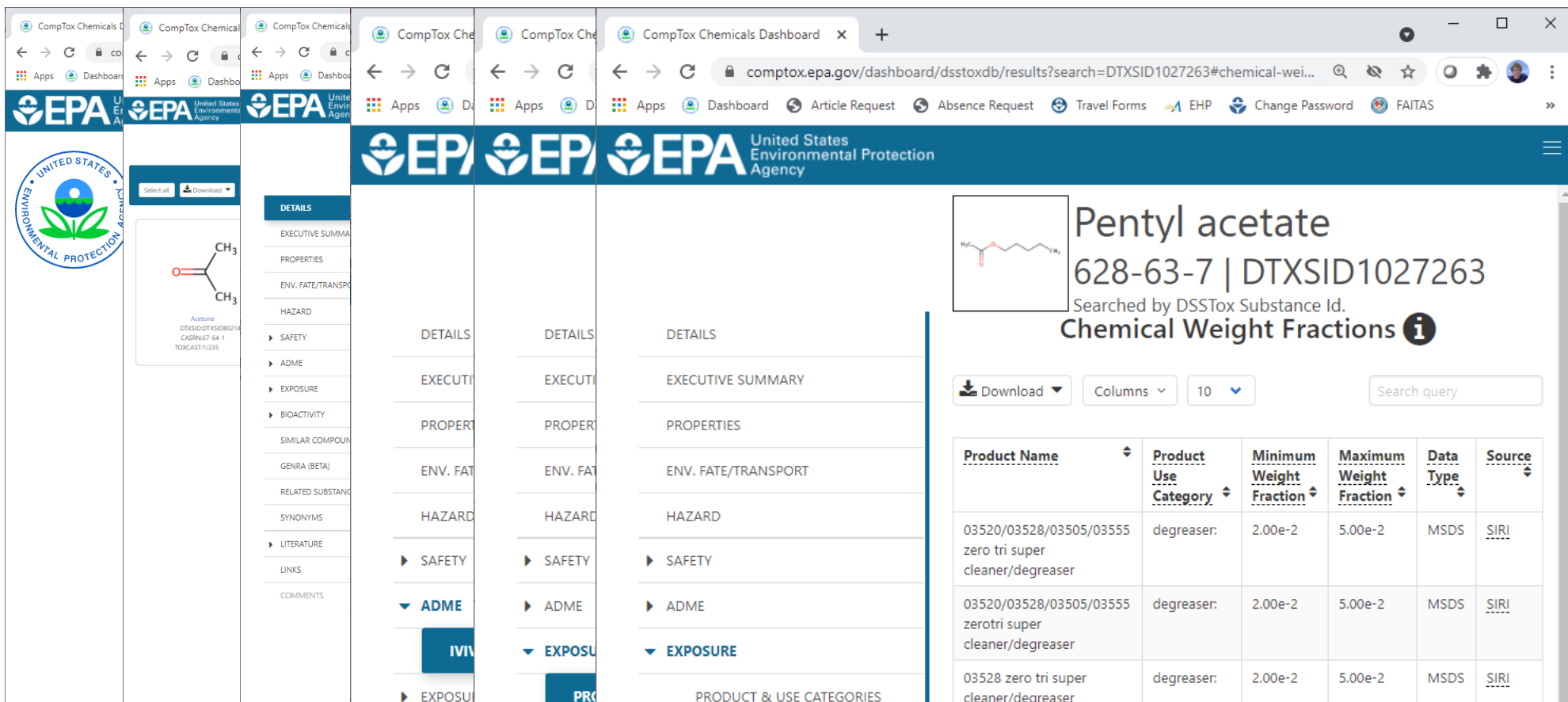
The main content area displays search results for **Pentyl acetate** (DTXSID1027263). The chemical structure is shown as CCCCC(=O)OC. The search was performed by DSSTox Substance Id. Below the title, there is a section for **Product and Use Categories (PUCs)** with a search query input field and a download button.

Product or Use Categorization	Categorization type	Number of Unique Products
Not Yet Categorized:	PUC	1228
paint/stain and related products:	PUC	22
degreaser:	PUC	4
gun cleaner:	PUC	2
nails: nail polish	PUC	2
active_ingredient, Pesticides	CPCat Cassette	1

The left sidebar contains a list of navigation options: DETAILS, EXECUTIVE SUMMARY, PROPERTIES, ENV. FATE/TRANSPORT, HAZARD, SAFETY, ADME, EXPOSURE, BIOACTIVITY, SIMILAR COMPOUNDS, GENRA (BETA), RELATED SUBSTANCES, SYNONYMS, LITERATURE, LINKS, and COMMENTS. The 'EXPOSURE' section is currently selected.

Dashboard Information

<https://comptox.epa.gov/dashboard>



Pentyl acetate
628-63-7 | DTXSID1027263
Searched by DSSTox Substance Id.

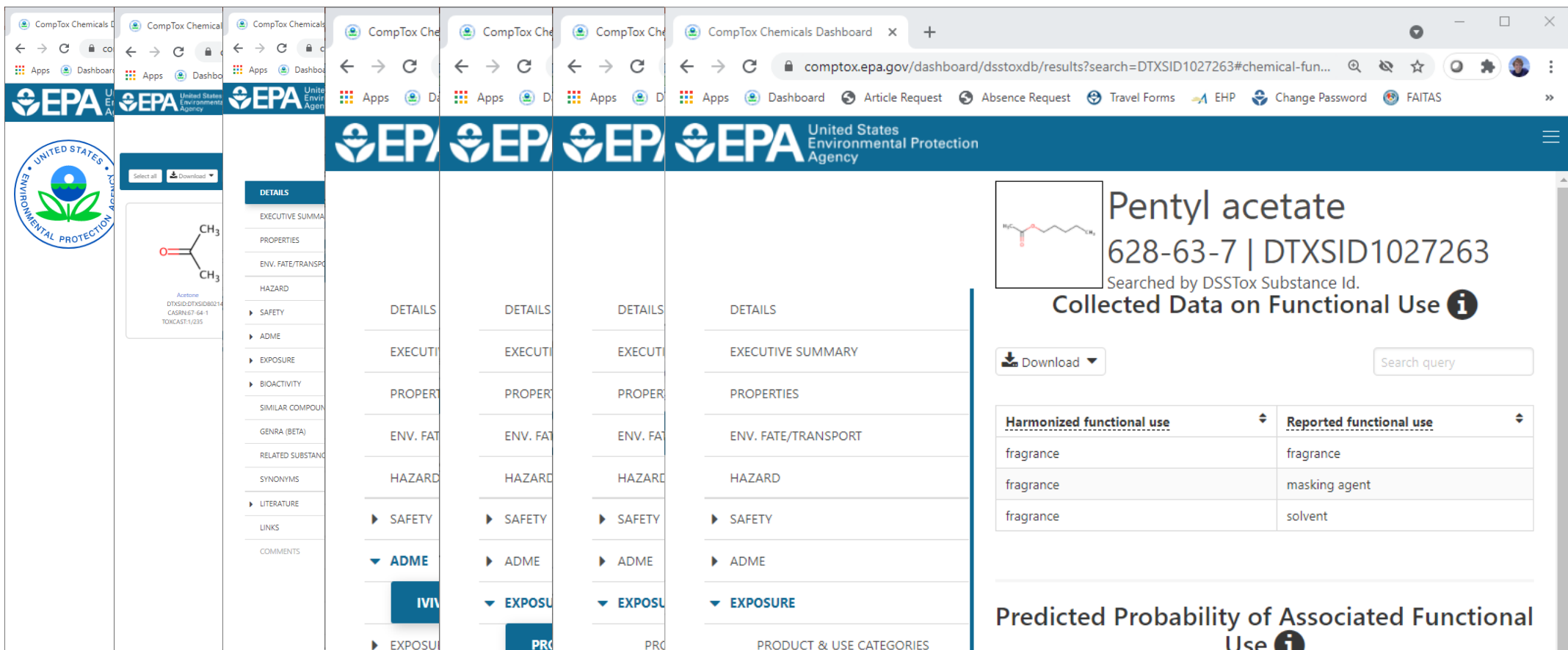
Chemical Weight Fractions

Download Columns 10 Search query

Product Name	Product Use Category	Minimum Weight Fraction	Maximum Weight Fraction	Data Type	Source
03520/03528/03505/03555 zero tri super cleaner/degreaser	degreaser:	2.00e-2	5.00e-2	MSDS	SIRI
03520/03528/03505/03555 zero tri super cleaner/degreaser	degreaser:	2.00e-2	5.00e-2	MSDS	SIRI
03528 zero tri super cleaner/degreaser	degreaser:	2.00e-2	5.00e-2	MSDS	SIRI

Dashboard Information

<https://comptox.epa.gov/dashboard>



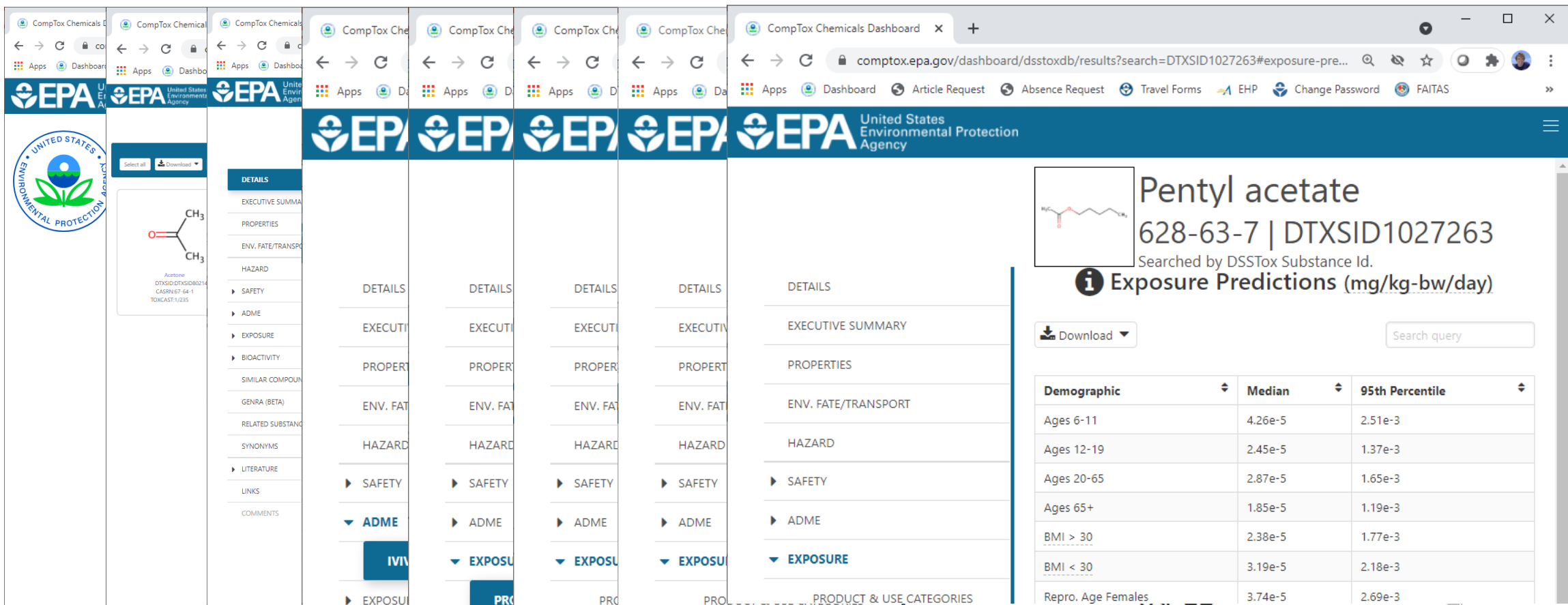
The screenshot displays the EPA Comptox Chemicals Dashboard with multiple browser tabs open. The main view shows the profile for **Pentyl acetate** (DTXSID1027263). The chemical structure is shown as CCCCC(=O)OC. The dashboard includes a sidebar with navigation options like DETAILS, EXECUTIVE SUMMARY, PROPERTIES, ENV. FATE/TRANSPORT, HAZARD, SAFETY, ADME, EXPOSURE, BIOACTIVITY, SIMILAR COMPOUNDS, GENRA (BETA), RELATED SUBSTANCES, SYNONYMS, LITERATURE, LINKS, and COMMENTS. The main content area displays the chemical's name, DTXSID, and a section for **Collected Data on Functional Use**. This section includes a table comparing **Harmonized functional use** and **Reported functional use**.

Harmonized functional use	Reported functional use
fragrance	fragrance
fragrance	masking agent
fragrance	solvent

Below the table, there is a section for **Predicted Probability of Associated Functional Use**.

Dashboard Information

<https://comptox.epa.gov/dashboard>



The screenshot displays the EPA CompTox Chemicals Dashboard. The top navigation bar includes the EPA logo and links to various tools: Apps, Dashboard, Article Request, Absence Request, Travel Forms, EHP, Change Password, and FAITAS. The main content area shows a grid of dashboard tabs. The active tab, 'CompTox Chemicals Dashboard', displays the profile for 'Pentyl acetate' (DTXSID1027263). The profile includes a chemical structure, name, and search ID. Below this, there is a section for 'Exposure Predictions (mg/kg-bw/day)' with a table showing demographic data.

Pentyl acetate
628-63-7 | DTXSID1027263
Searched by DSSTox Substance Id.

Exposure Predictions (mg/kg-bw/day)

Demographic	Median	95th Percentile
Ages 6-11	4.26e-5	2.51e-3
Ages 12-19	2.45e-5	1.37e-3
Ages 20-65	2.87e-5	1.65e-3
Ages 65+	1.85e-5	1.19e-3
BMI > 30	2.38e-5	1.77e-3
BMI < 30	3.19e-5	2.18e-3
Repro. Age Females	3.74e-5	2.69e-3

US EPA's ExpoCast Project:

New Approach Methodologies for Exposure Forecasting

"Investment in 21st century exposure science is now required to fully realize the potential of the NRC vision for toxicity testing."

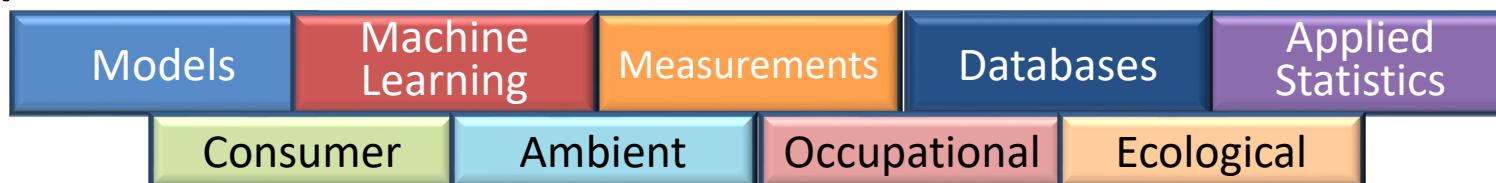
Cohen Hubal (2009)

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

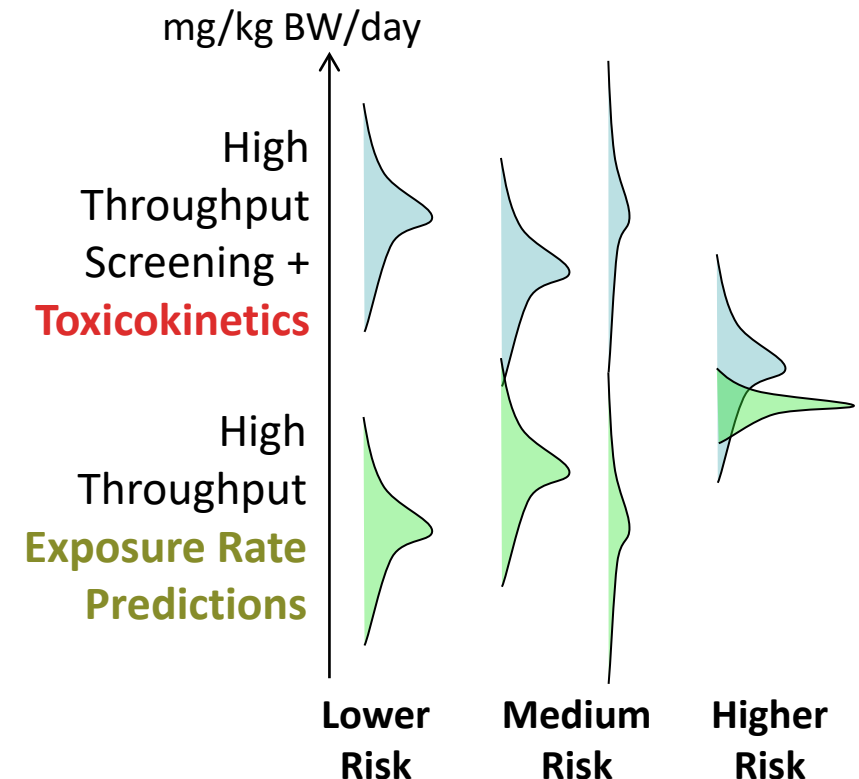


ExpoCast is



Since 2010:

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





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*

Paul 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

Lesla Aylward

Technical University of Denmark

Peter Fantke

Unilever

Beate Nicol

Cecilie Rendal

Ian Sorrell

United States Air Force

Heather Pangburn

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Deborah Bennett

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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

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