



# An Update on Public Tools for Prediction of Endocrine Hazard and Risk

Katie Paul Friedman

November 4, 2019

Presentation to SETAC North America 40<sup>th</sup> Annual Meeting

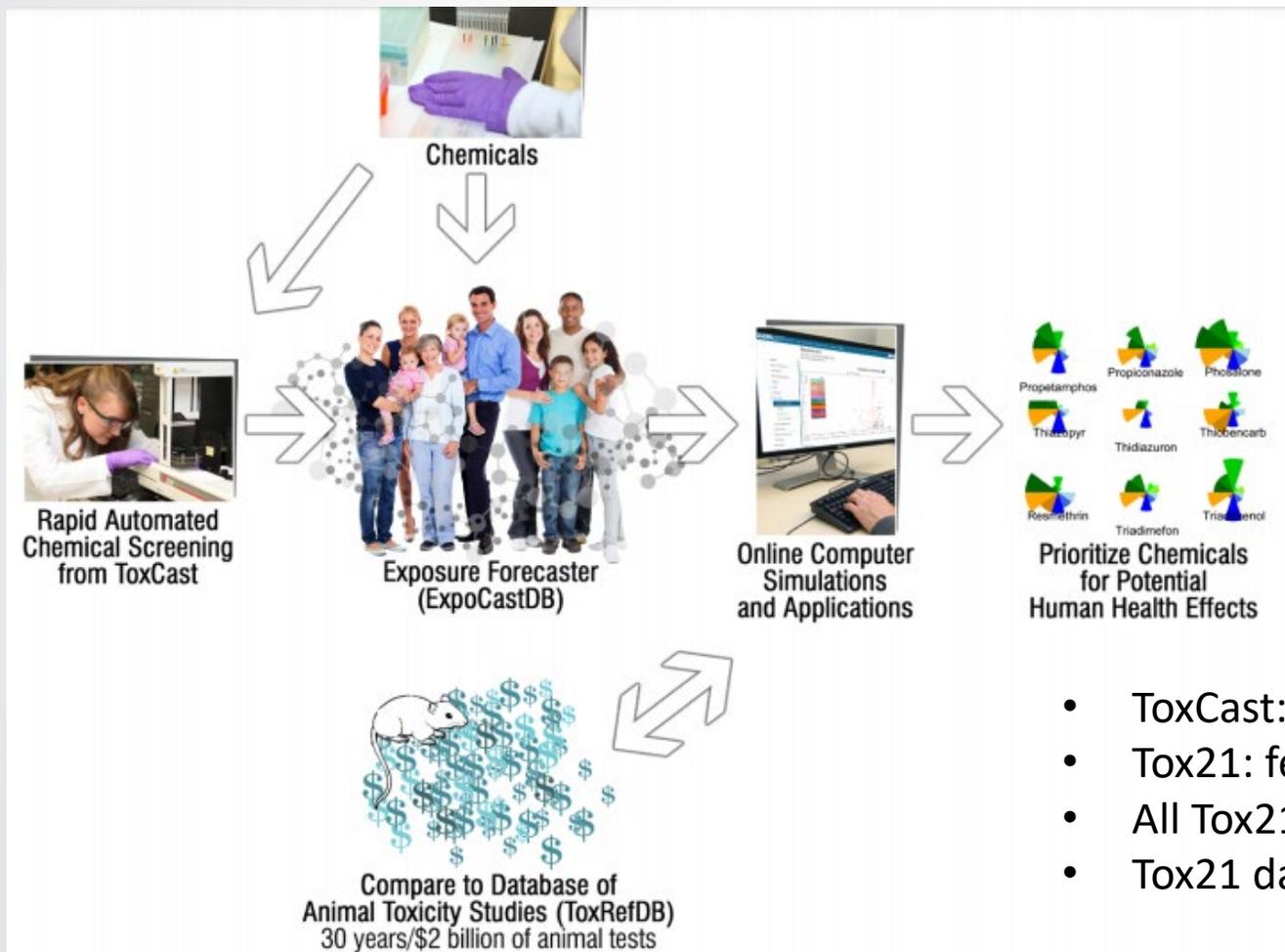
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*The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the  
U.S. EPA*



ToxCast and Tox21 have generated a lot of publicly available bioactivity data for hazard screening and prediction.

### EPA's ToxCast program at a glance



Tox21 robot

- ToxCast: more assays, fewer chemicals, EPA-driven
- Tox21: fewer assays, all 1536, driven by consortium
- All Tox21 data are analyzed by multiple partners
- Tox21 data is available analyzed in the ToxCast Data Pipeline



# Endocrine hazard and risk evaluation using public tools: approach outline

- Publicly available data from ToxCast is actively being applied to endocrine hazard labeling in the EU.
- Risk-based approaches that incorporate bioactivity and exposure make the best use of new approach methodologies.



*This presentation will demonstrate where to find these information and suggest an approach for utilizing them in endocrine hazard and risk evaluation.*



# CompTox Chemicals Dashboard

The screenshot shows the EPA CompTox Chemicals Dashboard. At the top left is the EPA logo and the text "United States Environmental Protection Agency". To the right are navigation links: "Home", "Advanced Search", "Batch Search", "Lists", "Predictions", and "Downloads". A "Share" button is in the top right corner. The main content area features a circular EPA seal on the left and the text "875 Thousand Chemicals" on the right. Below this is a search bar with the placeholder "Search for chemical by systematic name, synonym, CAS number, DTXSID or InChIKey" and a "Chemicals" tab selected. A checkbox for "Identifier substring search" is present. Below the search bar are links to "See what people are saying, read the dashboard comments!" and "Cite the Dashboard Publication click here". The "Latest News" section features a headline "August 9th 2019 - New release (3.0.9) in time for ACS Fall Meeting" with a timestamp "August 14th, 2019 at 4:39:37 PM" and a paragraph of text: "A new version of the Dashboard has been released in time for the ACS Fall meeting. Included in this release are updates to data in the ToxVal database, an update to the in vitro database (version 3.2), and the release also addresses a number of minor bugs and includes a short list of additional functionality as described in the Release Notes here." The URL "https://comptox.epa.gov/dashboard" is displayed at the bottom of the screenshot.



Examine physicochemical properties such as logP, vapor pressure, and MW to get a better sense of whether the chemical was suitable for the current *in vitro* assay suite

Analytical chemistry: was the chemical present and in the DOA for current ToxCast?

ToxCast negatives: what does a negative mean? Outside of domain of applicability?

Consider some aspects of the Lipinski's rules: logP -0.4 to 5.6 range; MW 180-480; log<sub>10</sub> Vapor Pressure < 1.

EPA United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Predictions Downloads

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### Bisphenol A

80-05-7 | DTXSID7020182

Searched by DSSTox Substance Id.

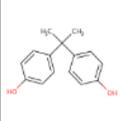
Property Summary

Download Columns

Property	Experimental average	Predicted average	Experimental median	Predicted median	Experimental range	Predicted range	Unit
LogP: Octanol-Water	3.32 (1)	3.29		3.43	3.32	2.40 to 3.64	-
Melting Point	155 (7)	139	156	138	153 to 156	125 to 157	°C
Boiling Point	200 (1)	363		360	200	343 to 401	°C
Water Solubility	5.26e-4 (1)	9.62e-4		1.00e-3	5.26e-4	5.35e-4 to 1.31e-3	mol/L
Vapor Pressure	-	8.37e-7		3.43e-7	-	6.83e-8 to 2.59e-6	mmHg
Flash Point	-	190		190	-	188 to 192	°C
Surface Tension	-	46.0			-	46.0	dyn/cm
Index of Refraction	-	1.60			-	1.60	-
Molar Refractivity	-	68.2			-	68.2	cm <sup>3</sup>
Polarizability	-	27.0			-	27.0	Å <sup>3</sup>
Density	-	1.17		1.17	-	1.14 to 1.20	g/cm <sup>3</sup>
Molar Volume	-	200			-	200	cm <sup>3</sup>
Thermal Conductivity	-	150			-	150	mW/(m*K)
Viscosity	-	9.66			-	9.66	cP
Henry's Law	-	1.26e-7			-	1.26e-7	atm-m <sup>3</sup> /mole
LogKoa: Octanol-Air	-	8.38			-	8.38	-

16 records

# Examine QC data (if available) to see if we expect that the chemical was present for screening



**Bisphenol A**  
80-05-7 | DTXSID7020182  
Searched by DSSTox Substance Id.

- DETAILS
- EXECUTIVE SUMMARY
- PROPERTIES
- ENV. FATE/TRANSPORT
- HAZARD
- ADME
- EXPOSURE
- BIOACTIVITY
  - TOXCAST: SUMMARY
  - EDSP21
  - TOXCAST/TOX21**

### ToxCast/Tox21

QC Data ID	Grade	Description
Tox21_202992	Pass	Purity>90% and MW confirmed
Tox21_400088	Pass	Purity>90% and MW confirmed



Selection 0 Selected | A Single Assay Can Have Multiple Charts |  Representative Samples Only | Bioactivity Summary | Number of Charts: 0

Filter assays | Inactive | All

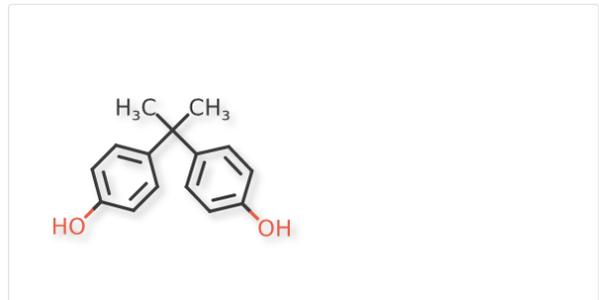
Odyssey Thera (0 of 165) | Attagene (0 of 165) | CellzDirect (0 of 48) | Bioseek (0 of 174) | Apremica (0 of 108)

Select one or more assays from the list of assays to view the associated bioactivity curves

Structure Search | Search...

Analytical chemistry: was the chemical present and in the DOA for current ToxCast?

### Bisphenol A



QC Grade		
T0	A	MW Confirmed, Purity > 90%
T4	A	MW Confirmed, Purity > 90%

Identifiers	
Tox21	Tox21_202992
NCATS	NCGC00260537-01
CAS	80-05-7
PubChem	144210190



# Models >>> single assays. And equivocals happen.

Endocrine models available?

Advanced Search Batch Search Lists Predictions Downloads

Copy Share Submit Comment Search all data

## Bisphenol A

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### ToxCast: Models

ToxCast Model Predictions

Download ToxCast Model Predictions

>0.1 = positive; 0.001-0.1 = equivocal

Model	Receptor	Agonist	Antagonist	Binding
ToxCast Pathway Model (AUC)	Androgen	0.00	0.345	-
ToxCast Pathway Model (AUC)	Estrogen	0.450	0.00	-
COMPARA (Consensus)	Androgen	Inactive	Active	Active
CERAPP Potency Level (From Literature)	Estrogen	Active (Weak)	-	Active (Weak)
CERAPP Potency Level (Consensus)	Estrogen	Active (Weak)	Active (Strong)	Active (Weak)

CERAPP = consensus ER QSAR (from 17 groups)  
COMPARA = consensus AR QSAR  
ToxCast Pathway Model AUC ER = full ER model (18 assays)  
ToxCast Pathway Model AUC AR = full AR model (11 assays)

Endocrine models available?

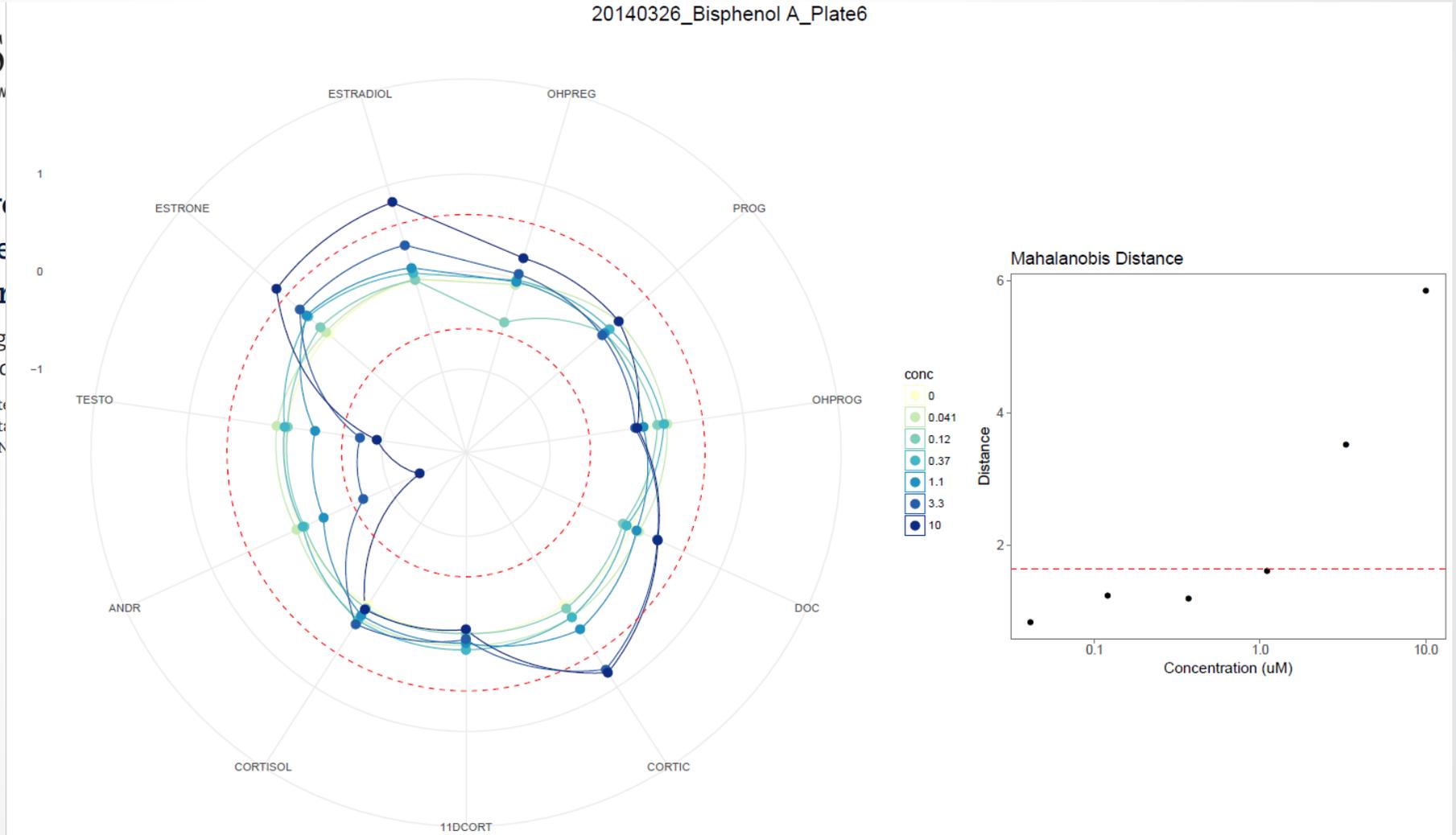


## High-Throughput Screening as an Alternative Characterization

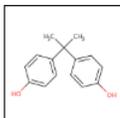
Derik E. Hagg  
Richard S. Jud

\*Oak Ridge Institute  
Center for Computat  
Agency, Durham, N

- Supplemental File 4 has fold-change by hormone
- Supplemental File 9 has mMd (model values)
- Invitrodb v3.2 has a hth295r model table with both of these included in it.
- Hope to include this in future release of the Dashboard.



Selective or non-selective?



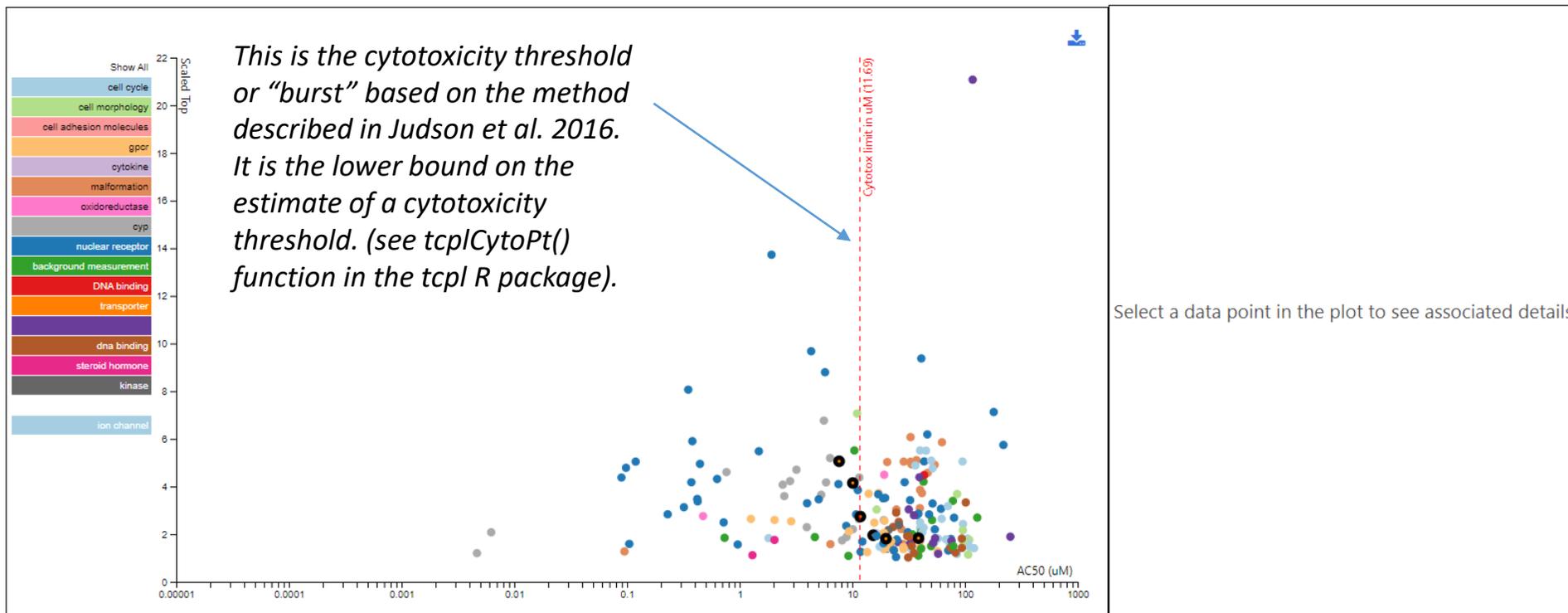
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- DETAILS
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- HAZARD
- ▶ ADME
- ▶ EXPOSURE
- ▼ BIOACTIVITY
  - TOXCAS: SUMMARY**
  - EDSP21
  - TOXCAS/TOX21
  - PUBCHEM
  - TOXCAS: MODELS
  - SIMILAR COMPOUNDS
  - GENRA (BETA)
  - RELATED SUBSTANCES
  - SYNONYMS
  - ▶ LITERATURE
  - LINKS

## Chemical Activity Summary i

TOXCAS DATA

ASSAY DETAILS



Select a data point in the plot to see associated details

211 active of 989 assays



# User application dictates “selectivity”

Selective or non-selective?

- AC50 < burst?
- AC50  $0.5\log_{10}$  distance from burst?
- AC50 < parallel viability assays?
- How else to filter ToxCast data: 3+ caution flags & hit-percent
- Other related ideas:
  - What other assays appear active in a similar concentration range?
  - Is there consistent support for MOA(s), or is it nonspecific activity?

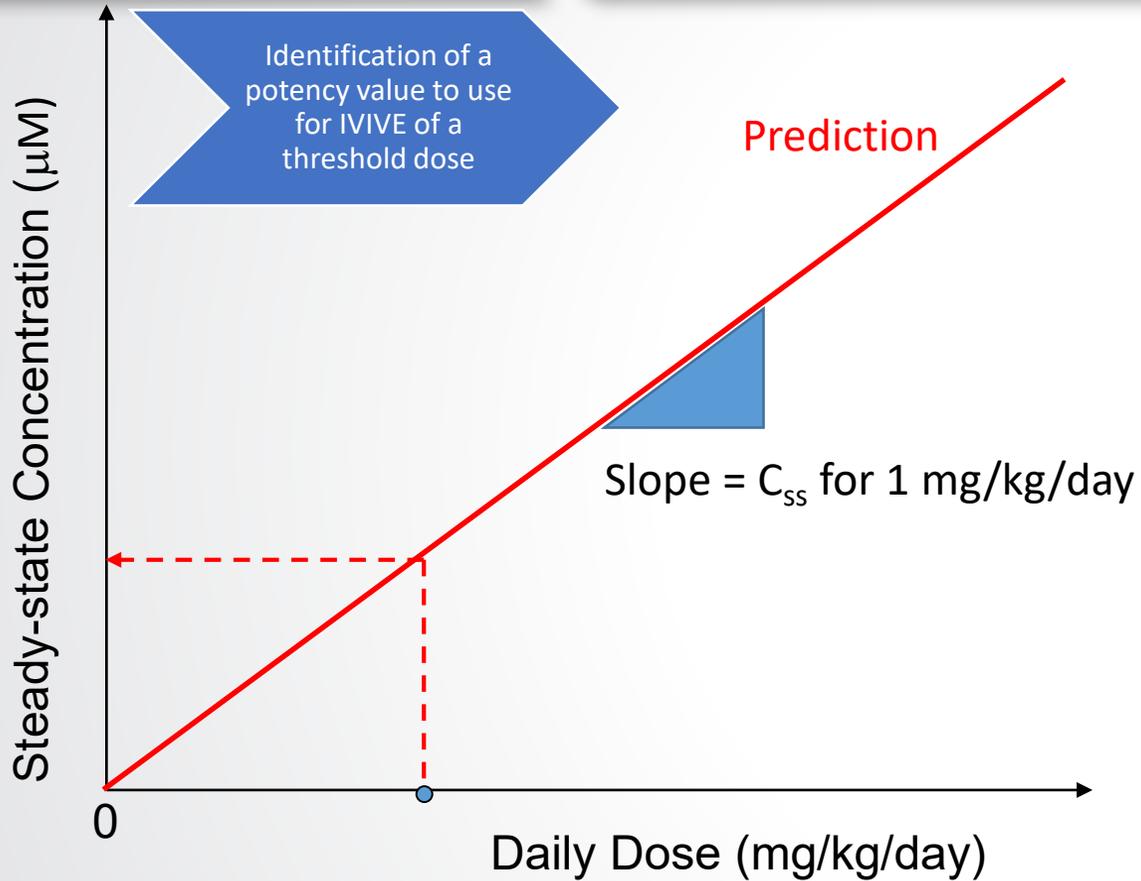


# A note on ToxCast versioning

- Data change: curve-fitting, addition of new data
- Models change: improvements, more data, etc.
- The CompTox Chemicals Dashboard release from August 9, 2019 is now using ToxCast invitrodb version 3.2:  
<https://doi.org/10.23645/epacomptox.6062623.v4>
- All ToxCast data and endocrine models (CERAPP, COMPARA, ER, AR, steroidogenesis) can currently be accessed from within invitrodb.
- Data downloads for NCCT: <https://www.epa.gov/chemical-research/exploring-toxcast-data-downloadable-data>

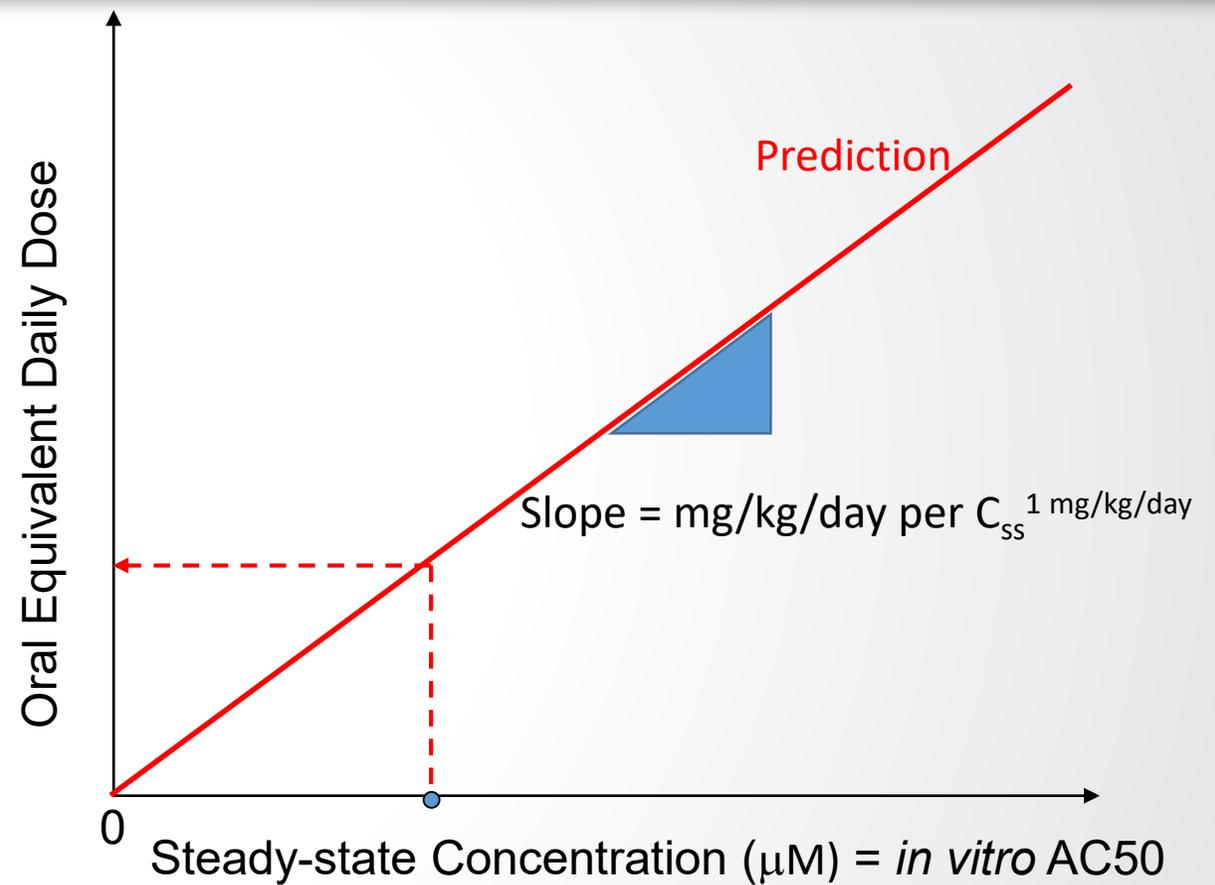


# Steady state in vitro-in vivo extrapolation assumption: blood::tissue partitioning $\approx$ cells::medium partitioning



$$C_{ss} = \frac{\text{oral dose rate}}{\left( \text{GFR} * F_{ub} \right) + \left( Q_l * F_{ub} * \frac{Cl_{int}}{Q_l + F_{ub} * Cl_{int}} \right)}$$

Wetmore *et al.* (2012)



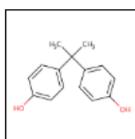
- Swap the axes (this is the “reverse” part of reverse dosimetry)
- Can divide bioactive concentration by  $C_{ss}$  for for a 1 mg/kg/day dose to get oral equivalent dose



# IVIVE via high-throughput toxicokinetic data and models

Identification of a potency value to use for IVIVE of a threshold dose

- Operationally, the htk R package (v 1.10.0) can be downloaded from CRAN or GitHub for reproducible generation of administered equivalent doses (AEDs)
- For some substances, there is a beta tab in the Dashboard with C<sub>ss</sub> and other values needed (no models). More chemicals have information in the htk package.
- AC50 or LEC (micromolar) \* (1 mg/kg/day/C<sub>ss</sub> (micromolar)) = AED prediction
- Htk package optionally implements multiple models that can have increasing complexity based on data available



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## IVIVE

Download Columns

Search query

Label	Measured	Predicted	Computed	Unit
In Vitro Intrinsic Hepatic Clearance	19.29	-	-	uL/min/million hepatocytes
Fraction Unbound in Human Plasma	0.07	-	-	
Volume of Distribution	-	-	6.69	L/kg
Days to Steady State	-	-	8	Days
PK Half Life	-	-	29.83	hours
Human Steady-State Plasma Concentration	-	-	1.98	mg/L

6 records

DETAILS

EXECUTIVE SUMMARY

PROPERTIES

ENV. FATE/TRANSPORT

HAZARD

ADME

IVIVE

EXPOSURE

BIOACTIVITY

SIMILAR COMPOUNDS



# Bioactivity:exposure ratio requires exposure

Comparison to exposure predictions for a bioactivity:exposure ratio

- Currently the Dashboard shows SEEM2 (2014) values

United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Predictions Downloads

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### Exposure Predictions (mg/kg-bw/day)

Demographic	Median	95th Percentile
Ages 6-11	6.30e-5	5.82e-3
Ages 12-19	2.68e-5	2.00e-3
Ages 20-65	2.05e-5	1.61e-3
Ages 65+	1.61e-5	2.18e-3
BMI > 30	1.69e-5	1.45e-3
BMI < 30	2.67e-5	2.26e-3
Repro. Age Females	1.11e-5	1.57e-3
Females	1.11e-5	9.09e-4
Males	3.89e-5	3.34e-3
Total	2.11e-5	2.00e-3

10 records

Navigation: DETAILS, EXECUTIVE SUMMARY, PROPERTIES, ENV. FATE/TRANSPORT, HAZARD, ADME, EXPOSURE (selected), PRODUCT & USE CATEGORIES, CHEMICAL WEIGHT FRACTION, CHEMICAL FUNCTIONAL USE, TOXICS RELEASE INVENTORY, MONITORING DATA, EXPOSURE PREDICTIONS (selected), PRODUCTION VOLUME



# Consensus modeling of chemical exposure based on pathways: ExpoCast SEEM3

Comparison to exposure predictions for a bioactivity:exposure ratio

- “ExpoCast SEEM3” model:
  - uses twelve different exposure predictors including both near- and far-field models;
  - covers four distinct exposure pathways: non-pesticidal dietary, consumer products, far-field pesticide, and far-field industrial.
  - In SEEM3 each exposure predictor is scaled and centered such that chemicals without a value for a predictor relevant to its exposure pathways are assigned the average value.

ENVIRONMENTAL  
Science & Technology

Cite This: *Environ. Sci. Technol.* 2019, 53, 719–732

Article

[pubs.acs.org/est](https://pubs.acs.org/est)

## Consensus Modeling of Median Chemical Intake for the U.S. Population Based on Predictions of Exposure Pathways

Caroline L. Ring,<sup>†,§,∞</sup> Jon A. Arnot,<sup>||,⊥,#</sup> Deborah H. Bennett,<sup>∇</sup> Peter P. Egeghy,<sup>‡</sup> Peter Fantke,<sup>○</sup> Lei Huang,<sup>◆</sup> Kristin K. Isaacs,<sup>‡</sup> Olivier Jolliet,<sup>◆</sup> Katherine A. Phillips,<sup>‡</sup> Paul S. Price,<sup>‡</sup> Hyeong-Moo Shin,<sup>¶</sup> John N. Westgate,<sup>||,○</sup> R. Woodrow Setzer,<sup>†</sup> and John F. Wambaugh<sup>\*,†</sup>



# Screening level assessment example: combine NAMs for exposure, *in vitro* bioactivity, and toxicokinetics

- Conducted by Accelerating the Pace of Chemical Risk Assessment (APCRA)
  - *“international cooperative collaboration of government agencies convened to address barriers and opportunities for the use of new approach methodologies (NAMs) in chemical risk assessment” (Paul Friedman et al., accepted)*

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ACCEPTED MANUSCRIPT

### Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization

Katie Paul Friedman, Matthew Gagne, Lit-Hsin Loo, Panagiotis Karamertzanis, Tatiana Netzeva, Tomasz Sobanski, Jill Franzosa, Ann Richard, Ryan Lougee, Andrea Gissi ... Show more

*Toxicological Sciences*, kfz201, <https://doi.org/10.1093/toxsci/kfz201>

Published: 18 September 2019 Article history

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(APCRA partners for these two case studies)



# Acknowledgments

- Thank you for listening.
- Thank you: Tony Williams, John Wambaugh, and Richard Judson.
- Please reach out to us if you need support or explanations for a specific case, or if you find issues.
- [Paul-friedman.katie@epa.gov](mailto:Paul-friedman.katie@epa.gov)



EPA's Center for Computational Toxicology and Exposure