

SETAC Europe Continuing Education Course:  
TC07-The Endocrine System: Global Perspectives on  
Testing Methods and Evaluation of Endocrine Activity  
([https://dublin.setac.org/programme/scientific-  
programme/training-courses/](https://dublin.setac.org/programme/scientific-programme/training-courses/))

Slides given as part of this training course in a virtual  
training recorded on May 8, 2020

Katie Paul Friedman and Antony Williams

*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*

# What does the future hold?



**TOXICITY TESTING IN THE 21ST CENTURY  
A VISION AND A STRATEGY**



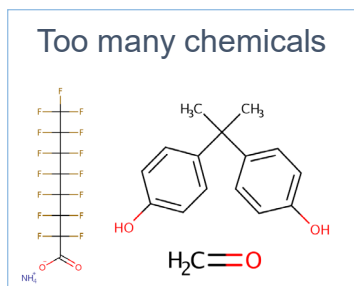
## Goals

---

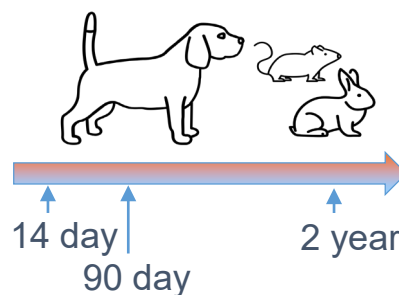
1. To provide broad coverage of chemicals, chemical mixtures, outcomes, and life stages
  2. To reduce the cost and time of testing
  3. To use fewer animals and cause minimal suffering in the animals used
  4. To develop a more robust scientific basis for assessing health effects of environmental agents
-

# Why can't we just use traditional approaches?

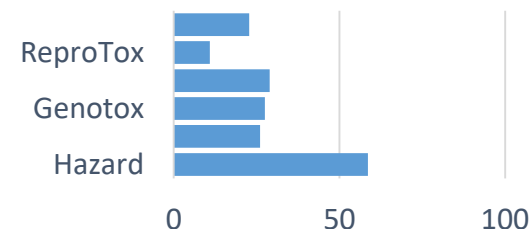
## Challenge



Traditional methods are slow, costly



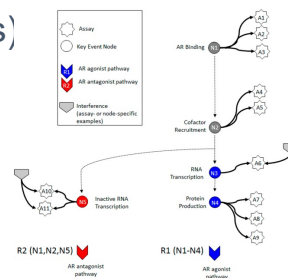
Not enough data



Judson *et al* 2009

## Solution

### New Approach Methods (NAMs)



Interagency Collaboration  
Toxicity Testing in the 21<sup>st</sup>  
century (Tox21)

- >10K chemicals
- >100 biological targets

Cell painting, transcriptomics  
(HTTr, S1500+)

USEPA's Toxicity Forecaster  
(ToxCast) program

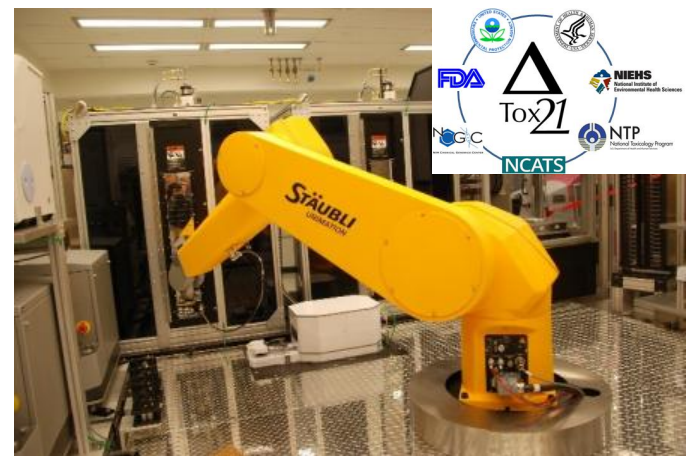
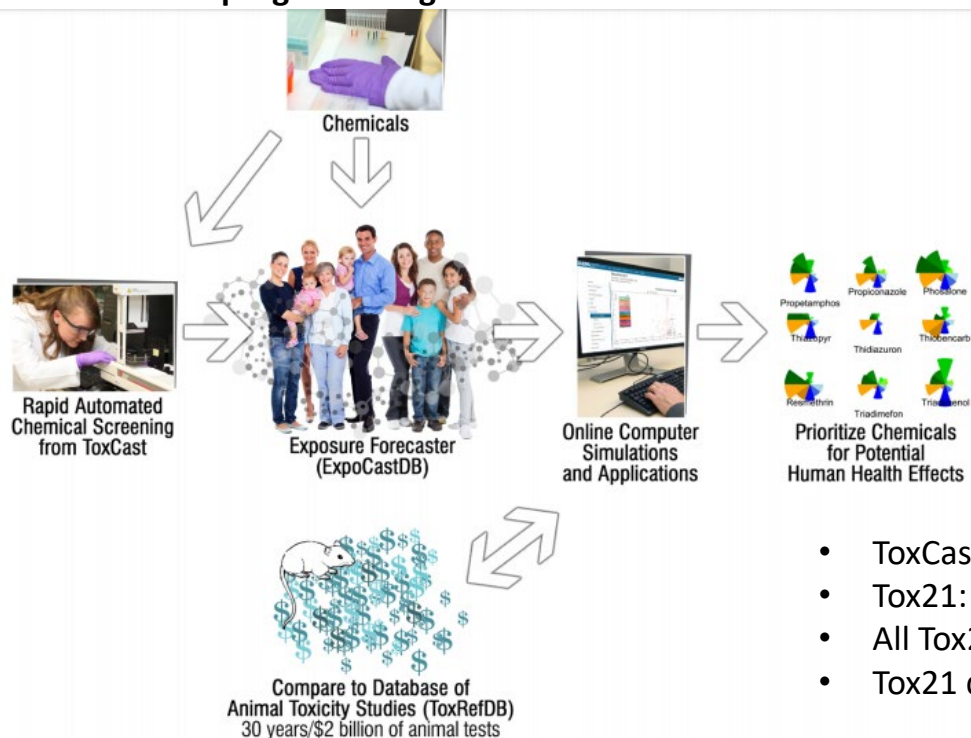
- > 3K chemicals screened in
- > 1K assays
- ~400 biological targets

# New Assessment Methodologies

- Animal testing isn't always the answer
  - Time consuming, expensive, ethically challenging
- New Assessment Methodologies (NAMs)
  - Categories, read across, (Q)SARs, and other model predictions
    - Need for regulatory acceptance (e.g., confidence in applying data to decisions)
    - Challenges in interpretation (e.g., linking molecular/cellular changes to adversity)
    - Need for flexibility (e.g., NAMs may be context/pathway specific)

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

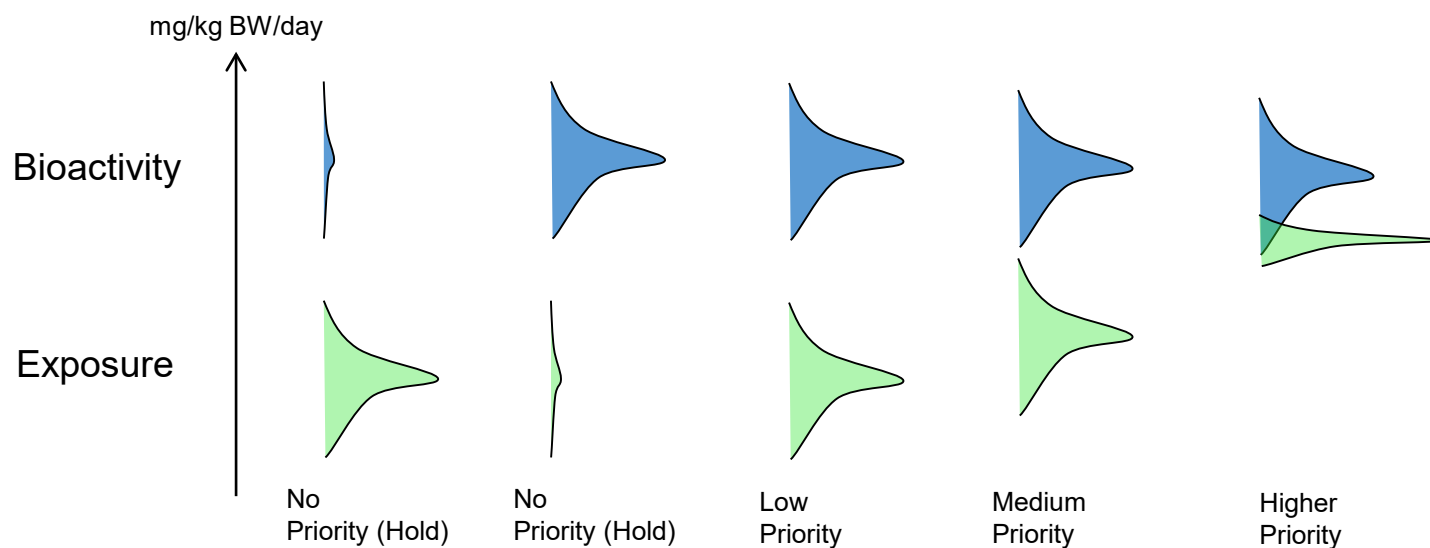
## EPA's ToxCast program at a glance



Tox21 robot

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

# Exposure provides context for high-throughput science



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

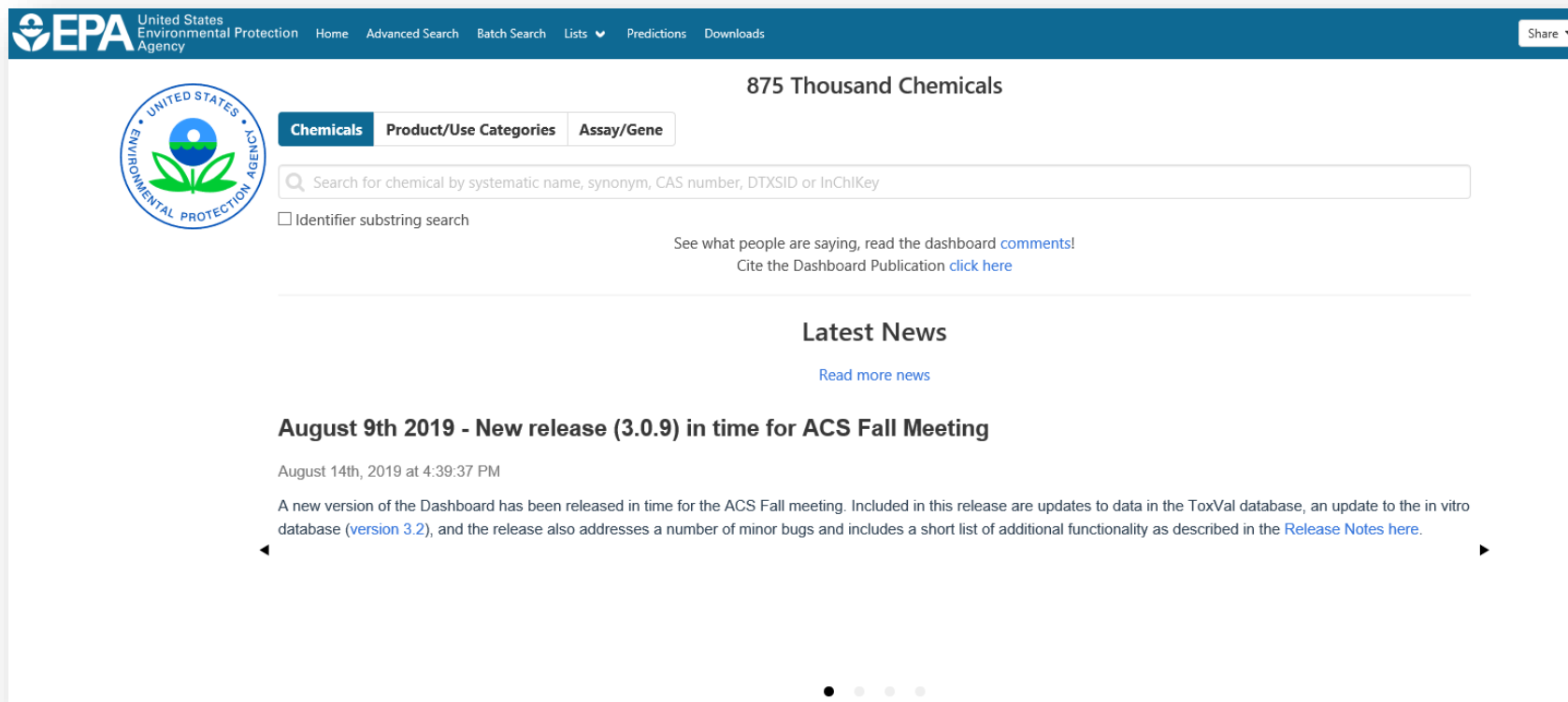
- Publicly available data from ToxCast is actively being applied to endocrine hazard labeling in the EU.
- Risk-based approaches that incorporate bioactivity and exposure make the best use of new approach methodologies.



*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's CompTox Chemicals Dashboard. At the top is the EPA logo and navigation links: Home, Advanced Search, Batch Search, Lists, Predictions, and Downloads. A 'Share' button is in the top right. The main header displays '875 Thousand Chemicals'. Below this are three tabs: 'Chemicals' (selected), 'Product/Use Categories', and 'Assay/Gene'. A search bar prompts users to search by systematic name, synonym, CAS number, DTXSID, or InChIKey. An 'Identifier substring search' checkbox is also present. Links for 'comments!' and 'click here' are provided. The 'Latest News' section features a headline about the August 9th 2019 release (3.0.9) for the ACS Fall Meeting, dated August 14th, 2019 at 4:39:37 PM. The news text describes updates to the ToxVal database, an update to the in vitro database (version 3.2), and minor bug fixes. A SETAC logo is in the bottom right corner of the dashboard area.

EPA United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Predictions Downloads

Share

875 Thousand Chemicals

Chemicals Product/Use Categories Assay/Gene

Search for chemical by systematic name, synonym, CAS number, DTXSID or InChIKey

☐ Identifier substring search

See what people are saying, read the dashboard [comments!](#)  
Cite the Dashboard Publication [click here](#)

Latest News

[Read more news](#)

**August 9th 2019 - New release (3.0.9) in time for ACS Fall Meeting**

August 14th, 2019 at 4:39:37 PM

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](#).

SETAC

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



# The CompTox Chemical Dashboard

- **Freely accessible website and integration hub:**
  - Chemical substances – the majority with structures
  - Searchable by chemical, product use, and gene
  - Experimental and predicted physicochemical property data
  - Experimental and predicted fate and transport data
  - Information regarding consumer products containing chemicals
  - Bioactivity data for the ToxCast/Tox21 project
  - “Literature” searches for chemicals using public resources
  - Links to other agency websites and public data resources
  - “Batch searching” for thousands of chemicals
  - Chemical lists of interest – pesticides, leachables, PFAS, (but not a list of endocrine disruptors)
- 10- Downloadable Open Data for reuse and repurposing



# A single application integrating...

United States Environmental Protection Agency

Home

Advanced Search

Batch Search

Lists

Predictions

Downloads

875 Thousand Chemicals

SEARCH

Search for chemical by systematic name, synonym, CAS number, DTXSID or InChIKey

Identifier substring search

United States Environmental Protection Agency

Home

Advanced Search

Batch Search

Lists

Predictions

Downloads

Batch Search

Step Four: Select Data Output Format and Choose Data Fields to Download

Select Input Type(s)

Identifiers

Chemical Name

CASRN

InChIKey

DTXSID Substance

DSSTox Compound ID

InChIKey Substance

MS-Ready Formula(s)

Exact Formula(s)

Monoisotopic Mass

Enter Identifiers to Search (searches should be limited to <5000 identifiers)

107-26-2

88-39-2

14024-55-6

33468-75-5

7784-40-9

1933-40-9

60332-96-5

2122-76-5

126833-17-8

7786-81-4

Select Output Format

Excel

Download

Customize Results

Select All

Select All in Lists

Chemical Identifiers

DTXSID

Chemical Name

DTXSID

Presence in Lists

Pharmaceuticals from DTNCTC

ACQRES55 Extremely Hazardous Substance List and Threshold Planning Quantities

AEGL: Acute Exposure Guideline Levels

Amphibols Minerals

ANNOGAM Androgen Receptor Chemistry

United States Environmental Protection Agency

Home

Advanced Search

Batch Search

Lists

Predictions

Downloads

Details

EXECUTIVE SUMMARY

PROPERTIES

ENV. RATE/TRANSPORT

HAZARD

ACME

EXPOSURE

BIOTOXICITY

SIMILAR COMPOUNDS

GENRA (BETA)

RELATED SUBSTANCES

Bisphenol A

80-05-7 | DTXTSID7020182

Searched by Expert Validated Synonym.

Hazard

Download

Columns

Max	Type	Subtype	Risk assessment class	Value	Units	Study type	Exposure route	Species	Substance	Source
MES	Short-term Critical Air		short-term	500	mg/m3	-	inhalation	-	TG 230 Military Exposure Guidelines Table	DOO
MES	Short-term Marginal Air		short-term	100	mg/m3	-	inhalation	-	TG 230 Military Exposure Guidelines Table	DOO
MES	Short-term Negligible Air		short-term	15	mg/m3	-	inhalation	-	TG 230 Military Exposure Guidelines Table	DOO
MES	Soil Negligible Soil		chronic	100000	mg/kg	-	soil	-	TG 230 Military Exposure Guidelines Table	DOO
MES	Long-Term Soil Negligible Water		chronic	7	mg/L	-	oral	-	TG 230 Military Exposure Guidelines Table	DOO

United States Environmental Protection Agency

Home

Advanced Search

Batch Search

Lists

Predictions

Downloads

Details

EXECUTIVE SUMMARY

PROPERTIES

ENV. RATE/TRANSPORT

HAZARD

ACME

EXPOSURE

BIOTOXICITY

SIMILAR COMPOUNDS

GENRA (BETA)

RELATED SUBSTANCES

Bisphenol A

80-05-7 | DTXTSID7020182

Searched by Expert Validated Synonym.

Chemical Activity Summary

TOXCAST DATA

ASSAY DETAILS

ACSR (pM): 5.73

Scaled log: 8.91

Assay Description: 742

Gene Symbol: ESR1

Organism: human

Tissue: Uterine

Assay Format: Type cell-based

Biological Process: Target: protein stabilization

Detection Technology: Western blotting/Competition

Analysis: Disruption: positive

Intended Target Family: Nuclear receptor

Description: Data from the assay component OT\_ER\_ESR1\_0400 was analyzed into 1 assay endpoint. OT\_ER\_ESR1\_0400 was analyzed in the positive filtering direction relative to DMSO as the negative control and baseline of activity. Using a type of binding reporter, measure of receptor for gene of signal activity can be used to understand the binding at the pathway level as this relates to the gene ESR1. Furthermore, this assay endpoint can be referred to as a primary readout, because the performed assay has only produced 1 assay endpoint. To generalize the intended target to other suitable targets, this assay endpoint is associated to the "Nuclear receptor" intended target family, where the subfamily is "steroidal".

United States Environmental Protection Agency

Home

Advanced Search

Batch Search

Lists

Predictions

Downloads

Details

EXECUTIVE SUMMARY

PROPERTIES

ENV. RATE/TRANSPORT

HAZARD

ACME

EXPOSURE

BIOTOXICITY

SIMILAR COMPOUNDS

GENRA (BETA)

RELATED SUBSTANCES

Bisphenol A

80-05-7 | DTXTSID7020182

Searched by Expert Validated Synonym.

Similarity

Searched with a similarity threshold of 0.8

376 of 390 chemicals visible

Chemical Name	CASRN	DTXSID	Similarity
4-(1,1-dichloroethyl)phenol	505-60-2	DTXSID015028712	TOXCAT-1
4-(1,1-dichloroethyl)phenol	505-60-2	DTXSID015028712	TOXCAT-1
4-(1,1-dichloroethyl)phenol	505-60-2	DTXSID015028712	TOXCAT-1
4-(1,1-dichloroethyl)phenol	505-60-2	DTXSID015028712	TOXCAT-1
4-(1,1-dichloroethyl)phenol	505-60-2	DTXSID015028712	TOXCAT-1




# A data integration hub

## LOTS of data!

- >875,000 chemicals curated over 20 years
- >700,000 toxicity data points from >30 sources
- Millions of synonyms and identifiers
- Tens of thousands of experimental data points
- Millions of QSAR prediction reports
- Millions of bioactivity data points for >4000 chemicals and hundreds of assay end points
- Searching of Pubmed's 30 million abstracts

# Review of Bioassay Data

United States  
Environmental Protection  
Agency

[Home](#) [Advanced Search](#) [Batch Search](#) [Lists](#) [Predictions](#) [Downloads](#)

Copy

Share

Submit Comment

Search all data

EXECUTIVE SUMMARY

PROPERTIES

ENV. FATE/TRANSPORT

HAZARD

ADME

EXPOSURE


BIOACTIVITY

TOXCAST: SUMMARY

EDSP21

TOXCAST/TOX21

TOXCAST DATA



ASSAY DETAILS

AC50 (uM): 40.99  
Scaled top: 9.38  
Assay Endpoint Name: ACEA\_AR\_antagonist\_80hr  
Gene Symbol: AR  
Organism: human  
Tissue: prostate  
Assay Format Type: cell-based  
Biological Process Target: cell proliferation  
Detection Technology: RT-CES  
Analysis Direction: NA  
Intended Target Family: nuclear receptor  
Description: Data from the assay component ACEA\_AR\_agonist\_80hr was analyzed in the positive fitting direction relative to DMSO as the negative control and baseline of activity. Using a type of growth reporter, measures of the cells for gain-of-signal activity can be used to understand the signaling at the pathway-level as they relate to the gene AR. Furthermore, this assay endpoint can be referred to as a primary readout, because this assay has produced multiple assay endpoints where this one serves a signaling function. To generalize the intended target to other soluble targets, this assay endpoint is

211 active of 989 assays

Download

Columns

50

Search query

Show Inactive

Show Background

Name	Description	Gene Symbol	AOP	Hit Call	Scaled Top	AC50	logAC50	Intended Target Family
NVS_LGIC_rGluNMDA_Agonist	-	Grin1	13	ACTIVE	1.48	17.5	1.24	ion channel
NVS_GPCR_p5HT2C	-	HTR2C	33	ACTIVE	2.00	18.3	1.26	gpcr
TOX21_PPARD_BLA_antagonist_ratio	1125	PPARD	36	ACTIVE	2.80	37.2	1.57	nuclear receptor
ATG_PPARE_CIS_up	102	PPARA	58	ACTIVE	1.04	24.4	1.39	nuclear receptor
NVS_NR_hPPARa	718	PPARA	58	ACTIVE	1.59	0.105	-0.979	nuclear receptor
ATG_DR4_LXR_CIS_dn	-	NR1H3	58	ACTIVE	1.78	24.8	1.40	nuclear receptor
ATG_PXRE_CIS_up	-	NR1I2	60	ACTIVE	5.48	1.48	0.171	nuclear receptor
ATG_PXR_TRANS_up	-	NR1I2	60	ACTIVE	2.49	0.722	-0.141	nuclear receptor
NVS_NR_hPXR	-	NR1I2	60	ACTIVE	1.69	12.3	1.09	nuclear receptor
NVS_NR_hFXR_Antagonist	716	NR1H4	61	ACTIVE	1.93	16.4	1.22	nuclear receptor
OT_FXR_FXR SRC1_0480	753	NR1H4	61	ACTIVE	2.08	31.1	1.49	nuclear receptor
OT_FXR_FXR SRC1_1440	754	NR1H4	61	ACTIVE	3.43	32.6	1.51	nuclear receptor

# Endocrine-related subset of assays

## EDSP21

QC Data ID	Grade	Description
<a href="#">Tox21_202992</a>	Pass	Purity>90% and MW confirmed
<a href="#">Tox21_400088</a>	Pass	Purity>90% and MW confirmed

Assay Selection 34 Selected

☒ Active ☐ Inactive ☐ All

Filter assays

Set: ER (18 of 28 selected)

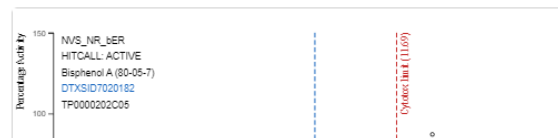
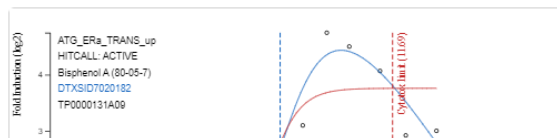
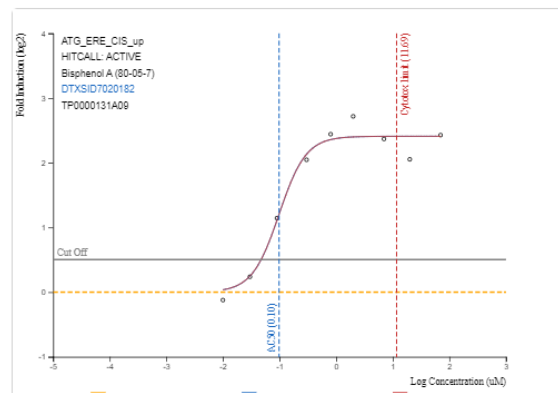
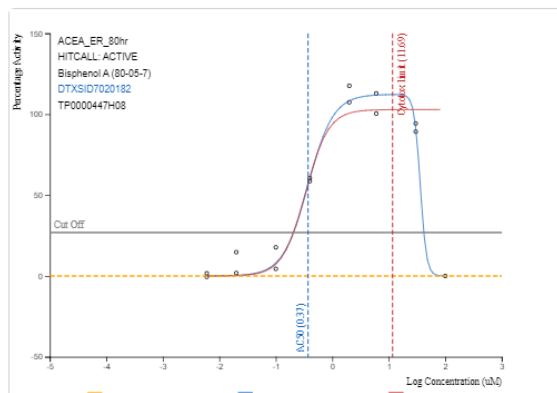
- ☒ ACEA\_ER\_80hr
- ☒ ATG\_ERE\_CIS\_up
- ☒ ATG\_ERa\_TRANS\_up
- ☒ NVS\_NR\_bER
- ☒ NVS\_NR\_hER
- ☒ OT\_ER\_ERaERa\_0480
- ☒ OT\_ER\_ERaERa\_1440
- ☒ OT\_ER\_ERbERb\_0480
- ☒ OT\_ER\_ERbERb\_1440
- ☒ OT\_ERa\_EREGFP\_0120
- ☒ OT\_ERa\_EREGFP\_0480

A Single Assay Can Have Multiple Charts

☒ Representative Samples Only

Bioactivity Summary

Number of Charts: 34



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; Vapor Pressure < 1.

**EPA** United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Predictions Downloads

Copy Share Submit Comment Search all data

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

Property  
Summary

Download Columns

Summary

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 <sup>2</sup> K)
Viscosity	-	9.66			-	9.66	cP
Henry's Law	-	1.26e-7			-	1.26e-7	atm-m <sup>3</sup> /mole
LogKow: Octanol-Air	-	8.38			-	8.38	-

16 records

DETAILS  
EXECUTIVE SUMMARY  
**PROPERTIES**  
ENV. FATE/TRANSPORT  
HAZARD  
ADME  
EXPOSURE  
BIOACTIVITY  
TOXCAST: SUMMARY  
EDSP21  
TOXCAST/TOX21  
PUBCHEM  
TOXCAST: MODELS  
SIMILAR COMPOUNDS  
GENRA (BETA)  
RELATED SUBSTANCES  
SYNONYMS  
LITERATURE  
LINKS



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

**EPA** United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Predictions Downloads

Copy Share Submit Comment Search all data

## 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

Download Bioactivity Summary

Number of Charts: 0

Select one or more assays from the list of assays to view the

Filter assay

Odyssey Therapeutics

Attagene (0 of 1)

CellzDirect (0 of 1)

Bioseek (0 of 1)

Apredica (0 of 1)

### Bisphenol A

QC Grade

TO	Grade	Description
T0	A	MW Confirmed, Purity > 90%
T4	A	MW Confirmed, Purity > 90%

Identifiers

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

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

Cc1ccc(cc1)C(C)(C)c2ccc(O)cc2



# 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:

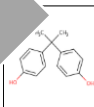
<https://doi.org/10.23645/epacomptox.6062623.v4>

- All ToxCast data and endocrine models (CERAPP, COMPARA, ER, AR, steroidogenesis) can currently be accessed from within invitrodb.
- Data downloads for CCTE:  
<https://www.epa.gov/chemical-research/exploring-toxcast-data-downloadable-data>

# Models >>> single assays. And equivocal happens.

Endocrine models available?

[Home](#) [Advanced Search](#) [Batch Search](#) [Lists](#) [Predictions](#) [Downloads](#) [Copy](#) [Share](#) [Submit Comment](#)



## Bisphenol A

80-05-7 | DTXSID7020182

Searched by DSSTox Substance Id.

### 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)

- DETAILS
- EXECUTIVE SUMMARY
- PROPERTIES
- ENV. FATE/TRANSPORT
- HAZARD
- ADME
- EXPOSURE
- BIOACTIVITY
  - TOXCAST: SUMMARY
  - EDSP21
  - TOXCAST/TOX21
  - PUBCHEM
  - TOXCAST: MODELS**
  - SIMILAR COMPOUNDS
  - GENRA (BETA)

# HT-H295R model for steroidogenesis

Endocrine models available?

OXFORD

SW

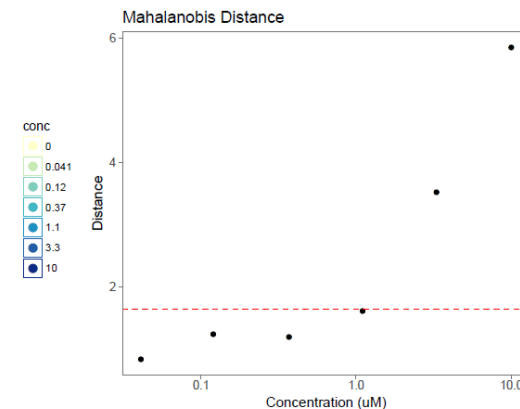
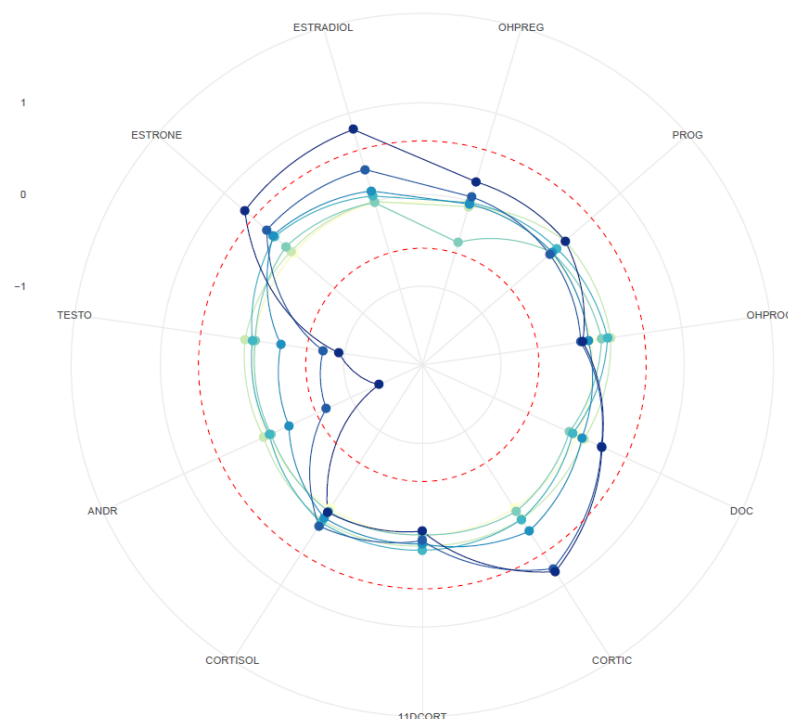
High-Thro  
as an Alte  
Character

Derik E. Hagg  
Richard S. Ju

\*Oak Ridge Institute  
Center for Comput  
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.

20140326\_Bisphenol A\_Plate6



# Bioactivity Summary in the Dashboard

Selective or non-selective?

- DETAILS
- EXECUTIVE SUMMARY
- PROPERTIES
- ENV. FATE/TRANSPORT
- HAZARD
- ADME
- EXPOSURE
- BIOACTIVITY
  - TOXCAST: SUMMARY
  - EDSP21
  - TOXCAST/TOX21
  - PUBCHEM
  - TOXCAST: MODELS
- SIMILAR COMPOUNDS
- GENRA (BETA)
- RELATED SUBSTANCES
- SYNONYMS
- LITERATURE
- LINKS



Bisphenol A

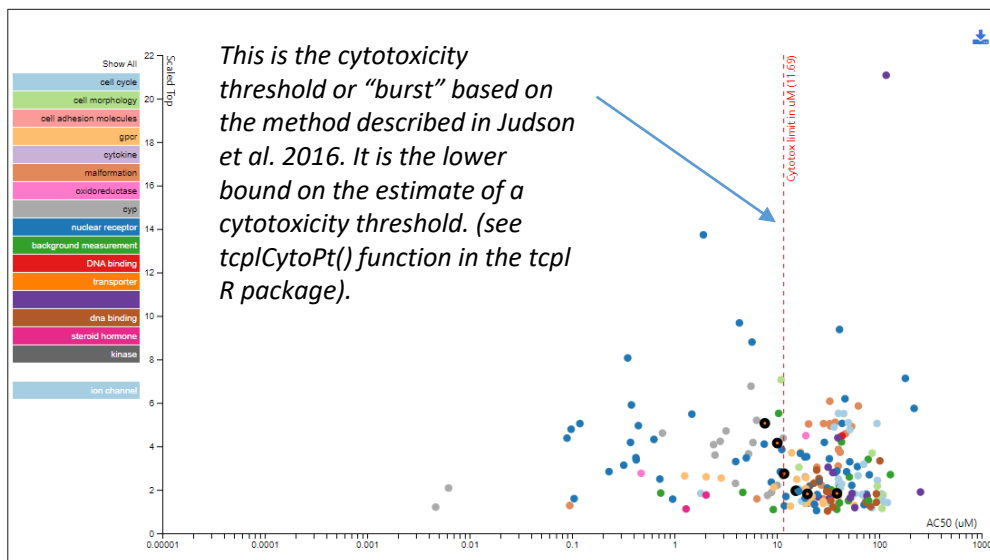
80-05-7 | DTXSID7020182

Searched by DSSTox Substance Id.

## Chemical Activity Summary i

TOXCAST DATA

ASSAY DETAILS



Select a data point in the plot to see associated details

# Summary of the assay data is in a table

Selective or non-selective?

211 active of 989 assays

Search query  ☐ Show Inactive ☒ Show Background

	Modal	Description	SeqAPASS	AOP	Event	Hit Call	Top	Scaled Top	AC50	logAC50	Bmad	MaxMed	MaxMedConc	Cutoff	Flags	ModIAcc	ModIAC10	ModIACb	Intended Target Family
ACEA_ER_80hr		2	<a href="#">NP_000116.2</a>	200	1181	ACTIVE	112	4.18	0.373	-0.428	8.96	113 - percent_activity	0.301	26.9		-0.686	113	-0.686	nuclear receptor
APR_HepG2_CellLoss_24h_dn		-	-	-	-	ACTIVE	1.20	1.81	106	2.02	6.63e-2	1.20 - log2_fold_induction	2.30	0.663		2.04	1.20	1.94	cell cycle
APR_HepG2_MitoMass_24h_dn		-	-	-	-	ACTIVE	0.874	1.76	109	2.04	4.96e-2	0.867 - log2_fold_induction	2.30	0.496		2.05	0.867	1.95	cell morphology
APR_HepG2_MitoMembPot_24h_dn		-	-	-	-	ACTIVE	5.92	7.07	11.0	1.04	8.38e-2	6.45 - log2_fold_induction	1.70	0.838		0.813	6.45	0.646	cell morphology
APR_HepG2_OxidativeStress_24h_up		-	-	-	-	ACTIVE	1.20	1.47	110	2.04	8.19e-2	1.19 - log2_fold_induction	2.30	0.819		2.08	1.19	1.97	cell cycle
APR_HepG2_CellLoss_72h_dn		-	-	-	-	ACTIVE	4.49	5.05	95.2	1.98	8.89e-2	4.43 - log2_fold_induction	2.30	0.889		1.75	4.43	1.52	cell cycle
APR_HepG2_MitoMembPot_72h_dn		-	-	-	-	ACTIVE	2.71	3.69	85.3	1.93	7.33e-2	2.26 - log2_fold_induction	2.30	0.733		1.70	2.26	1.36	cell morphology
APR_HepG2_MitoticArrest_72h_up		-	-	-	-	ACTIVE	1.66	1.17	84.7	1.93	0.142	1.44 - log2_fold_induction	2.30	1.42	Borderline active	2.29	1.44	1.71	cell cycle
APR_HepG2_OxidativeStress_72h_up		-	-	-	-	ACTIVE	1.80	1.65	106	2.02	0.110	1.60 - log2_fold_induction	2.30	1.10		2.08	1.60	1.82	cell cycle
ATG_Ahr_CIS-up		-	<a href="#">NP_001612.1</a>	150	18	ACTIVE	1.31	1.32	23.4	1.37	0.199	1.28 - log2_fold_induction	2.00	0.994		1.56	1.28	1.34	dna binding

First << < 1 2 3 4 5 6 7 8 9 10 > >> Last

Showing 1 to 10 of 211 records

# “Burst:” thinking and updates

Selective or non-selective?

- The latest Comptox Chemicals Dashboard release (version 3.0.9, August 9, 2019) demonstrates a cytotoxicity threshold based on the latest ToxCast database (invitrodb version 3.2, released August 2019). This value can change as more cytotoxicity data become available, curve-fitting approaches for existing data change, or the “burst” calculation approach is updated.
- In invitrodb version 3.2, 88 assays are considered for the cytotoxicity threshold. A positive hit must be observed in 5% of these assays (noting that not all chemicals are screened in all 88 assays) in order to assign a cytotoxicity threshold. The cytotoxicity threshold is a median of AC50 potency values from the N assays with a hit. The cytotoxicity threshold visualized in the Dashboard is a lower bound on this estimate, calculated as the median cytotoxicity potency minus 3 times the global median absolute deviation.
- This is discussed further in a publication ([10.1093/toxsci/kfw148](https://doi.org/10.1093/toxsci/kfw148)) and the ToxCast Pipeline R package (tcpl) function, tcplCytoPt() (available on CRAN: <https://cran.r-project.org/web/packages/tcpl/index.html>).
- If fewer than 5 cytotoxicity assays demonstrate a positive hit, a default of 1000 micromolar is assigned for the chemical.
- The lower bound estimate of the cytotoxicity threshold or “burst” is useful context for ToxCast results. Bioactivity observed below the cytotoxicity threshold may represent more specific activity that is less likely to be confounded by cytotoxicity.
- It is possible that AC50 values above the cytotoxicity threshold are informative. If an assay has a parallel cytotoxicity assay in the same cell type, that may be more informative for interpreting that assay. Or, if a result is consistent with an AOP relevant to the chemical with assay AC50 values above and below the cytotoxicity threshold, those data may be meaningful.

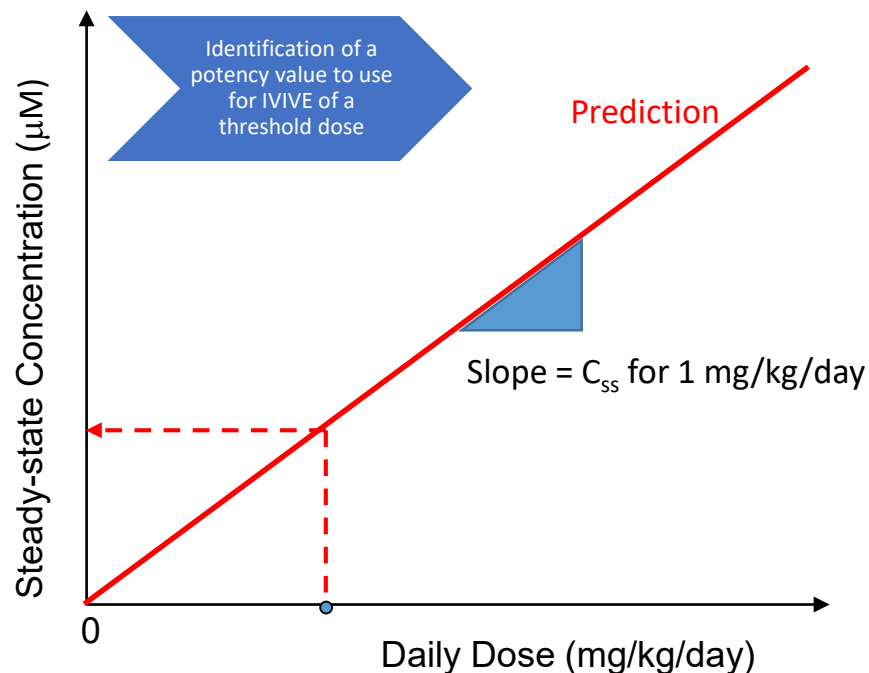
# User application dictates “selectivity”

Selective or non-selective?

- $AC50 < \text{burst?}$
- $AC50 \ 0.5\log_{10}$  distance from burst?
- $AC50 < \text{parallel viability assays?}$
- 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?

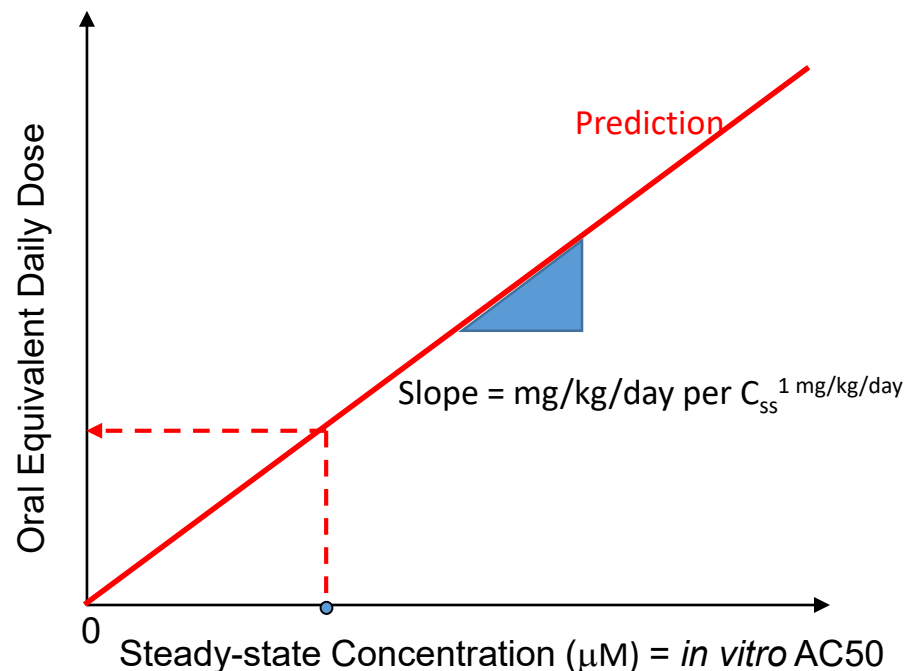
# Steady state in vitro-in vivo extrapolation (IVIVE)

assumption: blood::tissue partitioning  $\approx$  cells::medium partitioning



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

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 Css and other values needed (no models). More chemicals have information in the htk package.
- $AC_{50}$  or  $LEC$  (micromolar) \* (1 mg/kg/day/Css (micromolar)) = AED prediction
- Htk package optionally implements multiple models that can have increasing complexity based on data available

**EPA** United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Predictions Downloads

Copy Share Submit Comment Search all data

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

Download Columns

IVIVE

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

# Bioactivity:exposure ratio requires exposure

Comparison to  
exposure predictions  
for a  
bioactivity:exposure  
ratio

- Currently the Dashboard shows SEEM2 (2014) values

**EPA** United States Environmental Protection Agency

Home Advanced Search Batch Search Lists Predictions Downloads

Copy

DETAILS

EXECUTIVE SUMMARY

PROPERTIES

ENV. FATE/TRANSPORT

HAZARD

▶ ADME

▼ EXPOSURE

PRODUCT & USE CATEGORIES

CHEMICAL WEIGHT FRACTION

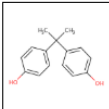
CHEMICAL FUNCTIONAL USE

TOXICS RELEASE INVENTORY

MONITORING DATA

EXPOSURE PREDICTIONS

PRODUCTION VOLUME



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

Download

**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

# 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

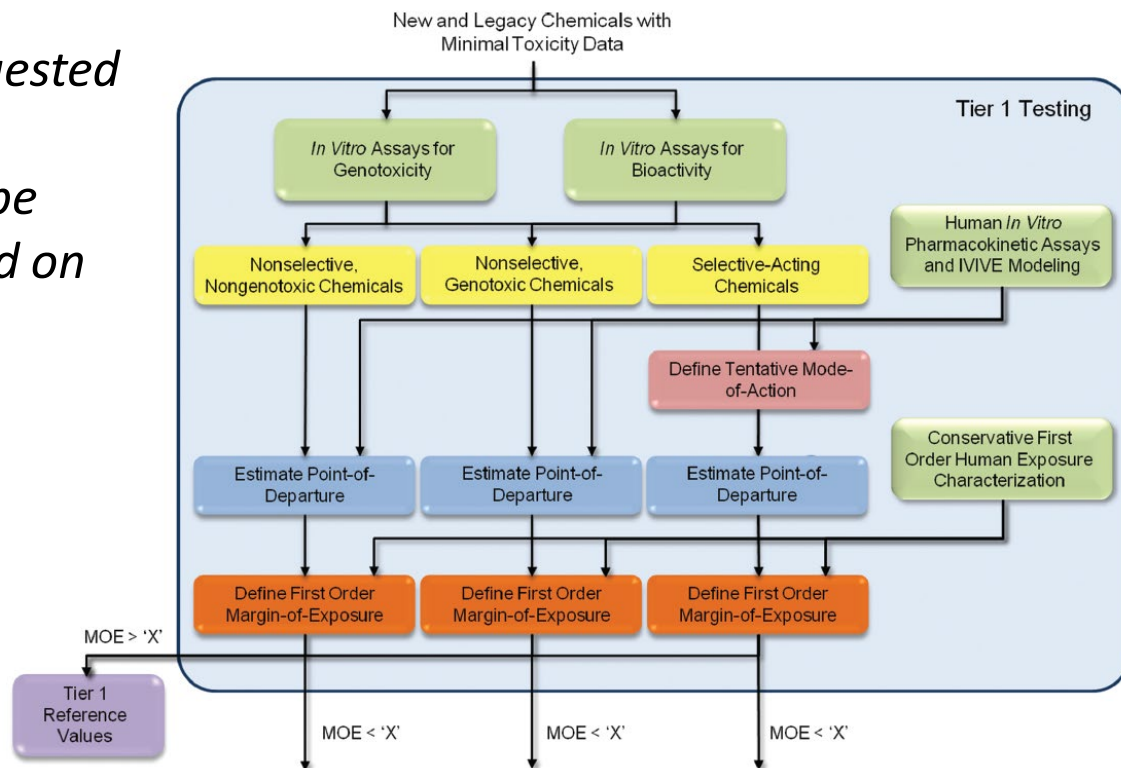
Caroline L. Ring,<sup>†,§,∞</sup> Jon A. Arnot,<sup>||,⊥,#</sup> Deborah H. Bennett,<sup>▽</sup> Peter P. Egeghy,<sup>‡</sup> Peter Fantke,<sup>○</sup>  
Lei Huang,<sup>◆</sup> Kristin K. Isaacs,<sup>‡</sup> Olivier Jolliet,<sup>◆</sup> Katherine A. Phillips,<sup>‡</sup> Paul S. Price,<sup>‡</sup>  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



# Including risk-based approaches like BER in chemical safety decisions

- Specific vs. nonspecific modes-of-action and the challenge of hazard labeling

*Thomas et al. 2013 suggested a framework for hazard assessment that would be largely customized based on MOE (or now, BER).*



# Including risk-based approaches like BER in chemical safety decisions

- Now, ~6 years later, Thomas et al. (2019) suggest a computational toxicology blueprint that represents evolution of the same concept

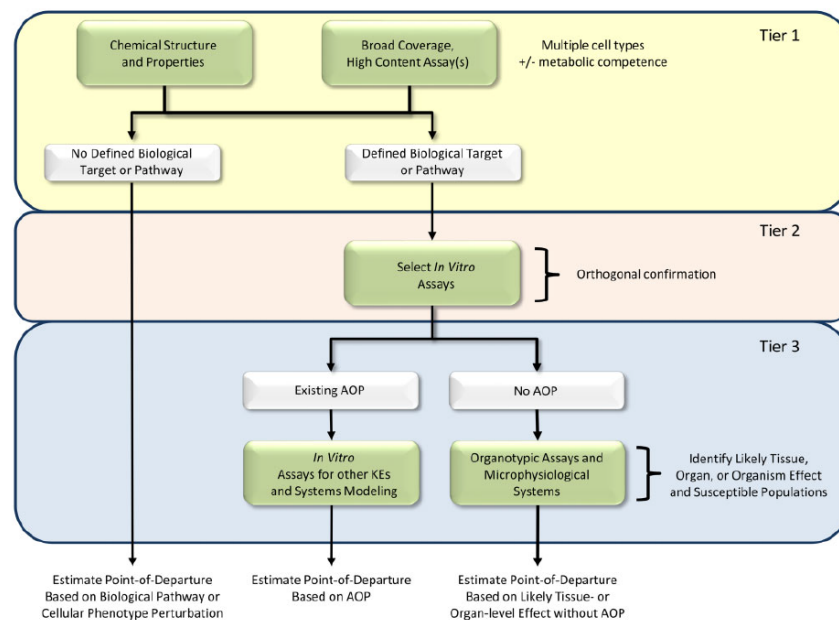
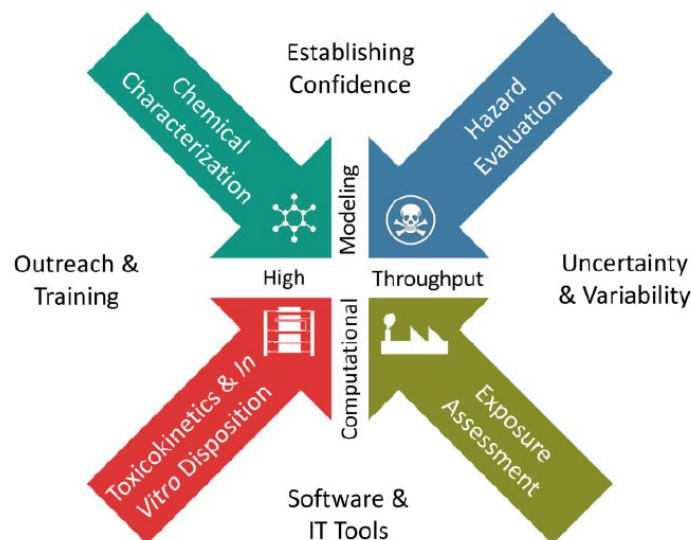


Figure 2. Tiered testing framework for hazard characterization. Tier 1 uses both chemical structure and broad coverage, high content assays across multiple cell types for comprehensively evaluating the potential effects of chemicals and grouping them based on similarity in potential hazards. For chemicals from Tier 1 without a defined biological target / pathway, a quantitative point-of-departure for hazard is estimated based on the absence of biological pathway or cellular phenotype perturbation. Chemicals from Tier 1 with a predicted biological target or pathway are evaluated Tier 2 using targeted follow-up assays. In Tier 3, the likely tissue, organ, or organism-level effects are considered based on either existing adverse outcome pathways (AOP) or more complex culture systems. Quantitative points-of-departure for hazard are estimated based on the AOP or responses in the complex culture system.

# 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)*



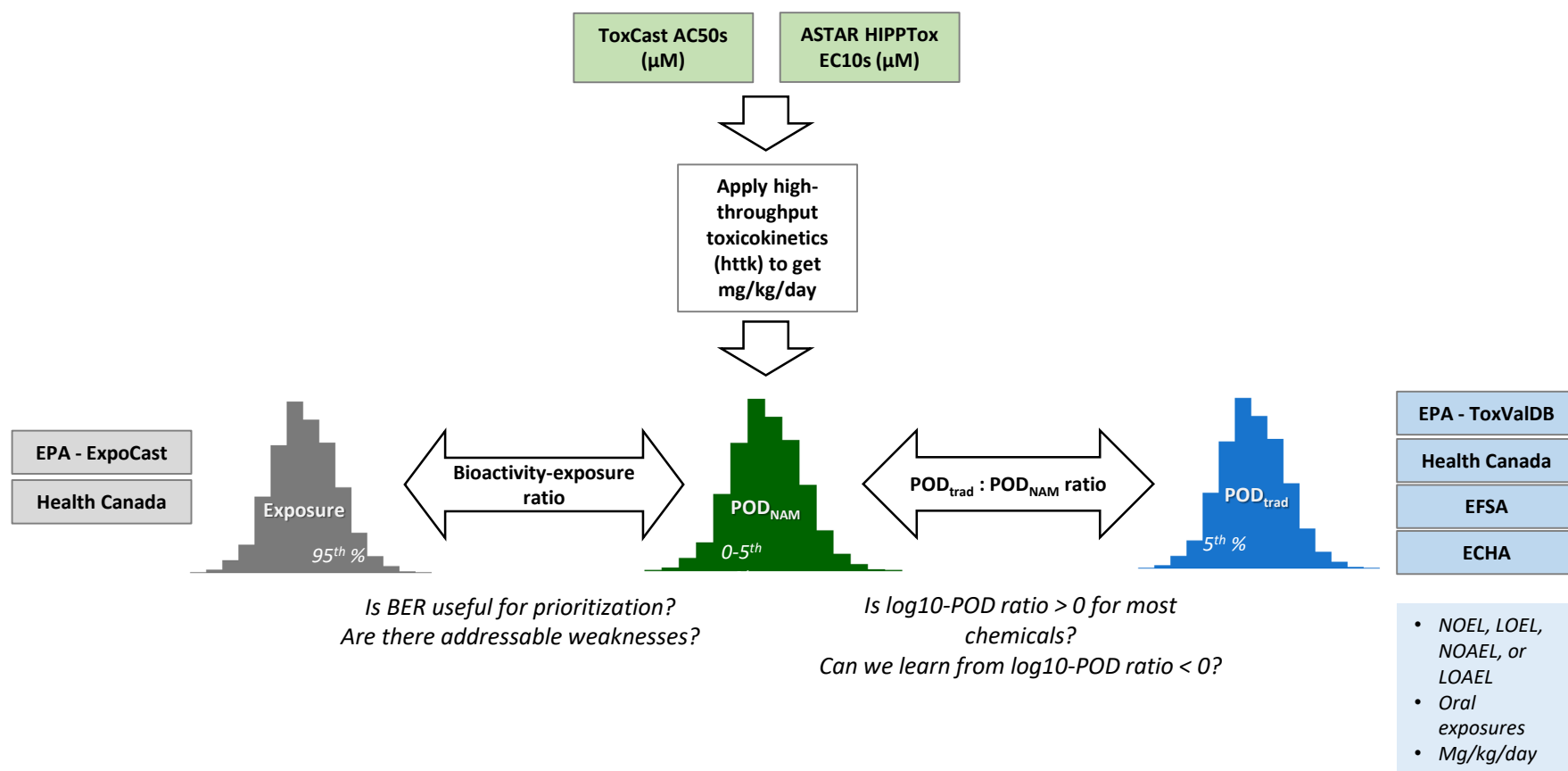
TOXICOLOGICAL SCIENCES, 2019, 1–24

doi: 10.1093/toxsci/kfz201  
Advance Access Publication Date: September 18, 2019  
Research Article

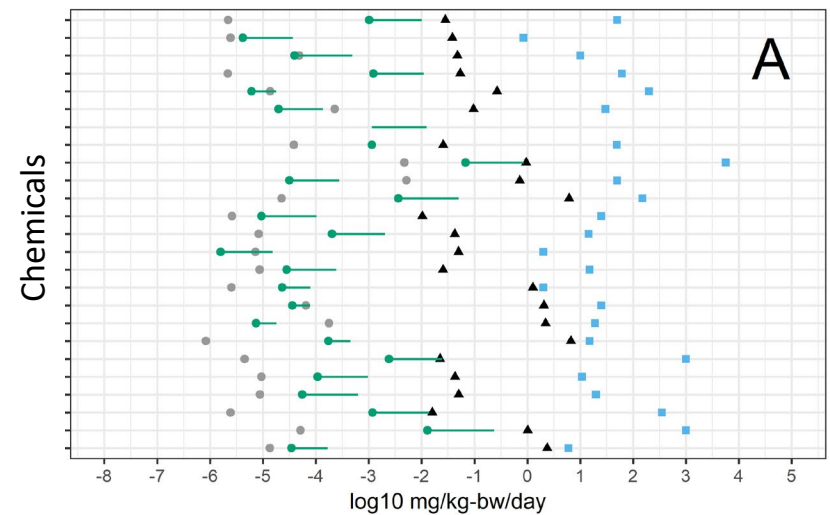
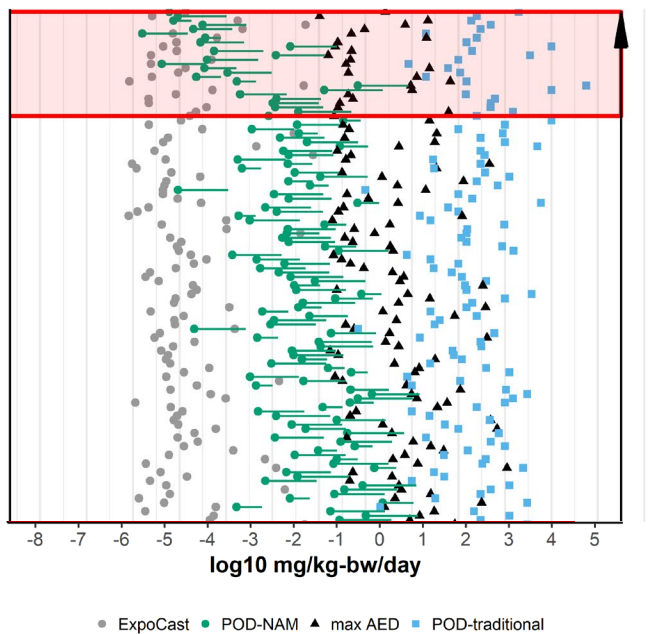
## Utility of In Vitro Bioactivity as a Lower Bound Estimate of In Vivo Adverse Effect Levels and in Risk-Based Prioritization



# Case study workflow



# Prioritizing chemicals based on BER for all bioactivity or for some target bioactivity



*For 448 substances, ~89% of the time, the point-of-departure based on ToxCast (POD-NAM) was less than the NOAEL/LOAEL values available from animals.*

Figure 3 from Paul Friedman et al.

<https://doi.org/10.1093/toxsci/kfz201>