



## **SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety**

# **Use of Computational and *In Vitro* Data in Cancer Hazard Assessment of Data-Rich Chemicals: Examples of IARC Monographs**

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# Conflict of Interest Statement

1. The author declares no relevant conflicts of interest with respect to the content of this presentation
2. This presentation does not reflect the official views of WHO, IARC, Texas A&M University, or any other organization or a third party, and contains personal opinions of Dr. Rusyn
3. The information in this presentation, as it pertains to evaluations by IARC Monographs Programme, is not final and may be subject to changes pending final editing of the Monographs



# Acknowledgements

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IARC Monographs Working Group Members for volumes 110 (2014), 112 (2015) and 113 (2015)

**Special THANK YOU to:** Weihsueh Chiu (Texas A&M), David Reif (NC State), Mathew Martin, Richard Judson, Keith Houck, Rusty Thomas, Kevin Crofton (all US EPA)

Data are from Tox21 and ToxCast toxicity testing programs



# IARC Evaluations: Sources of Data

All pertinent **epidemiological** studies and **cancer bioassays in rodents**

- Study designs and results are detailed in tables
- Descriptions of individual studies are in text [**comments in brackets**]

Representative **mechanistic data** judged to be important by the Working Group

- Includes information on (i) toxicokinetics, (ii) **representative data on the 10 key characteristics of carcinogens**, (iii) **data relevant to comparisons across agents and end-points**, (iv) cancer susceptibility, and (v) **other adverse effects**
- Mechanistic and other relevant data for the agent under consideration are drawn from representative studies in humans, animals, and ***in vitro***
- Written in the form of a review article [**comments in brackets**]

All studies must be publicly available (published or accepted)

- Includes studies published in languages other than English
- Does not consider research in progress, articles in preparation, consultant reports, or anything that is not publicly available
- **Databases (e.g. PubChem) and peer-reviewed government reports can also be searched**



# IARC Monographs for Evaluation of Cancer Hazard in Humans

Preamble

General Remarks

Several *Monographs* in one volume:

1. Exposure data **Critical review**
2. Cancer in humans
3. Cancer in animals
4. Mechanistic and other relevant data
5. Summary **Evaluation**
6. Evaluation and rationale

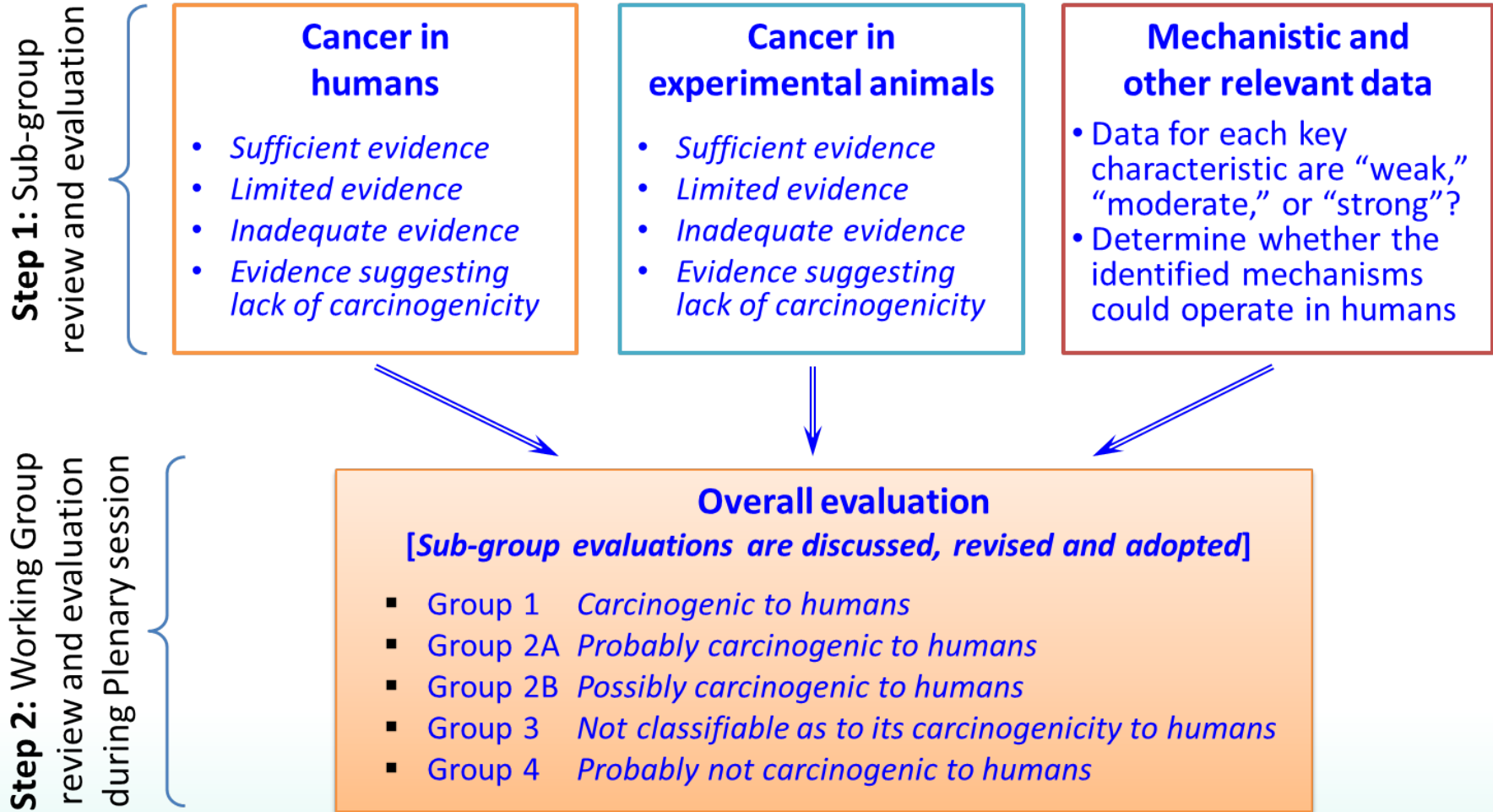
References



[http://www.toxicology.org/events/shm/fda/docs/FDA4\\_KZGUYTON.pdf](http://www.toxicology.org/events/shm/fda/docs/FDA4_KZGUYTON.pdf)



# Data Integration in IARC Evaluations



# Data Integration in IARC Evaluations: Role of “Mechanistic Evidence”

## EVIDENCE IN EXPERIMENTAL ANIMALS

		<i>Sufficient</i>	<i>Limited</i>	<i>Inadequate</i>	<i>ESLC</i>
<b>EVIDENCE IN HUMANS</b>	<i>Sufficient</i>	Group 1			
	<i>Limited</i>	↑ <u>1 strong evidence in exposed humans</u> Group 2A	↑ <u>2A</u> belongs to a mechanistic class where other members are classified in Groups 1 or 2A Group 2B (exceptionally, Group 2A)		
	<i>Inadequate</i>	↑ <u>1 strong evidence in exposed humans</u> ↑ <u>2A strong evidence ... mechanism also operates in humans</u> Group 2B	↑ <u>2A</u> belongs to a mechanistic class ↑ <u>2B with supporting evidence from mechanistic and other relevant data</u> Group 3	↑ <u>2A</u> belongs to a mechanistic class ↑ <u>2B with strong evidence from mechanistic and other relevant data</u> Group 3	Group 3 ↓ <u>4 consistently and strongly supported by a broad range of mechanistic and other relevant data</u>
	<i>ESLC</i>	Group 3			Group 4



# IARC Evaluations: Questions Addressed with Mechanistic Data

## Main questions that need to be addressed:

- Is there strong evidence of an operative carcinogenic mechanism(s)?
- Is the evidence from exposed humans, human *in vitro* systems, or animals?
- Does the mechanism only operate in animals?
- Does the agent belong to a class of agents evaluated as Group 1 or Group 2A?

## Additional questions that often come up:

- Are there data gaps in mechanistic information?
- There appears to be an imbalance in the number of studies on different mechanisms; is it because other mechanisms received less attention/funding, or because they are not operational/relevant?

<http://monographs.iarc.fr/ENG/Preamble/instructions.php>

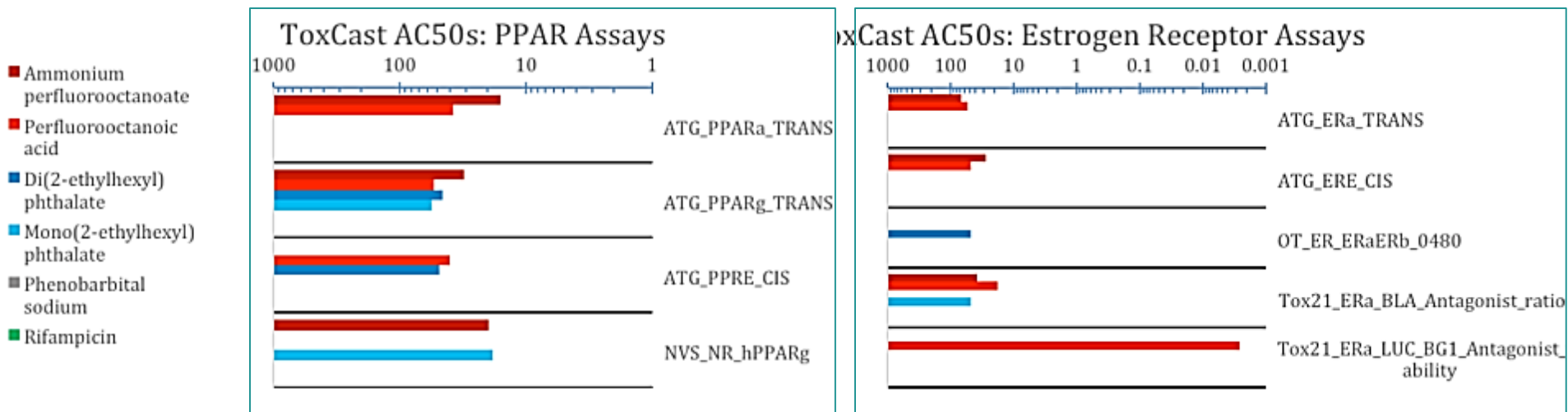
[http://www.toxicology.org/events/shm/fda/docs/FDA4\\_VJCogliano.pdf](http://www.toxicology.org/events/shm/fda/docs/FDA4_VJCogliano.pdf)



# An Example of Using *In Vitro* Screening Data in The IARC Monographs Volume 110 (2014) – PFOA

**Mechanistic Question:** Does PFOA act through activation of nuclear receptors? If yes, does it exclusively activate PPAR family of the receptors?

**How to answer:** A comparative analysis of *in vitro* screening results of PFOA with those of several prototypical nuclear receptor activating compounds



Each panel shows  $AC_{50s}$  (microM concentrations) from *in vitro* assays reported on the EPA iCSS Dashboard (<http://actor.epa.gov/dashboard/>) for PFOA or its ammonium salt and several prototypical nuclear receptor activators: rifampicin (PXR), phenobarbital (CAR), DEHP and MEHP (PPARs). All assays in which positive results were obtained for at least one of the six compounds were included in the analysis.



# An Example of Using *In Vitro* Screening Data in The IARC Monographs Volume 110 (2014) – PFOA

**Chapter 4 Question:** Does PFOA act through activation of nuclear receptors? If yes, does it exclusively activate PPAR family of the receptors?

**How to answer:** A comparative analysis of *in vitro* screening results of PFOA with those of several prototypical nuclear receptor activating compounds

Results were subdivided into six groups by each molecular target as follows:

- *estrogen receptor*,
- *PPAR*,
- *PXR*,
- *aromatase*,
- *enzyme assays*, and
- *other receptors*

**Example conclusion based on ToxCast data in Monograph 110:**

**Volume 110 (PFOA):** Liver toxicity observed in rodents has been associated with both PPAR $\alpha$ -dependent and -independent mechanisms. ***The Working Group's analysis of human in vitro data is consistent with multiple molecular pathways being operative.***



# IARC Evaluations: Key Characteristics of Known Human Carcinogens

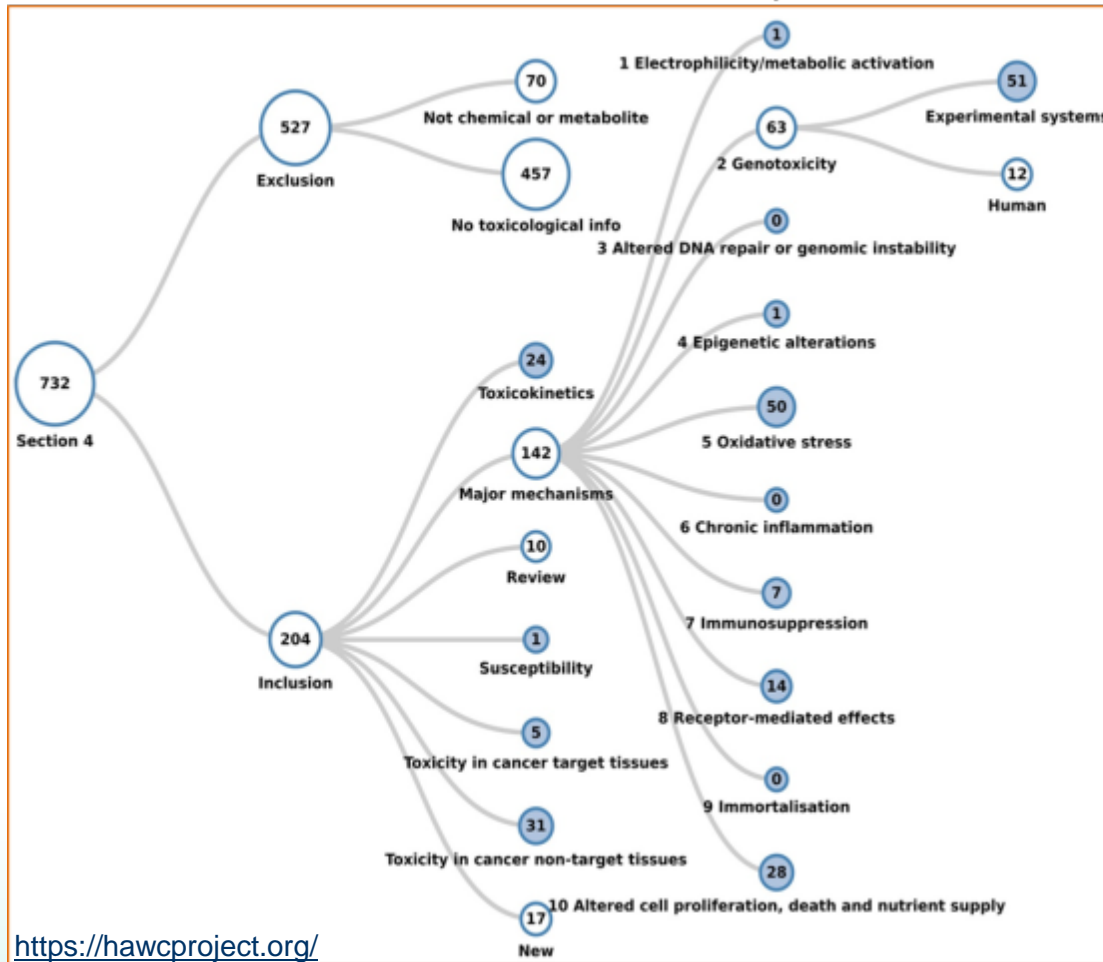
Key characteristic	Example of relevant evidence
<b>1. Electrophilic or ability to undergo metabolic activation</b>	Parent compound or metabolite with an electrophilic structure (e.g. epoxide, quinone, etc.), formation of DNA and protein adducts
<b>2. Genotoxic</b>	DNA damage, intercalation, gene mutations, cytogenetic changes (e.g. chromosome aberrations, micronucleus formation)
<b>3. Alters DNA repair or causes genomic instability</b>	Alterations of DNA replication or repair (e.g. topoisomerase II, base-excision or double-strand break repair)
<b>4. Epigenetic Alterations</b>	DNA methylation, histone modification, microRNAs
<b>5. Oxidative Stressor</b>	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g. DNA, proteins, lipids)
<b>6. Induces chronic inflammation</b>	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
<b>7. Immunosuppressant</b>	Decreased immuno-surveillance, immune system dysfunction
<b>8. Modulates receptor-mediated effects</b>	Receptor in/activation (e.g. ER, PPAR, AhR) or modulation of exogenous ligands (including hormones)
<b>9. Immortalization</b>	Inhibition of senescence, cell transformation
<b>10. Alters cell proliferation, cell death, or nutrient supply</b>	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell-cycle control, angiogenesis

Smith et al., *Environ Health Perspect* (in press) and [http://monographs.iarc.fr/ENG/Preamble/previous/Instructions\\_to\\_Authors\\_S4.pdf](http://monographs.iarc.fr/ENG/Preamble/previous/Instructions_to_Authors_S4.pdf)



# IARC Evaluations: Identifying Data Gaps

Systematic literature search tree for the Glyphosate Monograph:  
Last searches were conducted March 2, 2015



<https://hawcproject.org/>

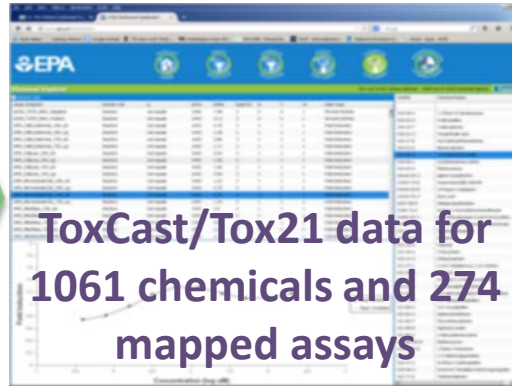
## Key characteristic

1. Electrophilic or ability to undergo metabolic activation
2. Genotoxic
3. Alters DNA repair or causes genomic instability
4. Epigenetic Alterations
5. Oxidative Stressor
6. Induces chronic inflammation
7. Immunosuppressant
8. Modulates receptor-mediated effects
9. Immortalization
10. Alters cell proliferation, cell death, or nutrient supply



# Use of Tox21/ToxCast Data in IARC Monographs: Overall Workflow

Map of ToxCast/Tox21 assays to IARC's "10 key characteristics"

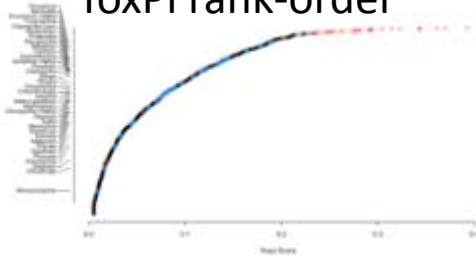


Calculated "active/inactive" for each chemical

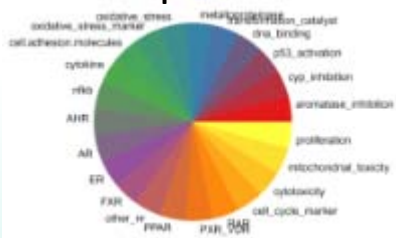


Run ToxPi software

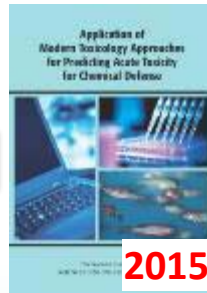
ToxPi rank-order



ToxPi pie charts



Report results



Endocrine Profiling and Prioritization of Environmental Chemicals Using ToxCast Data

David M. Reif,<sup>1</sup> Matthew T. Martin,<sup>1</sup> Shirlee W. Tan,<sup>2</sup> Keith A. Houck,<sup>1</sup> Richard S. Judson,<sup>1</sup> Ann M. Richard,<sup>1</sup> Thomas B. Knudsen,<sup>1</sup> David J. Dix,<sup>1</sup> and Robert J. Kavlock<sup>1</sup>

<sup>1</sup>National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Triangle Park, North Carolina, USA; <sup>2</sup>Office of Science Coordination and Policy, Office of Pollution Prevention, Pesticide Substances, U.S. Environmental Protection Agency, Washington, DC, USA

2010

BIOINFORMATICS APPLICATIONS NOTE Vol. 29 no. 3 2013, pages 402–403 doi:10.1093/bioinformatics/bts688

Systems biology

Advance Access publication November 29, 2012

ToxPi GUI: an interactive visualization tool for transparent integration of data from diverse sources of evidence

David M. Reif<sup>1\*</sup>, Myroslav Sypa<sup>2</sup>, Eric F. Lock<sup>2</sup>, Fred A. Wright<sup>3</sup>, Ander Wilson<sup>1</sup>, Tommy Cathey<sup>4</sup>, Richard R. Judson<sup>1</sup> and Ivan Rusyn<sup>2</sup>

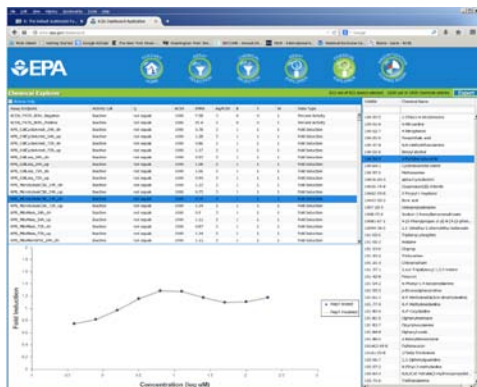
2013

# Use of Tox21/ToxCast Data in IARC Monographs: Mapping ToxCast/Tox21 Assays to “Characteristics”

## ToxCast iCSS dashboard

(<http://actor.epa.gov/dashboard/>)

- 821 assays
- 1860 chemicals
- Data are fully exportable



- 3 experts mapped each assay to 10 “key characteristics”
- 3 additional experts reviewed mapping and made suggestions
- Consensus cross-reference of assays to “key characteristics” and sub-categories was developed

## 274 ToxCast/Tox21 assays mapped to “key characteristics” of known human carcinogens:

Key characteristic	1. Electrophilic or ability to undergo metabolic activation	2. Genotoxic	4. Causes Epigenetic alterations	5. Oxidative stressor	6. Induces chronic inflammation	8. Modulates receptor-mediated effects	10. Alters cell proliferation, cell death and nutrient supply
Sub-characteristics	<b>31 assays:</b> • CYP inhibition (29) • Aromatase inhib. (2)	<b>9 assays:</b> • p53 activation	<b>11 assays:</b> • DNA binding (4) • Transformation (7)	<b>18 assays:</b> • Metalloproteinase (5) • Oxidative stress (7) • Oxidative stress marker (6)	<b>45 assays:</b> • Cell adhesion (14) • Cytokines (29) • NFkB (2)	<b>92 assays:</b> • AhR (2) • Others (18) • AR (11) • PPAR (12) • ER (18) • PXR_VDR (7) • FXR (7) • RAR (6)	<b>68 assays:</b> • Cell cycle (16) • Cytotoxicity (41) • Mitochondrial toxicity (7) • Proliferation (4)

No assay coverage for these “key characteristics”



**3. Alters DNA repair or causes genomic instability**

**7. Immunosuppressant**

**9. Immortalization**

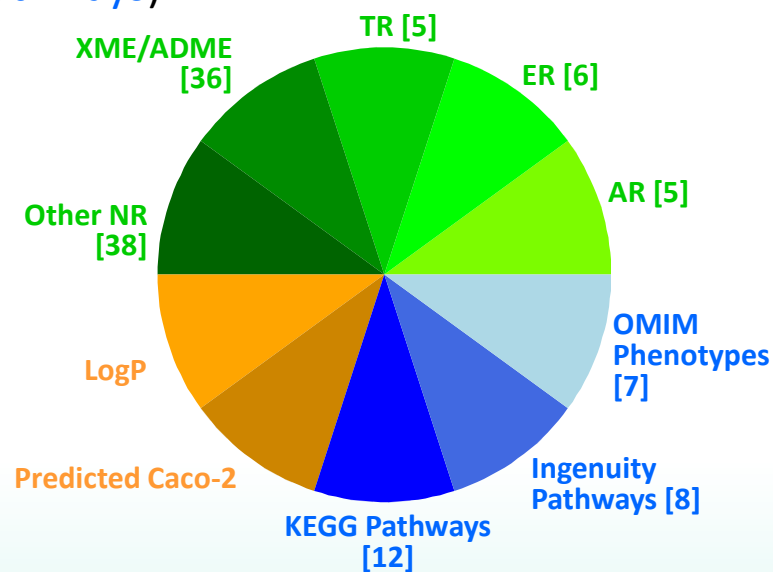
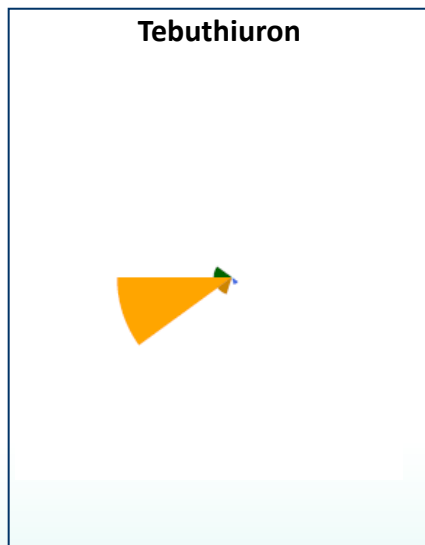
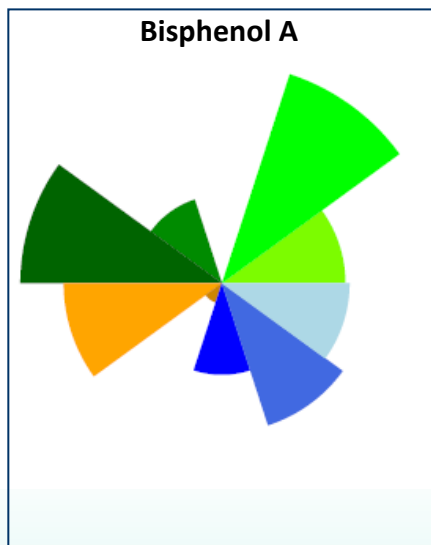


# Visualizing Complex Information: ToxPi

profile/  
Each chemical signature/ fingerprint gives a **Toxicological Priority Index (ToxPi)** score that is useful for ranking chemicals

$$\text{ToxPi} = \sum_1^I w_i * \text{assay}_i + \sum_1^C w_c * \text{chemProp}_c + \sum_1^P w_p * \text{pathway}_p$$

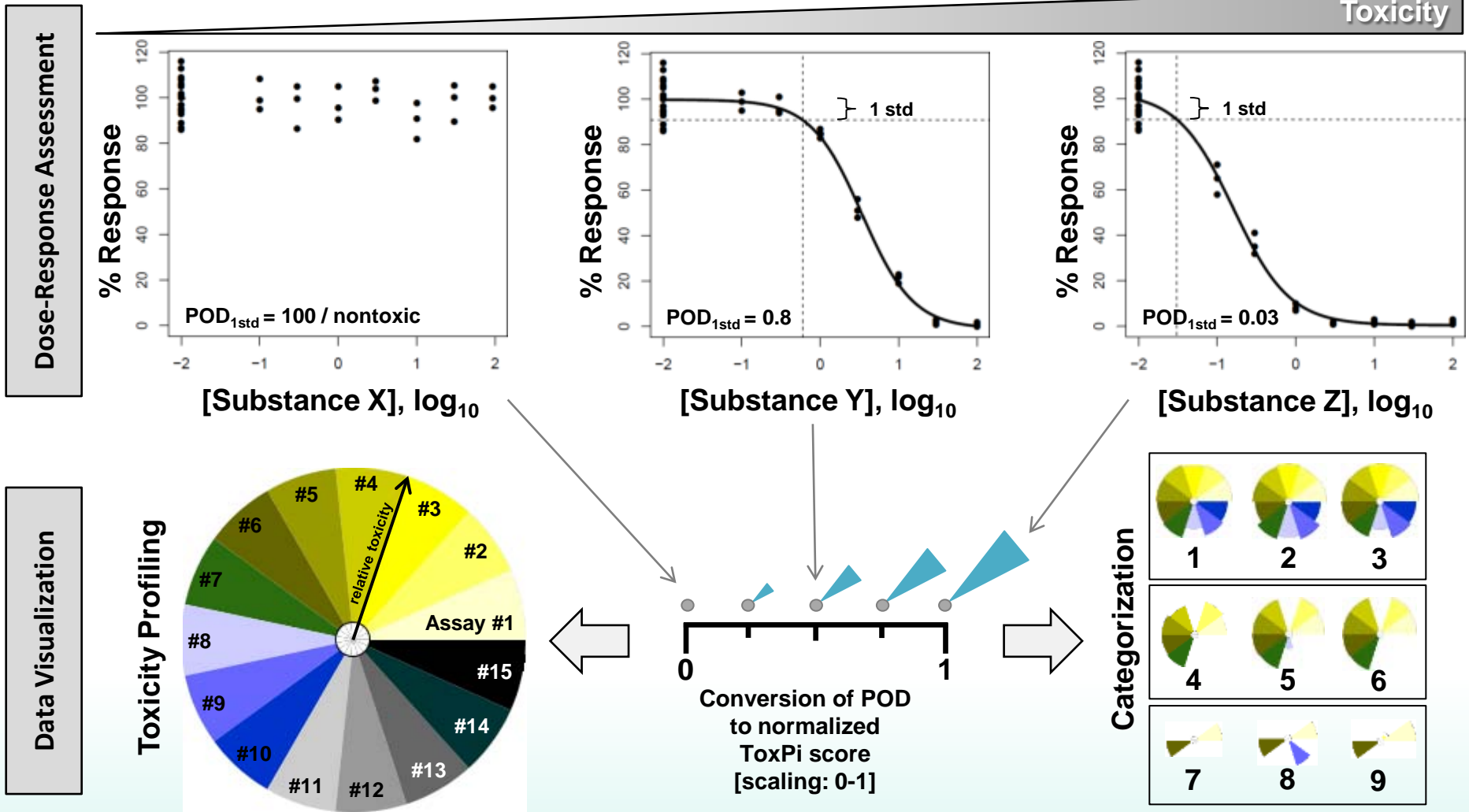
ToxPi = f(In vitro assays + Chemical properties + Pathways)



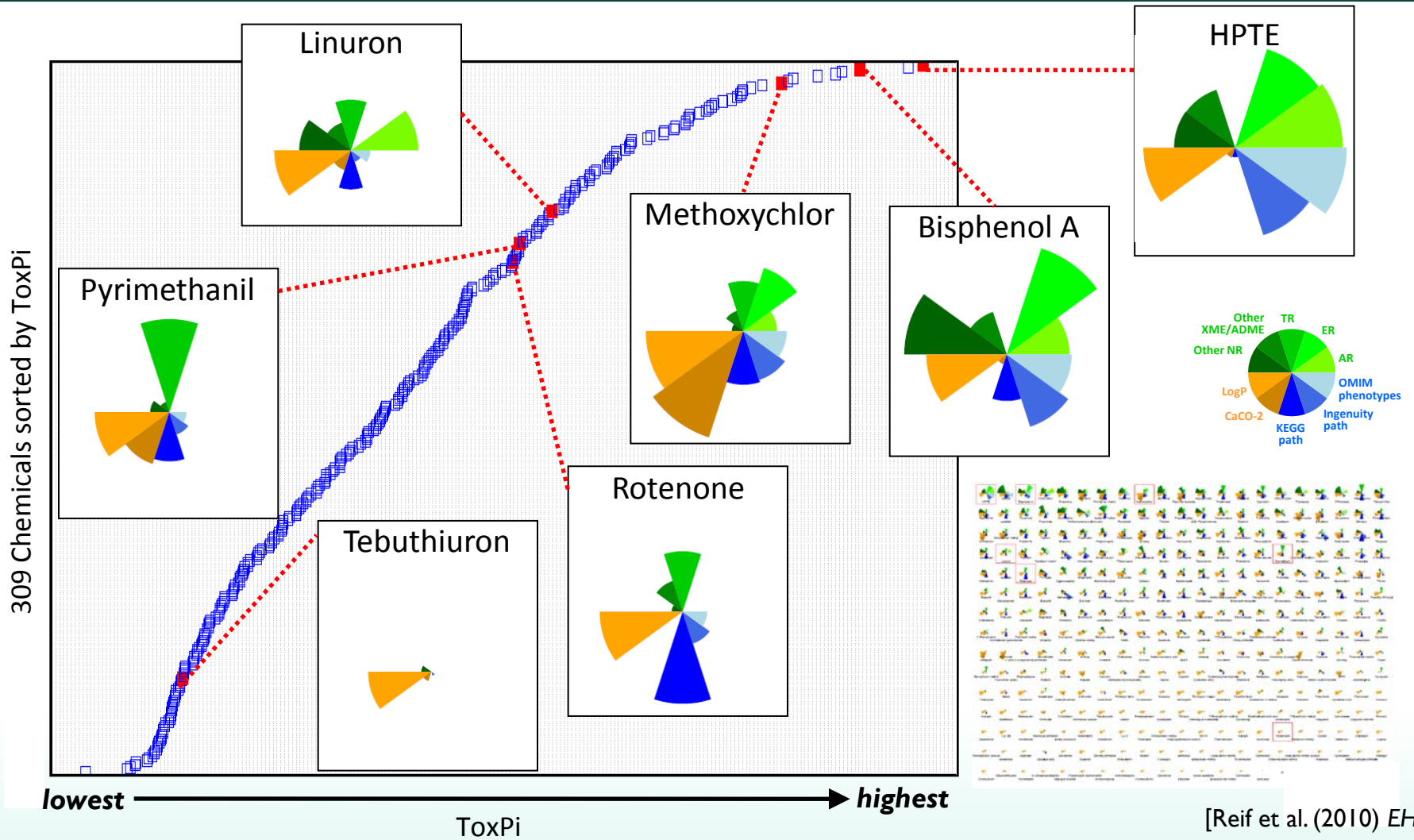
[Reif et al. (2010) EHP]



# Visualizing Complex Information: ToxPi



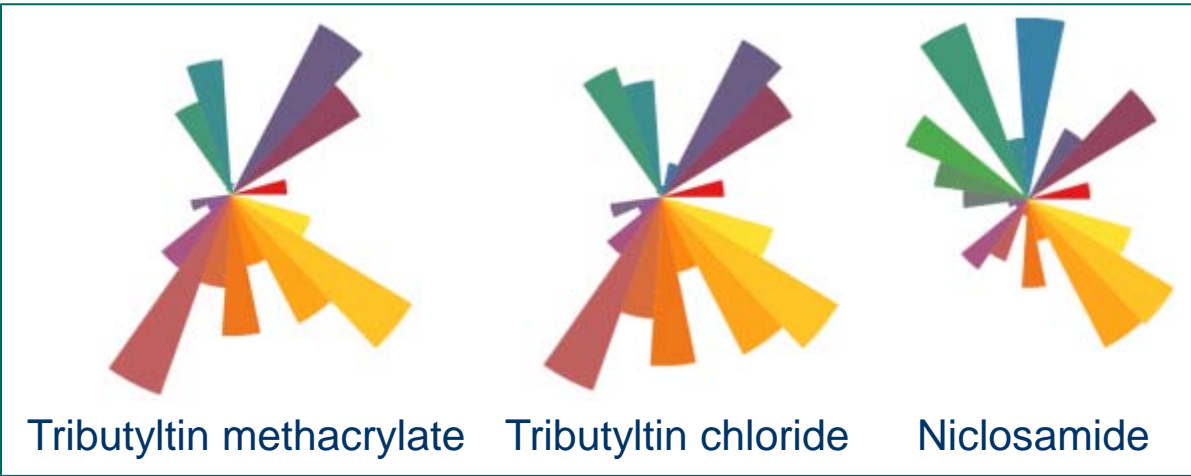
# Visualizing Complex Information: ToxPi



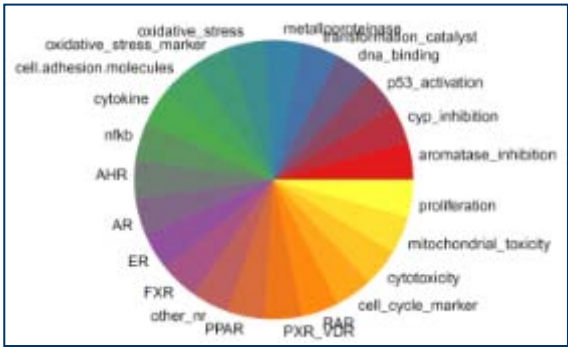


# ToxPi Analysis Based on 10 “Characteristics”: Common Pathways

Oxidative stress & cytotoxicity



Estrogen receptor activation



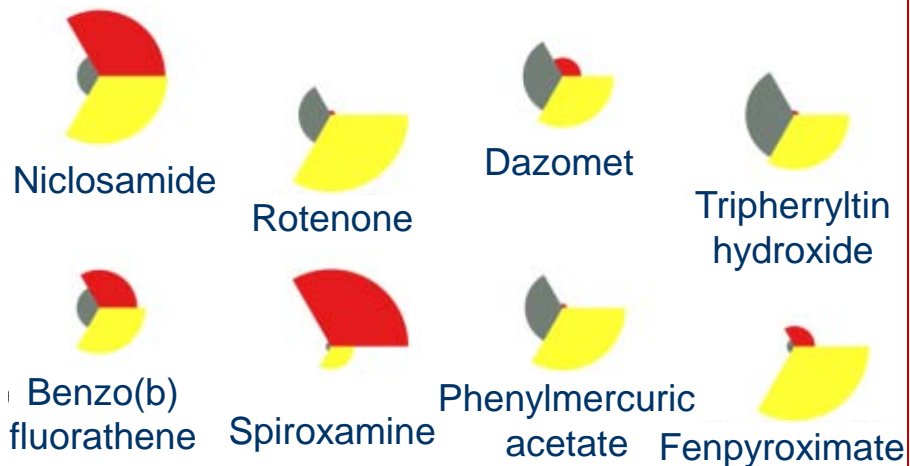
# Use of Tox21/ToxCast Data in IARC Monographs: General Considerations from Volumes 112 and 113

- Most agents (and their key metabolites and/or isomers) that were evaluated in IARC Monographs 112 (March 2015) and 113 (June 2015) were among the approximately 1000 chemicals tested across the full ToxCast/Tox21 assay battery as of 3 March 2015. This assay battery includes 342 assays, for which data on 821 assay endpoints are publicly available in the US EPA ToxCast Dashboard ([www.actor.epa.gov/dashboard](http://www.actor.epa.gov/dashboard))
- The match of an assay to the “key characteristic” was to **provide additional insights into the bioactivity profile of a chemical under evaluation** with respect to its potential to interact with, or have an effect on, targets that may be associated with carcinogenesis in humans
- For each chemical the results of the *in vitro* assays that represent each “key characteristic” can be **compared to the results for a larger compendium of substances with similar *in vitro* data** (either those screened in ToxCast/Tox21 or those that have been previously evaluated in the IARC monographs and were screened in ToxCast)

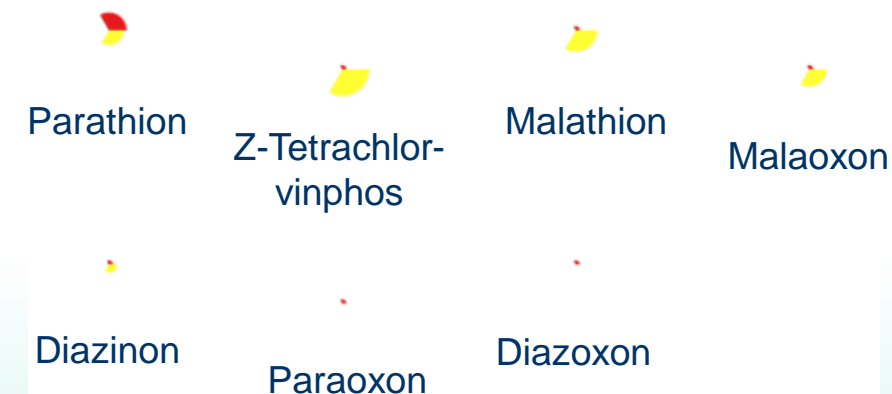


# Use of Tox21/ToxCast Data in IARC Monographs: Examples from Volume 112

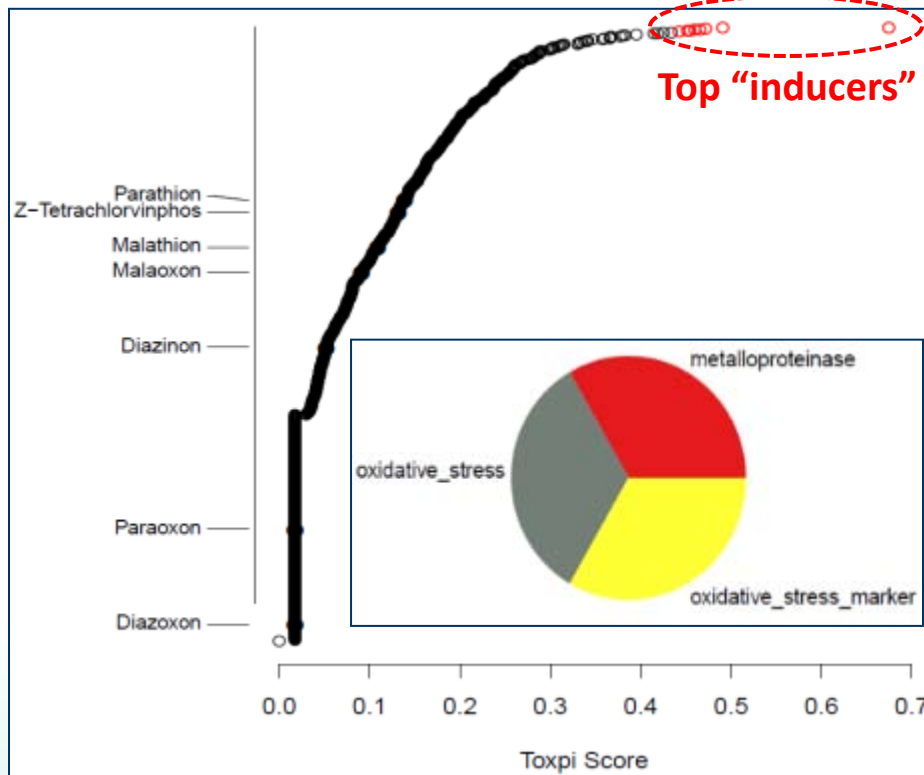
## Top "inducers" in ToxCast Phase II (1061 agents)



## IARC Mono 112 Chemicals/metabolites



<b>Key characteristic</b>	<b>5. Oxidative stressor</b>
<b>Sub-characteristics</b>	<b>18 assays:</b> Metalloproteinase (5); Oxidative stress marker (6); Oxidative stress (7)



# Use of Tox21/ToxCast Data in IARC Monographs: Examples from Volume 112

## Top "inducers" in ToxCast Phase II (1061 agents)



Mifepristone



Tributyltin chloride



Tributyltin methacrylate



17 $\alpha$ -Estradiol



trans-Retinoic acid



17 $\alpha$ -Ethynyl estradiol



SR271425



17 $\beta$ -Estradiol

## IARC Mono 112 Chemicals/metabolites



Parathion



Z-Tetrachlorvinphos



Diazinon



Malathion



Paraoxon

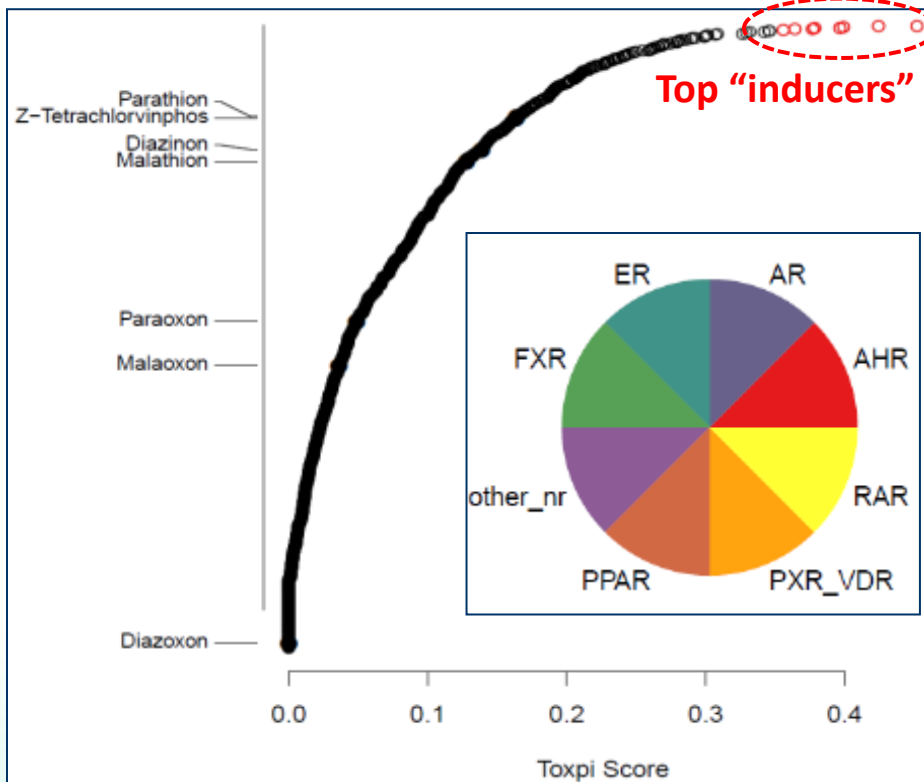


Malaoxon



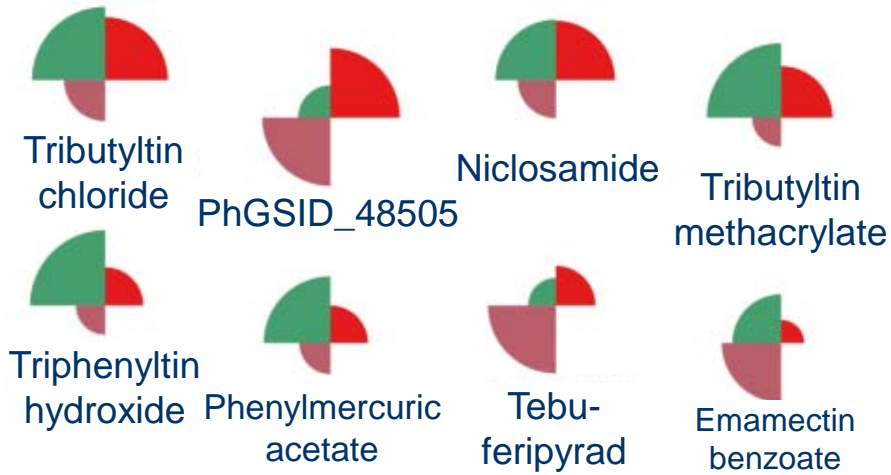
Diazoxon

Key characteristic	8. Modulates receptor-mediated events
Sub-characteristics	92 assays: AhR(2); AR(11); ER(18); FXR(7); Others (18); PPAR(12); PXR/VDR(7); RAR(6)

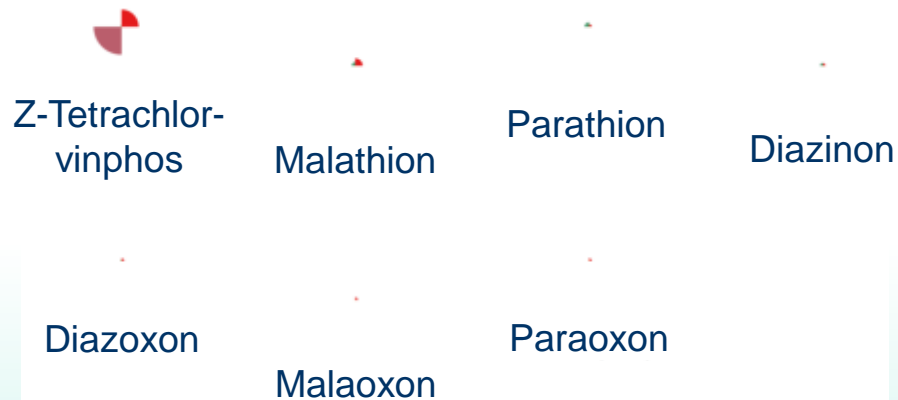


# Use of Tox21/ToxCast Data in IARC Monographs: Examples from Volume 112

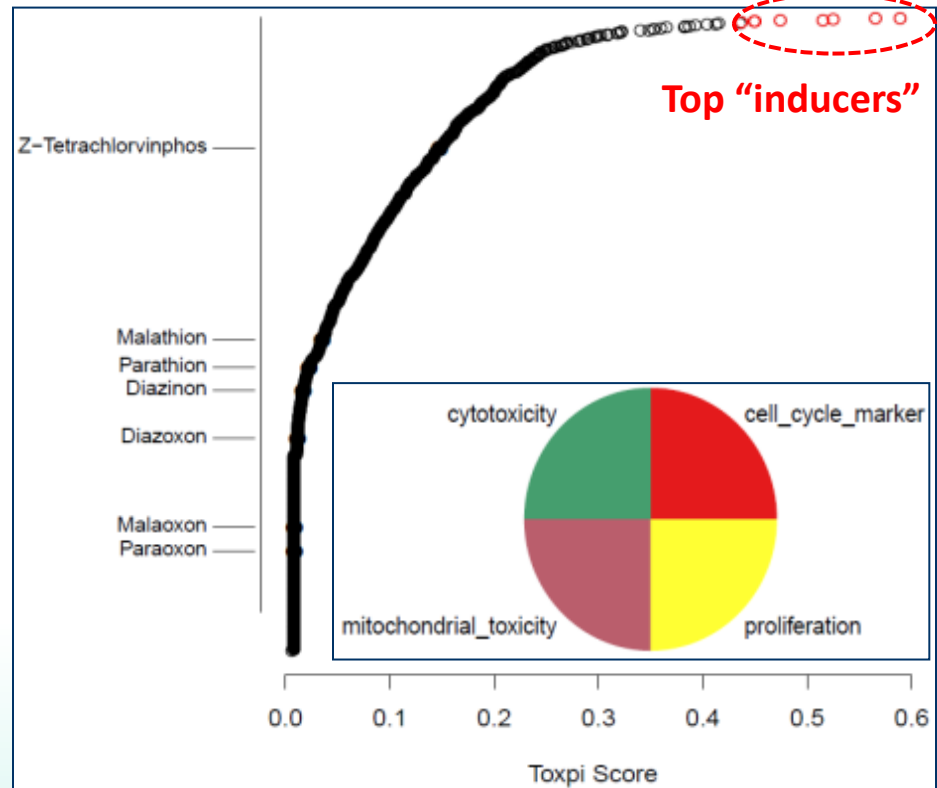
## Top "inducers" in ToxCast Phase II (1061 agents)



## IARC Mono 112 Chemicals/metabolites

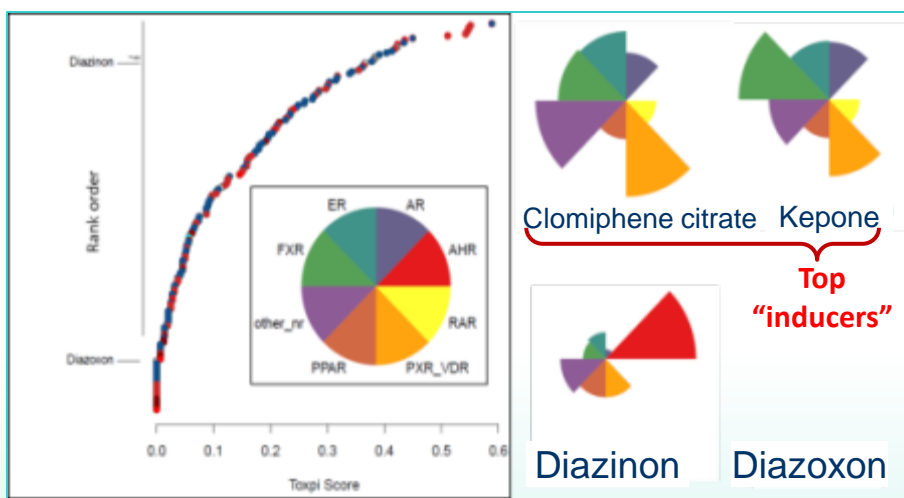
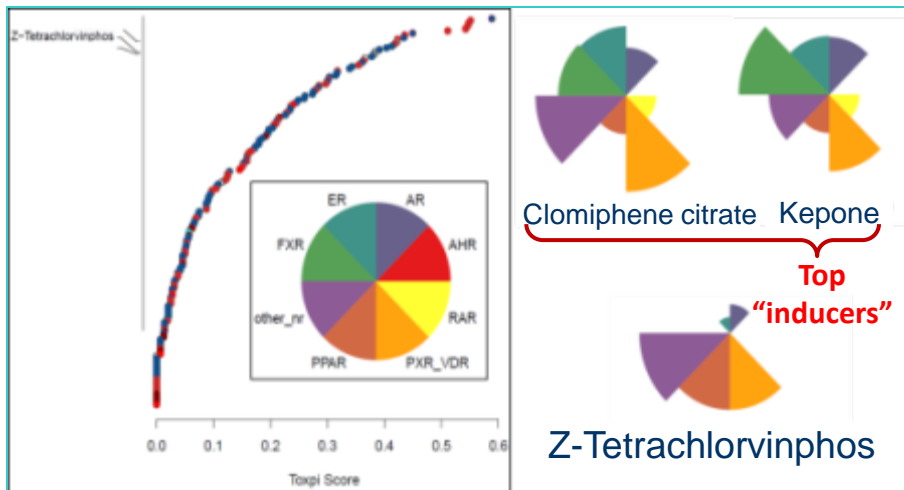


<b>Key characteristic</b>	<b>10. Alters cell proliferation, cell death and nutrient supply</b>
<b>Sub-characteristics</b>	<b>68 assays:</b> Cell cycle (16); Cytotoxicity (41); Mitochondrial toxicity(7); Proliferation(4)



# Use of Tox21/ToxCast Data in IARC Monographs: Examples from Volume 112

↑ IARC-evaluated compounds that have ToxCast/Tox21 data (n=178) ↓



Key characteristic	<b>8. Modulates receptor-mediated events</b>
Sub-characteristics	<b>92 assays:</b> AhR(2); AR(11); ER(18); FXR(7); Others (18); PPAR(12); PXR/VDR(7); RAR(6)

## *Volume 112 (Diazinon):*

Overall, **diazinon** demonstrated activity in both AhR assays and additional effects in a subset of estrogen receptor alpha and beta assay endpoints. **Diazoxon** exhibited little activity across the 274 assay endpoints with only 3 assay endpoints found as active. The limited activity of diazoxon may be attributed to high reactivity and short half-life of this compound making interpretation of the results of the assay endpoints difficult.

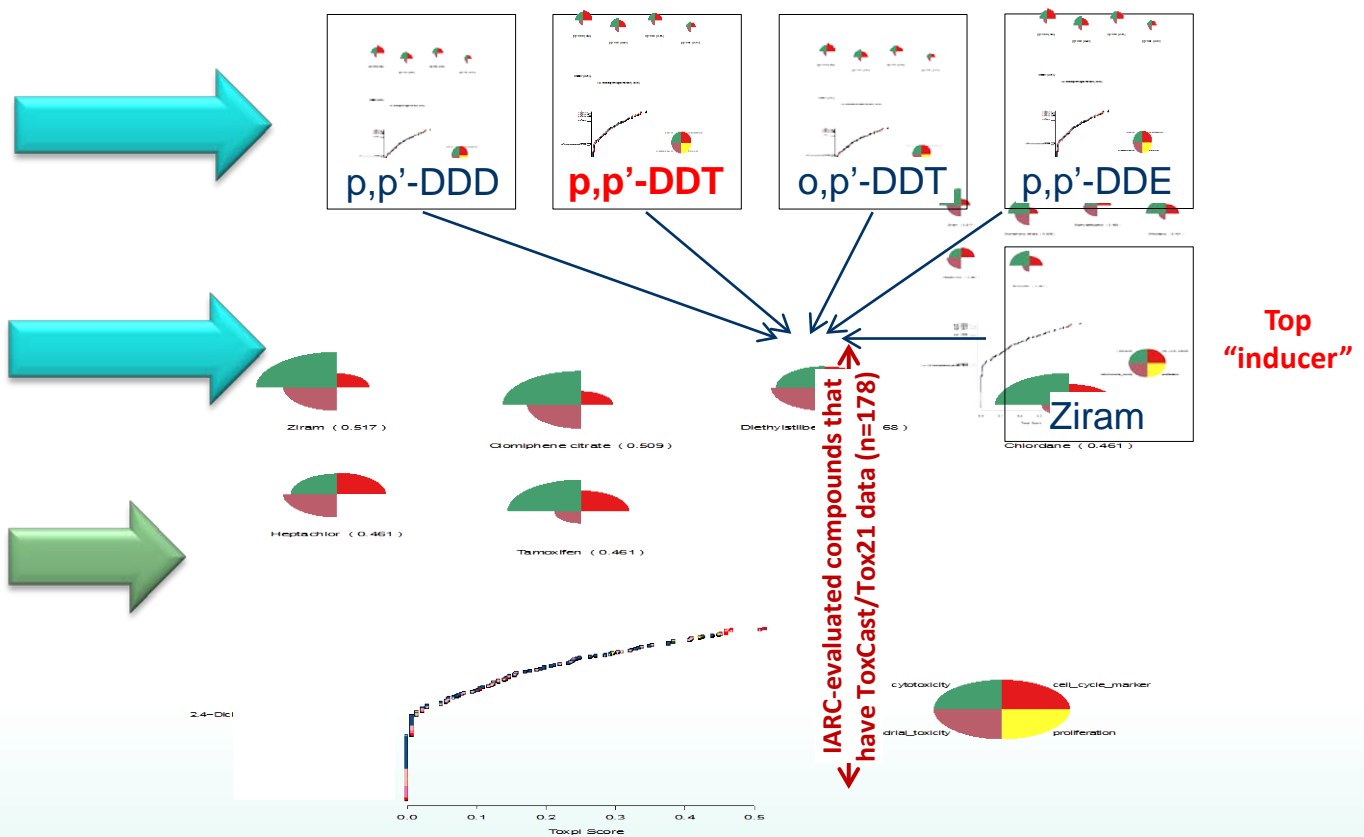


# Use of Tox21/ToxCast Data in IARC Monographs: Examples from Volume 113

Key characteristic	10. Alters cell proliferation, cell death and nutrient supply
Sub-characteristics	68 assays: Cytotoxicity (41); mitochondrial toxicity (7); cell cycle (16); cell proliferation (4)

DDT-related compounds share similar ToxPi *shape* and *overall rank*

Noticeably greater activity than lindane or 2,4-D



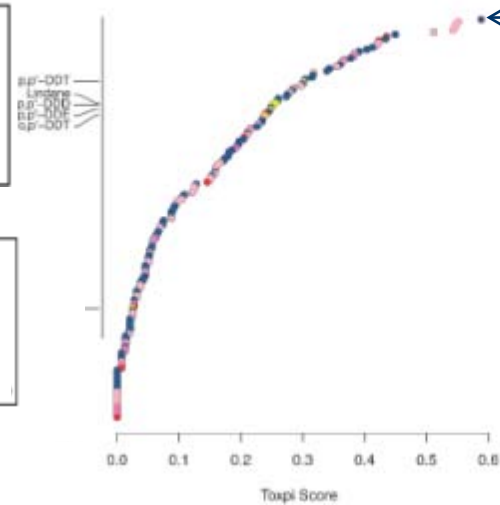
# Use of Tox21/ToxCast Data in IARC Monographs: Examples from Volume 113

Key characteristic	<b>8. Modulates receptor-mediated events</b>
Sub-characteristics	<b>92 assays:</b> AhR(2); AR(11); ER(18); FXR(7); Others (18); PPAR(12); PXR/VDR(7); RAR(6)

Compound	Evidence from “traditional” data
DDT	<b>Strong, can operate in humans</b>
Lindane	<b>Moderate</b>
2,4-D	<b>Weak</b>



Clomiphene citrate



**Volume 113 (DDT):**  
**p,p'-DDT, o,p'-DDT, p,p'-DDE, and p,p'-DDD** were positive in between 42 and 62 high throughput assays, mostly related to receptor-mediated effects or cell proliferation/cell death/nutrient supply, among the 265 assay endpoints relevant to the key characteristics of human carcinogens.



# Options for Accessing ToxCast/Tox21 data

**ACToR**  
 You are here: EPA Home » Computational Toxicology Research » ACToR » Home

Home | Basic Info | Data Collections | Structure Search | Assays By Toxicity | ACToR (Aggregated Computational Toxicology Resource) is EPA's online warehouse of 1000 public sources on over 500,000 environmental chemicals searchable by chemical name, CASRN, chemical structure, and other parameters. The data warehouse:

- Allows users to search and query data from other EPA chemical toxicity databases:
  - ToxRefDB (30 years and \$2 billion worth of animal toxicity studies).
  - ToxCastDB (data from screening 1,000 chemicals in over 500 high-throughput assays).
  - ExpoCastDB (consolidate and link human exposure and exposure factor data).
  - DSSTox (provides high quality chemical structures and annotations).
- Includes chemical structure, physico-chemical values, in vitro assay data and in vivo data.
- Includes, but not limited to, high and medium production volume industrial chemicals.

Chemical Name Parameters Match by

Search on Chemical Names  exact  
 Search on CAS Numbers  any

Enter Chemical Name:

**Search Results**

Details Image CASRN Preferred Name Hazard Chronic Toxicity Carcinogen

<http://actor.epa.gov/>

**Computational Toxicology Research**  
 You are here: EPA Home » Research & Development » CompTox » ToxCast™ » ToxCast™ Data

**Key Links**

CompTox Home	Research Projects	Research Publications	Staff
Basic Information	Chemical Databases	Scientific Reviews	Comp
Organization	ToxCast Stakeholder Events	Communities of Practice	Jobs
EPA Exposure Research	EPA Chemical Safety Research	ToxCast Data Challenges	

**ToxCast™ Data**

The most updated publicly available ToxCast data can be downloaded below. The data is organized into different data sets and includes: descriptions of ToxCast chemicals and assays as well as files summarizing the screening results from ToxCast (high-throughput data from ~1,800 chemicals), a MySQL database to download and run locally on a computer, EPA's analysis of the chemicals screened through the federal Toxicity Testing in the 21st century (Tox21) partnership, available data generated from existing animal toxicity studies, and archived ToxCast data from older data releases and publications. EPA does not recommend using the archived data for analysis. The files are posted for reference purposes only. A README file is included for most of the data below and users are encouraged to read this file to help use the data.

**Data Set**

Data Set	Description	Down
MySQL Database	A MySQL database that interacts with a beta version of the R software package which provides access to all ToxCast high-throughput in vitro data. Also includes an overview presentation of the pipeline used to process and analyze the ToxCast data and the R package.	What READ
ToxCast Chemicals	Chemical details for 8,599 unique substances (GSIDs) and DSSTox standard chemical fields (chemical name, CASRN, structure, etc) for EPA ToxCast chemicals and the larger Tox21 chemical list. Also includes chemical mapping files and quality control grades for chemicals.	What READ

<http://www.epa.gov/ncct/toxcast/data.html>

**EDSP21 Dashboard**  
 Endocrine Disruption Screening Program for the 21st Century

**Chemical Selection**

CASRN	Chemical Name	ToxCast
56-35-9	Eis(tri)butyltin(oxide)	✓
3004-79-8	Eis(trichloromethyl)sulfone	✓
26750-50-5	Eis(vinylsulphonylmethyl) ether	✓
3130-19-6	Eis(3,4-epoxycyclohexyl)methyl adipate	✓
141-17-3	Eis[2-(2-butylthioxy)ethyl] hexadecate	✓
3033-62-3	Eis[2-(dimethylamino)ethyl]ether	✓
13876-54-5	Bismaleimide	✓
7440-49-9	Bismuth	✓
21260-46-8	Bismuth dimethyldithiocarbamate	✓
1304-76-3	Bismuth oxide	✓
5892-10-4	Bismuth(III) carbonate	✓
80-05-7	Bisphenol A	✓
1675-54-3	Bisphenol A diglycidyl ether	✓
1668-94-2	Bisphenol A glycidyl methacrylate	✓
1478-61-1	Bisphenol AF	✓
125401-92-5	Bispyribac-sodium	✓
312600-89-8	Bis[1-cyclohexyl-1-(hydroxy-kappaO)-2-(oxo-kappaO)hydrazinyl]copper	✓

**ToxPI Graphs**

AR ER THR

**AC50 Values - AR**

Assay Er	AC50
ATG	Inactive
NVS...	18.7...
NVS...	7.5394
NVS...	18.9...

**AC50 Values - ER**

Assay Er	AC50
ACE	0.586
ATG...	0.0981
ATG...	0.1194
NVS...	0.421

**AC50 Values - THR**

Assay Er	AC50
ATG	Inact...
NVS...	Inact...
Tox2...	Inact...
Tox2...	99.7...

<http://actor.epa.gov/edsp21/>

EPA iCSS Dashboard Demo (08/24/2015): <https://epa.connectsolutions.com/p11xjgz2if9/>



# Additional Information

## ToxCast / Tox21: Characterizing chemical hazard using HTS

ToxCast data: <http://epa.gov/ncct/toxcast/data.html>

Source data used for IARC analysis:

[http://epa.gov/ncct/toxcast/files/ToxCast%20Summary%20Files/ToxCast\\_Summary\\_Files.zip](http://epa.gov/ncct/toxcast/files/ToxCast%20Summary%20Files/ToxCast_Summary_Files.zip)

Detailed information on source data:

<http://epa.gov/ncct/toxcast/files/ToxCast%20Summary%20Files/README%20Summary%20Files.pdf>

ToxCast data processing overview:

[http://www.epa.gov/ncct/download\\_files/chemical\\_prioritization/Judson\\_CoP\\_Dec2014.pdf](http://www.epa.gov/ncct/download_files/chemical_prioritization/Judson_CoP_Dec2014.pdf)

## Toxicological Prioritization Index (ToxPi): Visual analytic framework for data integration

ToxPi software and user manual available from: <http://comptox.us/toxpi.php>

Examples of models/rankings that have developed using ToxPi with/without ToxCast data:

Endocrine (using ToxCast Phase I data)

Reif et al. (2010) <http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.292.9039&rep=rep1&type=pdf>

Cardiotoxicity (using externally collected *in vitro* data)

Sirenko et al. (2013) <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3900303/>

Ranking chemicals based on exposure information

Gangwal et al (2012) <https://www.ncbi.nlm.nih.gov/pubmed/22863807>

