

# Toxicity Testing in the 21<sup>st</sup> Century

國家環境毒物中心

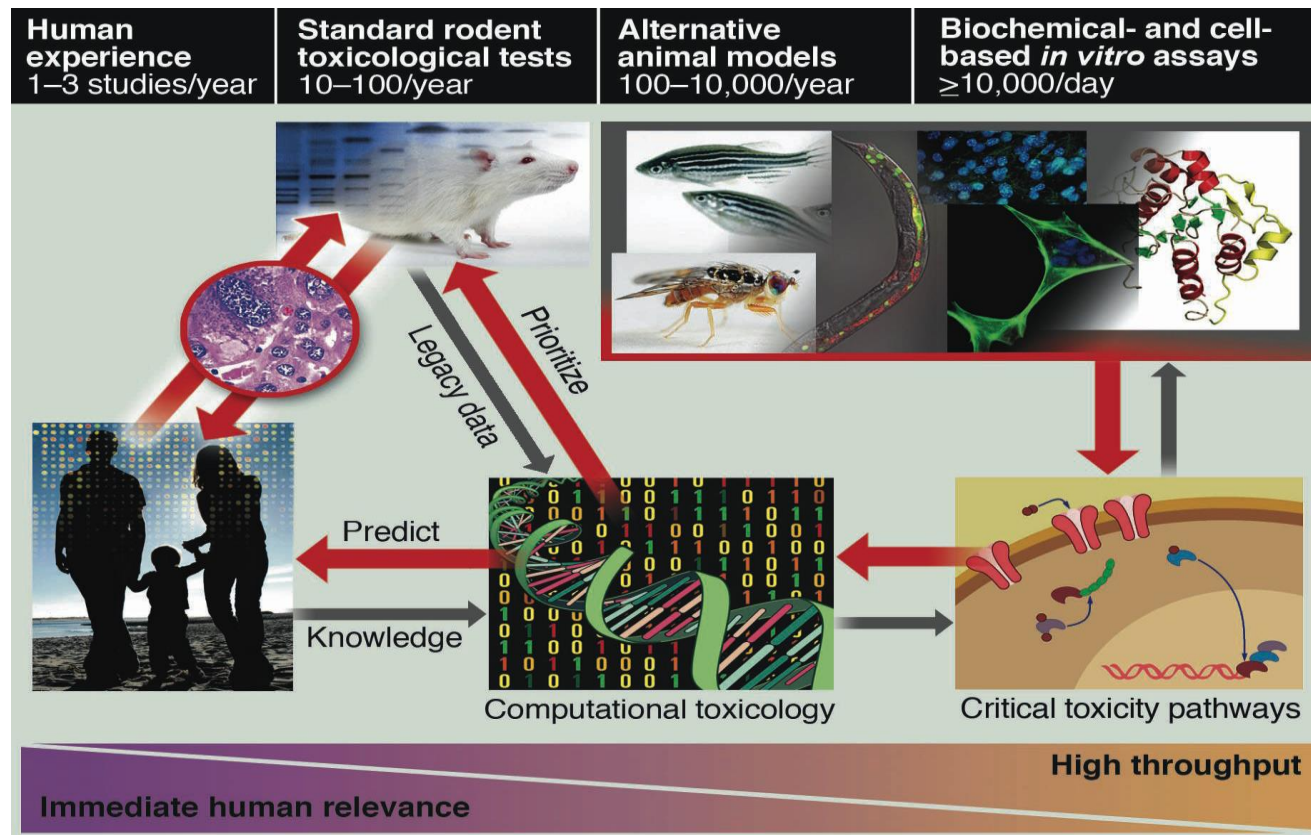
林嬪嬪、何佳琪 博士

2014.09.04



# Toxicity Testing in the 21<sup>st</sup> Century

\*This 2007 National Academy of Science report envisions a not-so-distant future in which virtually all routine toxicity testing would be conducted **in vitro in human cells or cell lines** by evaluating **perturbations of cellular responses in a suite of toxicity pathway assays** using **high throughput robotic assisted methodologies**.

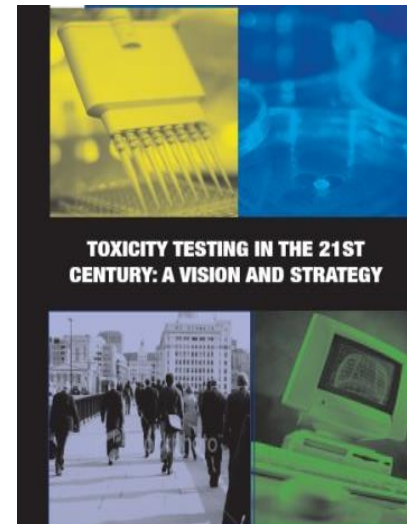


# Toxicity Testing in the 21<sup>st</sup> Century



\*The Toxicology in the 21st Century (Tox21) program, a federal collaboration involving the **National Institutes of Health (NIH), Environmental Protection Agency (EPA), and Food and Drug Administration (FDA)**, is aimed at developing better toxicity assessment methods.

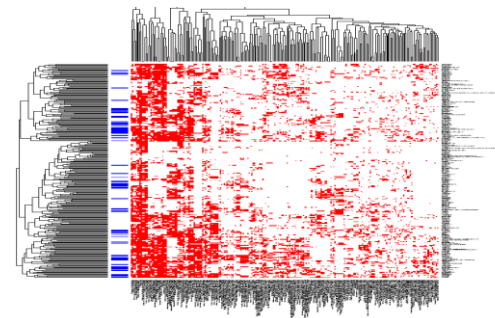
- National Institute of Environmental Health Sciences (NIEHS) / National Toxicology Program (NTP), National Institutes of Health (NIH)
- National Center for Advancing Translational Sciences (NCATS)/NIH Chemical Genomics Center (NCGC), National Institutes of Health (NIH)
- U.S. Food and Drug Administration (FDA)
- U.S. Environmental Protection Agency (EPA)



# Toxicity Testing in the 21<sup>st</sup> Century

## \*Tox21 Goals:

- Identify patterns of compound-induced biological response in order to:
  - characterize toxicity/disease pathways
  - facilitate cross-species extrapolation
  - model low-dose extrapolation
- Prioritize compounds for more extensive toxicological evaluation
- Develop predictive models for biological response in humans



# Tox21 Phase I – Proof of Principle (2005 – 2010)

\*EPA via ToxCast™ screened **320 compounds** (309 unique, **primarily pesticide actives** and some endocrine active compounds) in **~550 assays**.

➤ Data made public via ToxCastDB  
(<http://actor.epa.gov/actor/faces/ToxCastDB/Home.jsp>)

\*NCGC screened **1408 compounds** (1353 unique) from NTP and **1462 compounds** (1384 unique) from EPA in **140 qHTS assays** representing 77 predominantly cell-based reporter gene endpoints.

➤ Data made public via PubChem (<http://pubchem.ncbi.nlm.nih.gov/>) and CEBS (Chemical Effects in Biological Systems; <http://www.niehs.nih.gov/research/resources/databases/cebs/>)

# Tox21 Phase II – Expanded Compound Screening (2011 – 2014)

## \*EPA's ToxCast™ Phase II:

- ~700 compounds in ~700 assays, ~1000 compounds in endocrine activity assays

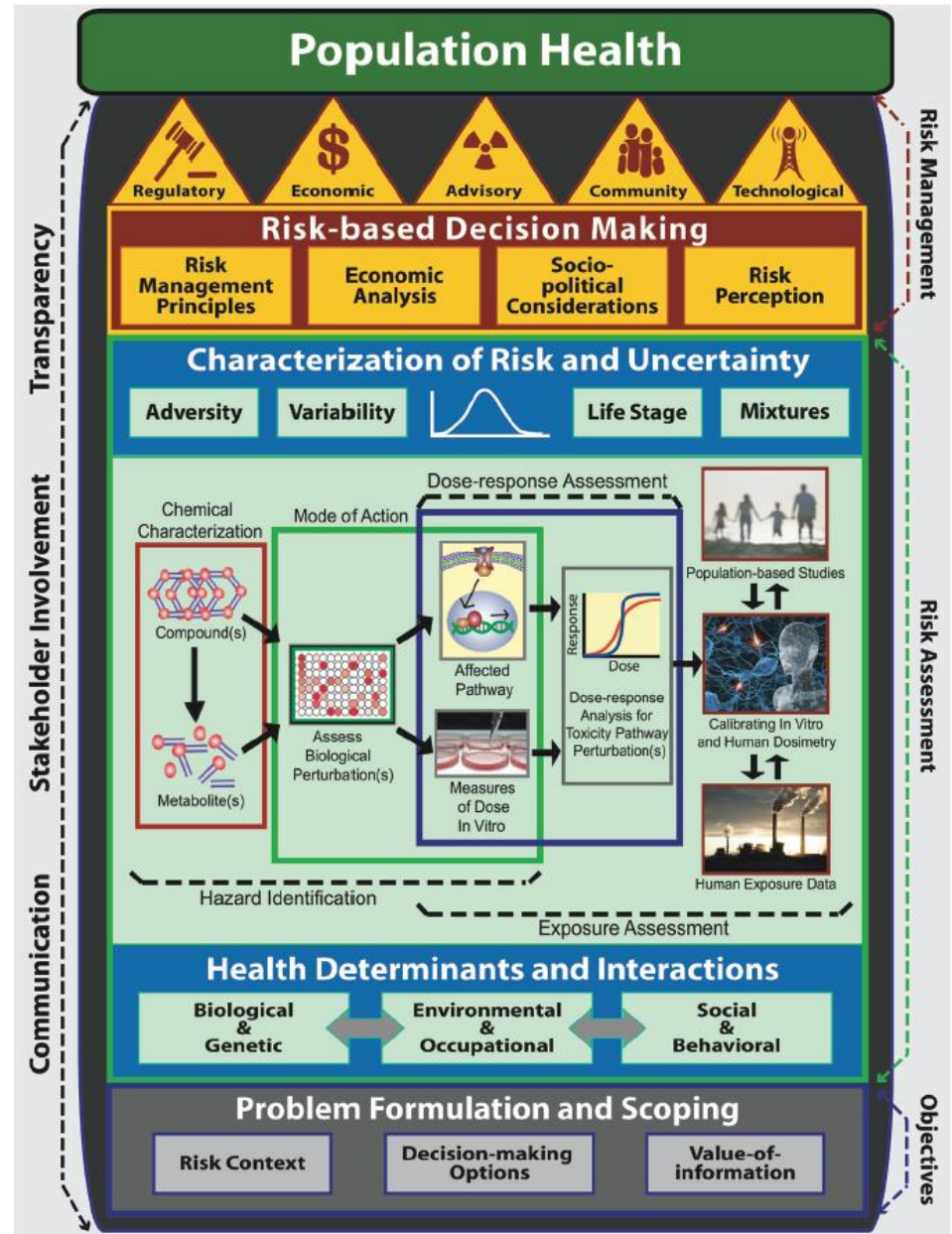
## \*NCGC qHTS Phase II:

- 10K compound library screened 3 times at 15 concentrations in each qHTS assay
- qHTS assays focused on:
  - nuclear receptor activation or inhibition
  - induction of cellular stress response pathways
  - characterizing human variability in response

# Toxicity Testing in the 21<sup>st</sup> Century

## \*Application of TOX21:

## A Framework for the Next Generation of Risk Science



Krewski, D., (2014).  
*Environ Health Perspect* **122**, 796-805.

# ToxCastDB in EPA



# ToxCastDB in EPA

## ToxCastDB

You are here: [EPA Home](#) » [Computational Toxicology Research](#) » [ToxCastDB](#) » Home



[Home](#) | [Basic Info](#) | [Data Collection List](#) | [Chemical List](#) | [Genes Associated with Assays](#) | [Help](#) | [ToxPi Wizard](#) | [ToxPi Results](#)

ToxCastDB provides access to all ToxCast data. ToxCast uses advanced science tools to help efficiently understand biological processes impacted by chemicals 1,000 chemicals in over 500 rapid tests (called high-throughput screening assays). ToxCastDB has many benefits.

- Users can search and download data for all ToxCast chemicals, assays, genes, pathways and endpoints.
- Database allows for statistical associations and biologically driven data mining.
- Provide links to available animal data through ToxRefDB.

### Chemical Name Parameters

- Enter Chemical Name:
- Enter CAS Numbers:

Enter Chemical Name:

### Match by

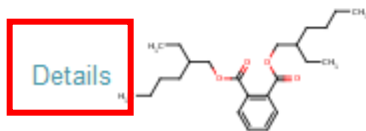
- exact
- any

## Chemical List

[Details](#) [Structure](#)

Name

CASRN



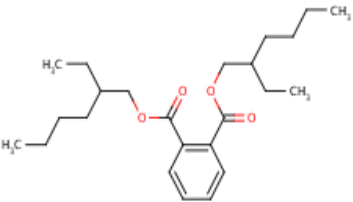
DEHP (Diethylhexyl phthalate) 117-81-7

搜尋結果跳出，  
選擇要查詢的物質

# ToxCastDB in EPA

[Home](#) | [Basic Info](#) | [Data Collection List](#) | [Chemical List](#) | [Genes Associated with Assays](#) | [Help](#) | [ToxPi Wizard](#) | [ToxPi Results](#)

## Chemical: DEHP (Diethylhexyl phthalate)



CASRN 117-81-7  
Smiles O=C(C1=C(C=CC=C1)C(=O)OCC(CCCC)CC)OCC(CCCC)CC  
Source Name SID DSSTOX\_40759  
Source Name CID DSSTOX\_607  
ACToR [Find in ACToR DB](#)

### Data

Source	Assay	Assay Name	Species	Gene	Value	Units
ACEA	<a href="#">ACEA_LOC2</a>	ACEA_LOC2	Homo sapiens		11.2	uM
ACEA	<a href="#">ACEA_LOCinc</a>	ACEA_LOCinc	Homo sapiens		11.2	uM
Attagene	<a href="#">ATG_CAR_TRANS</a>	Attagene Factorial trans CAR	Homo sapiens	NR113	50.0	uM
Attagene	<a href="#">ATG_PPARGa_TRANS</a>	Attagene Factorial trans PPARa	Homo sapiens	PPARA	50.0	uM
Attagene	<a href="#">ATG_PPARGg_TRANS</a>	Attagene Factorial trans PPARg	Homo sapiens	PPARG	46.0	uM
Attagene	<a href="#">ATG_PPARGc_CIS</a>	Attagene Factorial cis PPARG	Homo sapiens	PPARA PPARG	48.0	uM
Attagene	<a href="#">ATG_PXR_TRANS</a>	Attagene Factorial trans PXR	Homo sapiens	NR112	38.0	uM

點擊可看  
Assay詳細資料

PubChem Compound in NCBI

# PubChem Compound in NCBI

<https://www.ncbi.nlm.nih.gov/>

選擇 PubChem Compound

The screenshot shows the NCBI website interface. At the top, there is a search bar with a dropdown menu currently set to "PubChem Com". A red box highlights this dropdown menu, and a red arrow points to it from the text "選擇 PubChem Compound". Another red box highlights the "Search" button, and a red arrow points to it from the text "輸入物質名稱". The website header includes the NCBI logo and navigation links like "Resources" and "How To". The main content area features a "Welcome to NCBI" message, a "Get Started" section with links to Tools, Downloads, How-To's, and Submissions, and a "Popular Resources" list including PubMed, Bookshelf, and PubChem. The footer contains a navigation menu with categories like "GETTING STARTED", "RESOURCES", "POPULAR", "FEATURED", and "NCBI INFORMATION".

# PubChem Compound in NCBI

NCBI Resources How To

PubChem Compound PubChem Compound DEHP Search

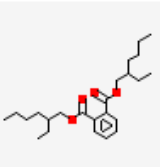
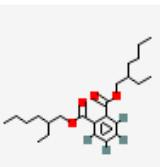
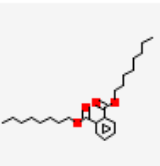

Save search Limits Advanced

Display Settings: Summary, Sorted by Default order

搜尋結果跳出，  
選擇要查詢的物質

Send to: Filters: Manage Filters

Results: 5

-  [DEHP: Bis\(2-ethylhexyl\) phthalate; Di\(2-ethylhexyl\) phthalate ...](#)  
MW: 390.556120 g/mol MF: C<sub>24</sub>H<sub>38</sub>O<sub>4</sub>  
IUPAC name: bis(2-ethylhexyl) benzene-1,2-dicarboxylate  
CID: 8343  
[Summary](#) [Similar Compounds](#) [Same Parent, Connectivity](#) [Mixture/Component Compounds](#) [PubMed \(MeSH Keyword\)](#)  
Active in 9 of 647 BioAssays
-  [Bis\(2-ethylhexyl\)phthalate-3,4,5,6-d4; Deuterated DEHP; Etalon-d4 ...](#)  
MW: 394.580767 g/mol MF: C<sub>24</sub>H<sub>38</sub>O<sub>4</sub>  
IUPAC name: bis(2-ethylhexyl) 3,4,5,6-tetradeuteriobenzene-1,2-dicarboxy...  
CID: 16213881  
[Summary](#) [Similar Compounds](#) [Same Parent, Connectivity](#)
-  [Diocetyl phthalate; DI-N-OCTYL PHTHALATE; 117-84-0 ...](#)  
MW: 390.556120 g/mol MF: C<sub>24</sub>H<sub>38</sub>O<sub>4</sub>  
IUPAC name: dioctyl benzene-1,2-dicarboxylate  
CID: 8346  
[Summary](#) [Similar Compounds](#) [Same Parent, Connectivity](#) [Mixture/Component Compounds](#) [PubMed \(MeSH Keyword\)](#)  
Active in 3 of 278 BioAssays
-  [C42K0PH13C](#)  
MW: 1171.668360 g/mol MF: C<sub>72</sub>H<sub>114</sub>O<sub>12</sub>  
IUPAC name: bis[(2R)-2-ethylhexyl] benzene-1,2-dicarboxylate;bis[(2S)-2-...  
CID: 76959176  
[Summary](#) [Mixture/Component Compounds](#) [PubMed \(MeSH Keyword\)](#)

## Actions on your results

-  BioActivity Analysis  
Analyze the BioActivities of the
-  Structure Clustering  
Cluster structures based on s  
similarity
-  Structure Download  
Download the structures in va

## Refine your results • What's this

### Chemical Properties

Rule of 5 (1)

### BioActivity Experiments

BioAssays, Active (2)

BioAssays, Tested (2)

### BioMedical Annotation

Pharmacological Actions (3)

Plasticizers (3)

### Depositor Category

Biological Properties (5)

Chemical Vendors (4)

# PubChem Compound in NCBI

NCBI  
PubChem Compound  
Limits Advanced search  
Search

SHARE

Compound Summary for: CID 8343



## Diethylhexyl Phthalate

Also known as: DEHP; Bis(2-ethylhexyl) phthalate; Di(2-ethylhexyl) phthalate; Di(2-ethylhexyl)phthalate; Octyl phthalate; 117-81-7; Di-sec-octyl phthalate

Molecular Formula:  $C_{24}H_{38}O_4$  Molecular Weight: 390.55612 InChIKey: BJQHLKABXJIVAM-UHFFFAOYSA-N

An ester of phthalic acid. It appears as a light-colored, odorless liquid and is used as a plasticizer for many resins and elastomers. From: MeSH

### Table of Contents [Show subcontent titles](#)

Identification

Related Records

Use and Manufacturing

Pharmacology

Biomedical Effects and Toxicity

Safety and Handling

Environmental Fate and Exposure Potential

Exposure Standards and Regulations

Monitoring and Analysis Methods

Literature

Patents

Biological Test Results

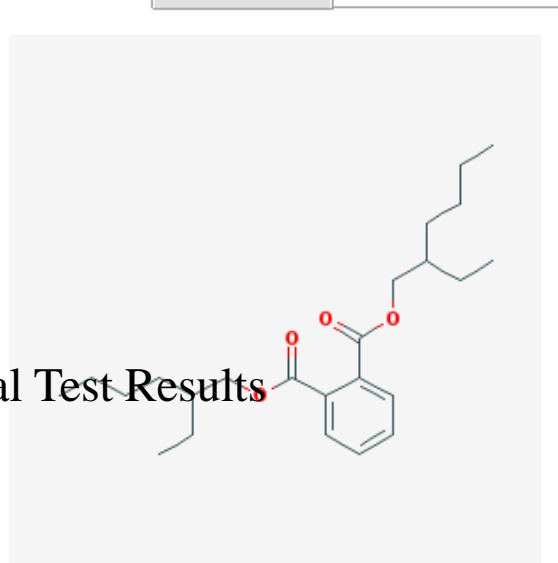
Classification

Chemical and Physical Properties

Expand all sub-sections

2D Structure

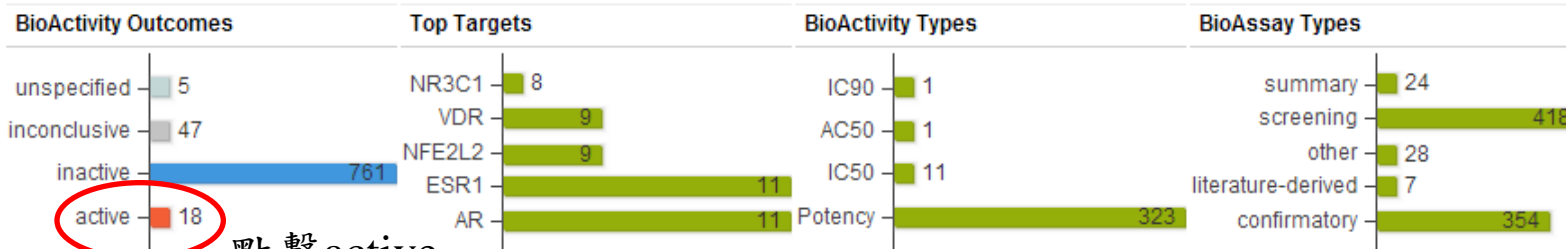
3D Conformer



點選 Biological Test Results

# PubChem Compound in NCBI

## Biological Test Results



點擊active

### Filters Applied

BioActivity Outcomes: active x

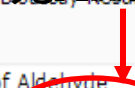
[Reset All Filters](#) [Apply Filters To Charts](#)

*i* Click the bar on the chart will add the filter, and click it again to remove

下載檔案，完成

Structure	Compound CID	Activity		Compound Name	Bioassay Name
		Outcome	Value [ $\mu$ M]		
					Database Summary Mouse Bioassay Results [AID:1199, Type: other]
	8343	active	22.3872	DEHP	qHTS Assay for Inhibitors of Aldehyde Dehydrogenase 1 (ALDH1A1) [AID:1030, Type: confirmatory]
	8343	active	11.2202	DEHP	qHTS assay for small molecule activators of the rat pregnane X receptor (rPXR) signaling pathway [AID:651751, Type: confirmatory]
	8343	active		DEHP	Cell Viability Assay [AID:1976, Type: screening]

點擊AID的數字可看此Assay詳細資料



# PubChem Compound in NCBI

Activity conc.

Bioassay

Target

F106 qHTS Assay for Inhibitors of Tyrosyl-DNA Phosphodiesterase (TDP1)									
No	Outcome	Activity Concentration Name	Activity Concentration[uM]	AID(PanelID)	BioAssay	BioAssay_Type	Target	PMID	
1	Active	AR Potency (uM)	1.14358	743054	qHTS assay to identify small molecule antagonists of the androgen receptor (AR) signaling pathway using the MDA cell line: Summary	summary	AR protein [Homo sapiens][gi:124375976]		
2	Active	Potency-Replicate_1	1.5449	720634	qHTS assay for small molecule disruptors of the mitochondrial membrane potential - cell viability	confirmatory			
3	Active	Potency-Replicate_1	1.5449	720635	qHTS assay for small molecule disruptors of the mitochondrial membrane potential	confirmatory			
4	Active	Potency	1.9012	504832	Primary qHTS for delayed death inhibitors of the malarial parasite plastid, 48 hour incubation	confirmatory			
5	Active	Potency-Replicate_1	1.9449	743015	qHTS assay for identifying genotoxic compounds that show differential cytotoxicity against isogenic chicken DT40 cell lines with known DNA damage response pathways - Rad54/Ku70 mutant cell line	confirmatory			
6	Active	Potency-Replicate_1	2.7473	743012	qHTS assay for identifying genotoxic compounds that show differential cytotoxicity against isogenic chicken DT40 cell lines with known DNA damage response pathways - wild type cell line	confirmatory			
7	Active	Ratio Potency (uM)	3.73452	743219	qHTS assay for small molecule agonists of the antioxidant response element (ARE) signaling pathway: Summary	summary	nuclear factor erythroid 2-related factor 2 isoform 1 [Homo sapiens][gi:20149576]		
8	Active	Potency-Replicate_1	3.8806	743014	qHTS assay for identifying genotoxic compounds that show differential cytotoxicity against isogenic chicken DT40 cell lines with known DNA damage response pathways - Rev3 mutant cell line	confirmatory			
9	Active	Potency-Replicate_1	5.308	720635	qHTS assay for small molecule disruptors of the mitochondrial membrane potential	confirmatory			
10	Active	Potency	5.3091	686978	qHTS for Inhibitors of human tyrosyl-DNA phosphodiesterase 1 (TDP1): qHTS in cells in absence of CPT	confirmatory	TDP1 protein [Homo sapiens][gi:79154014]		
11	Active	Potency-Replicate_1	7.4978	743080	qHTS assay to identify small molecule antagonists of the estrogen receptor alpha (ER-alpha) signaling pathway using the BGL cell line	confirmatory	estrogen nuclear receptor alpha [Homo sapiens][gi:348019627]		
12	Active	Potency-Replicate_1	8.4127	743012	qHTS assay for identifying genotoxic compounds that show differential cytotoxicity against isogenic chicken DT40 cell lines with known DNA damage response pathways - wild type cell line	confirmatory			
13	Active	Potency	8.5735	686978	qHTS for Inhibitors of human tyrosyl-DNA phosphodiesterase 1 (TDP1): qHTS in cells in absence of CPT	confirmatory	TDP1 protein [Homo sapiens][gi:79154014]		
14	Active	Potency-Replicate_1	9.4392	743015	qHTS assay for identifying genotoxic compounds that show differential cytotoxicity against isogenic chicken DT40 cell lines with known DNA damage response pathways - Rad54/Ku70 mutant cell line	confirmatory			
15	Active	Potency	9.4411	686979	qHTS for Inhibitors of human tyrosyl-DNA phosphodiesterase 1 (TDP1): qHTS in cells in presence of CPT	confirmatory	TDP1 protein [Homo sapiens][gi:79154014]		
16	Active	Potency	9.6196	686979	qHTS for Inhibitors of human tyrosyl-DNA phosphodiesterase 1 (TDP1): qHTS in cells in presence of CPT	confirmatory	TDP1 protein [Homo sapiens][gi:79154014]		



# CEBS in NIH



National Institute of Environmental Health Sciences  
Your Environment. Your Health.

[Health & Education](#)[Research](#)[Funding Opportunities](#)[Careers & Training](#)[News](#)[About NIEHS](#)

## Cytotoxicity

[A+](#) [A-](#) [Share](#)[CEBS Home](#)[Open My Data](#)[Chemical Effects in Biological](#)

### Search Study

Search studies using test article, CEBS accession number, NTP Study ID, NTP Study Type, CEBS data domain or institution.

### Workflows

### Search Across Studies

Search across the database for subjects meeting your criteria, filtering by:

- **Characteristics** (of studies, participants, stressor, or protocols)
- **Response** (of individual assays or pathology diagnosis)
- **Test Articles** (Chemicals or non-chemical stressors)

Combining search results and then viewing or downloading the results.

### Help

[Identify and download the list of all studies producing a positive result in the Ames test](#)[Add selected search result data to the Workspace](#)[Download additional depositor data](#)[Accessing Tox21 Phase 2 workflow](#)[Depositing Data to CEBS](#)[Tox21 Phase I: Filtering assay results by activity call](#)[Tox21 Phase I: Find all data for an assay](#)



# 國家環境毒物研究中心

National Environmental Health Research Center



首頁 單位介紹 中心計畫 國家重要環毒食安議題 研究資源 教學知識專區 最新消息 相關連結 聯絡我們

[English](#)

*Protect your health, protect your child*

字級：[小](#) [中](#) [大](#) [巨](#)

## 熱門專區

以科學研究的實證結果，預防或降低環境毒物對國人的健康負擔

食安議題



## 新聞資訊

[103.8.28] [新聞] 六輕事件簡要報告 **New**

[103.8.18] [新聞] 國衛院持續追蹤研究六輕附近學童健康 **New**

[103.8.15] [新聞解讀] 臺北市衛生局公布103年第2季生鮮蔬果殘留農藥抽驗結果 **New**

[103.8.14] [資訊] 硫代二乙酸(TdGA) **New**

[103.8.12] [資訊] 「環境毒物知多少」新增丙烯(Propylene)

環毒議題



塑化劑



站內搜尋

Google™ 自訂搜尋



國家環境毒物研究中心

facebook

Name:

國家環境毒物研究中心



國家衛生研究院  
電子報

[更多資訊](#)

# 學術活動預告

**[課程] Risk assessment of chemicals and its application in different situations**

**主講人：Dr. Anna Fan Ph D. DABT**

**時間：2014年10月底**

**目的及內容：**邀請前美國加州環保局的环境衛生危害評估辦公室 農藥與環境毒理科主任的Dr. Anna Fan規劃系列課程。Dr. Anna Fan將教授如何評估暴露環境毒物之健康風險，包含致癌物質和非致癌物質、NOEL/LOEL (benchmark dose)、劑量反應關係、單一或多種物質暴露、暴露的時間和來源，以及年齡上的差異等因素，彼此間相互影響，在風險評估上扮演什麼的角色。

# 2015年學術活動預告

## [課程] 毒理學家認證課程

主講人：各大學毒理所專業講師

時間：2015年 1~2月

### 課程內容：

1. Toxic Responses of the Reproductive System
2. Toxic Effects of Solvents and Vapors
3. Toxic Effects of Plants and Animal

*Thank you for attention*

# PubChem Compound in NCBI



## qHTS Assay for Inhibitors of Aldehyde Dehydrogenase 1 (ALDH1A1)

Aldehyde dehydrogenase 1 (ALDH1A1) catalyzes the NAD<sup>+</sup> dependent oxidation of a variety of endogenous and exogenous aldehydes to the corresponding acids. The enzyme is the critical step in the metabolic activation of retinoic acid, which plays essential roles as nuclear receptor ligand. Furthermore, retinaldehyde has recently been shown to play a fundamental role in adipogenesis and obesity, which makes inhibitor development a possible target for these diseases. See [1] through [4] for more information on ALDH1A1. [..more](#)

Follow us...

External link: Please  
our privacy policy.

### Table of Contents

- Target
- BioActive Compounds
- Related Experiments
- Description
- Protocol
- Comment
- Categorized Comment
- Result Definitions
- Additional Information
- Data Table (Concise)
- Classification

AID: 1030

Data Source: NCGC (ALDH101)

BioAssay Type: Confirmatory, Concentration-Response Relationship Observed

Depositor Category: NIH Molecular Libraries Probe Production Network

BioAssay Version: 2.1

Deposit Date: 2008-01-11

Modify Date: 2010-03-15

Data Table ( Complete ):

View Active Data

View All Data



# ToxCastDB in EPA

## ToxCastDB

You are here: [EPA Home](#) » [Computational Toxicology Research](#) » [ToxCastDB](#) » [Data Collection List](#)

[ACToR](#) | [ToxRefDB](#) | [ToxCastData](#) | [ExpoCastDB](#) | [DSSTox](#) | [CSS Dashboards](#) | [CPCat](#)

[Home](#) | [Basic Info](#) | [Data Collection List](#) | [Chemical List](#) | [Genes Associated with Assays](#) | [Help](#) | [ToxPi Wizard](#) | [ToxPi Results](#)

### Data Collection List

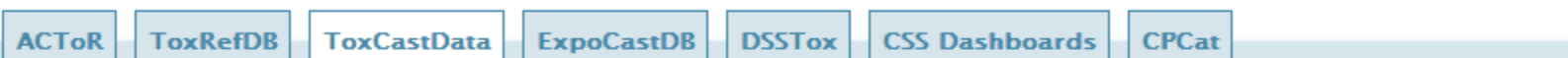
Name	Description	Assays	Chemicals	Data Points	All Data
<a href="#">ACEA</a>	ACEA - Real-time Cell Electronic Sensing	7	320	2240	<a href="#">Data Table</a>
<a href="#">Attogene</a>	Attogene - Transcription factor assays	81	320	23360	<a href="#">Data Table</a>
<a href="#">BioSeek</a>	BioSeek - Cell-based protein level assays	174	320	55680	<a href="#">Data Table</a>
<a href="#">Cellumen</a>	Cellumen - Cell imaging assays	19	320	18240	<a href="#">Data Table</a>
<a href="#">CellzDirect</a>	CellzDirect - Transcription assays	16	320	13440	<a href="#">Data Table</a>
<a href="#">Gentronix</a>	Gentronix - GreenScreen GeneTox assay	1	320	320	<a href="#">Data Table</a>
<a href="#">NCGC</a>	NCGC - nuclear receptor assays	19	320	6080	<a href="#">Data Table</a>
<a href="#">NHEERL MESC</a>	Mouse Embryonic Stem Cells from Sid Hunter and group	8	320	2560	<a href="#">Data Table</a>
<a href="#">NHEERL Zebrafish</a>	Zebrafish data from Stephanie Padilla and group	6	320	1824	<a href="#">Data Table</a>
<a href="#">Novascreen</a>	Novascreen / Caliper - receptor binding and enzyme inhibition assays	273	320	93440	<a href="#">Data Table</a>
<a href="#">Solidus</a>	Solidus - P450 vs. cytotoxicity assays	4	320	1280	<a href="#">Data Table</a>
<a href="#">ToxRefDB</a>	ToxRefDB - Toxicology Reference Database - Guideline animal study data	463	301	116305	<a href="#">Data Table</a>



# ToxCastDB in EPA

## ToxCastDB

You are here: [EPA Home](#) » [Computational Toxicology Research](#) » [ToxCastDB](#) » [Assay](#)



[Home](#) | [Basic Info](#) | [Data Collection List](#) | [Chemical List](#) | [Genes Associated with Assays](#) | [Help](#) | [ToxPi Wizard](#) | [ToxPi Results](#)

## Assay: Attagene Factorial trans CAR

Assay Id:	14
Source	Attagene
Source Name AID	ATG_CAR_TRANS
Name	Attagene Factorial trans CAR
Description	Factorial reporter gene assay
Number of Substances	320
Number of Components	1
Species	Homo sapiens

### Parameters

Parameter	Value
ASSAY CATEGORY	In vitro (Cellular)
ASSAY GENE ID	9970
ASSAY GENE NAME	<a href="#">NR113</a>
ASSAY MODE	DNA sequencer
ASSAY NOTE	Multiplexed reporter gene assay; Nuclear receptor pathway
ASSAY REFERENCE COMPOUND	CITCO
ASSAY TARGET	CAR
ASSAY TARGET FAMILY	Transcription Factor
ASSAY TARGET SOURCE	Cell line
ASSAY TARGET SOURCE TYPE	HepG2
ASSAY TECHNOLOGY	Reporter gene assay
ASSAY URL	<a href="#">Link Out</a> <a href="#">EXIT Disclaimer</a>

