# ACToR – Aggregated Computational Toxicology Resource &

# ToxRefDB – Toxicity Reference Database

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# Introduction

ACToR (Aggregated Computational Toxicology Resource) is a collection of databases collated or developed by the US EPA National Center for Computational Toxicology (NCCT). Over 580 sources of publicly available data on environmental chemicals have been brought together and made searchable by chemical names, <u>CAS</u> number, structure drawings, <u>InCHI</u> strings and <u>SMILES</u>. This database contains data such as <u>hazardous</u> testing results, chemical structure, physico-chemical values, *in vitro* assay data, exposure data, and *in vivo* toxicology data on hundreds of thousands of generic chemicals. These chemicals include, but are not limited to, <u>high and medium production volume industrial chemicals</u>, pesticides (active and inert ingredients), food additives and potential ground and drinking water contaminants. The overall structure of ACToR is composed of a series of domains, linked together by chemicals.



Domain	Description	Location
Chemicals	Structure, names and other basic chemical information	Main ACToR Database
Assays	Quantitative and other tabular data on chemicals	Main ACToR Database
Toxicology	<i>In vivo</i> study data from multiple domains	ACToR / ToxRefDB Database
Genomics Microarray Data	Full microarray data sets, in both original and transformed versions	Under Development
Biological Reference Data	Information on genes, proteins and pathways, downloaded from public sources	Main ACToR Database
ToxMiner	Detailed data from the ToxCast and ToxRefDB programs - used for ToxCast analyses.	Separate ToxMiner database - linked to ACToR by chemical ID

Currently, chemical toxicity data resides in a variety of specialized databases with incompatible formats and in many different locations. In the past, researchers needed to search many databases and manually organize the results in order to amass all the information on a given chemical. While this is possible for a few chemicals it is very difficult to compile comprehensive data sets on chemically-similar sets of compounds that can be explored with structure searching tools. Since the majority of chemicals in ACToR have chemical structures produced by the EPA <u>ToxCast</u> chemical prioritization program, ACToR will help to stimulate studies of structure-function relationships in sets of environmental chemicals. In addition, by bringing together data from a large number of sources and making the data structure-searchable, ACToR facilitates searches that transcend current databases in abundance of information and in number of generic chemicals.

The ACToR project is compiling data (both quantitative and qualitative) from a large number of sources (called <u>data collections</u>). Some of the sources include EPA, PubChem, other NIH, USDA and FDA databases; state, national, international and academic references. One novel data collection is <u>ToxRefDB</u> (Toxicity Reference Database), which includes detailed information on *in vivo* guideline study results for pesticides and other potentially toxic chemicals that has been assembled by the NCCT. ACToR is also the primary repository of data being produced by the EPA. Overall, ACToR is engineered to be flexible enough to add a variety of new data from sources with different formats in a straightforward manner. Because we have not already discovered and included all toxicology data, we are always interested in obtaining other data collections that could be incorporated into the system.

ToxRefDB was developed by the National Center for Computational Toxicology (NCCT) in partnership with EPA's Office of Pesticide Programs (OPP), to store data from in vivo animal toxicity studies. The database primarily contains pesticide registration toxicity data that used to be stored as hard-copy and scanned documents by OPP. Currently, ToxRefDB includes chronic, cancer, sub-chronic, developmental, and reproductive studies on hundreds of chemicals (many are pesticide active ingredients). Each study entered utilizes a detailed standardized vocabulary for capturing nearly every element in the database, including the toxicological outcomes. To date, ToxRefDB contains roughly 2000 studies on nearly 500 chemicals. Through this web interface the data is provided in an accessible and computable manner.

Additional background information and examples of the utility of ToxRefDB can be found in three published manuscripts:

Martin et al. (2009) "Profiling Chemicals Based on Chronic Toxicity Results from the U.S. EPA ToxRef Database" Environmental Health Perspectives doi:10.1289/ehp.0800074 Knudsen et al. (2009) "Profiling the Activity of Environmental Chemicals in Prenatal Developmental Toxicity Studies using the U.S. EPA's ToxRefDB" Reproductive Toxicology doi: 10.1016/j.reprotox.2009.03.016

Martin et al. (2009) "Profiling the Reproductive Toxicity of Chemicals from Multigeneration Studies in the Toxicity Reference Database (ToxRefDB)" Toxicological Sciences doi: 10.1093/toxsci/kfp080

Additionally, ToxRefDB provides reference toxicity data for Agency research and retrospective analyses, while maintaining its initial focus on providing toxicity endpoints for development of ToxCast predictive signatures that will be used for primary research applications. It should be noted that ToxRefDB contains only certain hazard information and does not represent all information needed for a complete risk assessment for pesticides or other chemicals. Effect designation should not be taken as determination that existing EPA risk assessments and risk management decisions need revisions. For example, in addition to studies in ToxRefDB, for purposes of registration or tolerance determination, EPA evaluated information on other mammalian toxicity effects, metabolism, aquatic life, wildlife and plant toxicity studies, and use patterns, environmental fate and persistence, and pesticide residue levels.

# **Overview: How to Use ACToR**

In ACToR chemicals are organized into three main classes, the first two of which are modeled closely after the corresponding PubChem data model. The three main classes are:

- <u>Substance</u>- a unique chemical from a single "<u>data collection</u>"
- <u>Compound</u>- holds chemical structure information
- <u>Generic Chemical</u>- aggregates a chemical structure plus all of the corresponding substances. The common link is that all substances share the same CAS registry number.

## Browsing

One can find information on ACToR information by either browsing or by searching for a particular chemical. A person can look through the ACToR database by browsing through either the data collections or the assay data.

- <u>Assay</u>: An assay is a collection of data for substances from one data collection.
- <u>Data collection</u>: A collection of chemical and assay data from a single source

# Searching

If a person has a particular chemical in mind, he or she can find it by either entering the name or CAS number or they can draw the structure.

- <u>Search by Name</u>- allows one to search for chemicals by their common and their many alternate names.
- <u>Search by CAS</u>- enables one to search by CAS number
- <u>Search by Structure</u>- allows a person to either draw a chemical or paste an INCHI or SMILES code onto the drawing pad to find chemicals.

After conducting a search, it is possible to go back and edit what has been entered. To do this, DO **NOT** CLICK ON THE BACK BUTTON. Clicking on the back button will erase all of the data. Instead re-click on the "Search by (name/CAS/structure)" link on the left navigation bar.

# Search Results



The search results are composed of a table with all the chemicals in that data table. The columns include:

<u>Details-</u> contains the generic chemical id and a link to the chemical's generic chemical page <u>Image</u> – Drawing of the chemical <u>CASRN</u>- <u>CAS Number</u> Preferred Name- the chemicals proper name

A series of red boxes will appear to the right of the "Preferred Name" column. The appearance of a red box indicates that there is toxicity data available for the substance that appears under the "Preferred Name" column. The initials within the box denote the specific type of toxicological information that is accessible with ACToR. It does not necessarily mean that the substance has tested positive for a particular effect.

**<u>H</u> (Hazard)**- This category includes substances that have been assessed for the potential to cause adverse health effects or damage to property.

<u>**Ca** (Carcinogenicity</u>)- This category includes substances that have been assessed for the potential to cause cancer.

<u>**G** (Genotoxicity</u>)- This category includes substances that have been assessed for the potential to cause damage to genetic material, such as DNA.

**<u>D</u> (Developmental)**- This category includes substances that have been assessed for the potential to affect the development and/or growth of an organism.

**<u>R</u> (Reproductive)**- This category includes substances that have been assessed for the potential to interfere with normal reproduction, such as causing changes in fertility.

<u>**Cr** (**Chronic**</u>)-Substances that have tested for adverse effects by exposure to the test agent over a substantial portion of the organism's lifespan.

**<u>FS</u>** (Food Safety)- Designation in this category means that the substance has been tested as to its safety as either: an additive to food, a food ingredient or present in food packaging.

**Ex (Exposure)-** Exposure information, including results of biomonitoring studies, concentrations in the air, water or soil, and allowable exposure limits.

# **Overview: How to Use ToxRefDB**

In ToxRefDB, toxicity study information is organized into four main tiers, chemical, study design, treatment group (animal) dosing information, and effects (i.e., endpoints):

- <u>Generic Chemical</u>- aggregates a chemical structure plus all of the corresponding substances. The common link is that all substances share the same CAS registry number.
- <u>Study Design</u>- captures the detailed study design information associated with a given study, including test animal species and strain, dose administration route and method, and study type, study quality, among others.
- <u>Treatment Group & Dosing Information</u>- captures the dose groups (primarily in mg per kg of body weight per day), gender, life-stage, generation, and sacrifice time.
- <u>Effect & Endpoint</u>- captures, for any treatment group, the effects and endpoints deemed to be treatment-related using a standardized effect vocabulary.

# Browsing

The "ToxRefDB Home" page enables quick browsing by chemical, either by name or by CAS number.

# Searching

If a person has a particular chemical in mind, he or she can find it by either entering the name or CAS number or they can draw the structure.

- ToxRefDB Home: Search on Chemical Names- allows one to search for chemicals by their common and their many alternate names (See "<u>Search by</u> <u>Name (ACToR Only)</u>" for general instructions).
- ToxRefDB Home: Search on CAS Numbers enables one to search by CAS number (See "Search by CAS Number (ACToR Only)" for general instructions)
- <u>Search by Endpoint</u>- allows a user to search ToxRefDB for a specific endpoint or set of endpoints across any single study type.

After conducting a search, it is possible to go back and edit what has been entered. To do this, DO **NOT** CLICK ON THE BACK BUTTON. Clicking on the back button will erase all of the data. Instead re-click on the "ToxRefDB Home" or "Search by Endpoint" page link on the left navigation bar.

# Search Results

Details	Image	CASRN	Chemical Name	Chronic/Cancer_RatC	hronic/Cancer_Mouse I	Reproductive_RatD	evelopmental_Rat	Previous 1-2 Developmental_Rabbit	5 of 46 💌 <u>Next 21</u> Subchronic_Rodent
	-020					R <sub>Rn</sub>			
<u>details</u>		106325-08-0	Epoxiconazole						
	* >>			C <sub>Rn</sub>		R <sub>Rn</sub>	D <sub>Rn</sub>	D <sub>Rb</sub>	S
<u>details</u>		112201-77-3	Tetraconazole						
details	<u>z</u> z	114369-43-6	Fenbuconazole	C <sub>Rn</sub>	C <sub>Mm</sub>	R <sub>Rn</sub>	D <sub>Rn</sub>	D <sub>Rb</sub>	S
	s-X		<b>_</b> .	C <sub>Rn</sub>	C <sub>Mm</sub>	R <sub>Rn</sub>	D <sub>Rn</sub>	D <sub>Rb</sub>	S

The search results are composed of a table with all the chemicals in that data table. The columns include:

<u>Details-</u> contains the generic chemical id and a link to the chemical's generic chemical page <u>Image</u> – Drawing of the chemical <u>CASRN</u>- <u>CAS Number</u> <u>Chemical Name</u>- the chemicals proper name

A series of red boxes will appear to the right of the "Chemical Name" column. The appearance of a red box indicates that there is toxicity data available for the substance that appears under the "Preferred Name" column. The initials within the box denote the specific type of toxicological information that is accessible with ACToR. It does not necessarily mean that the substance has tested positive for a particular effect.

<u> $C_{Rn}$  (Chronic/Cancer Rat</u>)- This category indicates that one or more long-term (usually 2-year) chronic and/or cancer rat studies have been conducted, entered into ToxRefDB, and considered of sufficient quality for public release.

 $\underline{C_{Mm}}$  (Chronic/Cancer Mouse)- This category indicates that one or more long-term (usually 18-month to 2-year) chronic and/or cancer mouse studies have been conducted, entered into ToxRefDB, and considered of sufficient quality for public release.

<u>**R**<sub>Rn</sub> (**Reproductive Rat**</u>)- This category indicates that one or more multigenerational reproductive rat studies have been conducted, entered into ToxRefDB, and considered of sufficient quality for public release.

<u>**D**<sub>Rb</sub> (**Developmental Rabbit**</u>)- This category indicates that one or more prenatal developmental rabbit studies have been conducted, entered into ToxRefDB, and considered of sufficient quality for public release.

<u>S (Subchronic Rodent</u>)- This category indicates that one or more medium-term (usually 90-day) sub-chronic rodent studies have been conducted, entered into ToxRefDB, and considered of sufficient quality for public release.

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# Data Collections (ACToR Only)

STED STAT			U.S. ENVIRONMENTAL PROTEC	TION AGENC				
	ACToR: A	ggregated Computati	ional Toxicology Resource	Share Share				
PROTECTION	Recent Additions   C You are here: EPA	Contact Us Search: O All EPA ( Home » National Center for Computation	This Area     Go     Inis Area     Go     ACTOR > Data Collections					
ACToR Home Basic Information	Data Col	lections						
Search By Name Search By CASRN					Number	Number Generic	Number Assay	
Search By Structure	Details	Data Collection	Description	Source Ty	Substances	Chemicals	Results	EXIT Disclaimer
Browse Toxicity Assays	<u>Details</u>	AIHA WEEL	Current AIHA Workplace Environmental Exposure Levels (WEEL) Guides (2007). Goal is to develop Workplace Environmental Exposure Level (MEEL) quides for chemical and physical agents	Chemicals+Assay	114	114	120	<u>Link</u> Out
External Links			and stresses					
Help	<u>Details</u>	ATSDR CEP 2007	ATSDR's Division of Toxicology and Environmental Medicine publishes the Completed Exposure Pathway Site Count Report. A completed exposure pathway (CEP) is an exposure pathway that links a contaminant source to a receptor population.	Chemicals+assay:	100	97	300	<u>Link</u> Out
	<u>Details</u>	ATSDR HSEES 2006	The Hazardous Substances Emergency Events Surveillance (HSEES) system was established by ATSDR to collect and analyze information about acute releases of hazardous substances and threatened releases that result in a public health action such as an evacuation. 14 state health departments currently participate.	Chemicals+Assay	40	40	471	<u>Link</u> Out
	Details	ATSDR Interactions	ATSDR Interaction Profiles for Toxic Substances; mixtures found at NPL sites	Chemicals+Assay	58	42	135	<u>Link</u> Out
	Details	ATSDR MMG	ATSDR Medical Management Guidelines (MMGs)	Chemicals+URLs	76	73	76	<u>Link</u> Out

All information ACToR is organized by <u>Data Collections</u>. A data collection often contains substances, chemical structures and <u>assays</u>. The entire list of data collections in ACToR can be seen by selecting the Data Collections in the left hand navigation bar. For each collection, the following data are presented:

Details- contains a link to individual data collection page

Data collection - a short synopsis of the data collection

Description - short synopsis of the data collection

<u>Source type</u>- the type of information contained in that data collection. It can include: *Chemical*- chemical list of substances

<u>Chemical + Assay</u>- a list of chemicals that have associated information <u>Chemical + Structure</u>- a list of chemicals and their corresponding structures <u>Chemicals + URL</u>- a list of chemicals having specific website for individual substances.

<u>EPA target list</u>- target list of chemicals to investigate created by the EPA <u>Search by CASRN and name</u>- chemical list with names and CAS numbers

<u>Number of substance</u>- the number of <u>substances</u> within the data collection <u>Number of generic chemicals</u>- the number of <u>generic chemicals</u> within the data collection. The number of generic chemicals may be less than number of substances if some substances do not have <u>CAS</u> numbers or if there are multiple substances with multiple names leaving identical CAS number.

<u>Number of assay results</u>- a measure of discrete assay for the substance contained in the collection.

Link out- provides a direct connection to the external website of a given data collection

To view the list of chemicals in the data collections, select the "Details" link at the left. This will take you to the <u>Data Collection View</u>. To navigate to the sources' external site select the "Link Out" hyperlink at the far right in data collections table.

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# Data Collection View (ACToR Only)

				U,	S. ENVIRONMENTAL	PROTECTION AGENCY		
	ACToR: Agg	gregated (	Computational To	xicology	Resource	2 Share		
50	Report Additions   Cont	lest Us Searc	th: 🔿 All EPA 💿 This Area		Go			
AND AL AND THE OWNER	You are here: EPA Horn	ne # National Cen	ter for Computational Toxicology ×	ACTOR + Data	Collection :			
ACTOR Home								
Basic Information	Data Colla	otion · /						
Data Collections	Data Colle	cuon . r						
Search By Name								
Search By CASRN	Name:	AIHA WEEL						
Search By Structure	EXIT Disclaimer	Link Out						
Browse Toxicity Assays	Description:	Current AIH/ Environment	A Workplace Environmental E al Exposure Level (WEEL) g	Exposure Level uides for chem	s (WEEL) Guides (2007). Go ical and physical agents and	al is to develop Workplace stresses		
External Links	ID:	126						
Help	Institutional Source:	AIHA						
	Source Type:	Chemicals+	Assays					
	Number of Substances	114						
	Number of Generic							
	Chemicals:	~ 114						
	Search Result	ts						
	Co	ompound				Chronic	Developmental	Reproductive Food
	GCID	ld	Image	casm	Preferred Name	Hazard Toxicity Carcinogenicity Genotoxic	tv Toxicity	Toxicity Safety
			нас — сна			Ha Cr Ca G	D	R
	<u>312437</u>	4194	он	75-86-5	2-Hydroxy-2- methylpropanenitrie			-
	202247					Ha Cr Ca G	D	R FS
	382917	1723		98-86-2	Acetophenone			

The data collection page shows a summary of the information contained within a specific <u>data collection</u>. This page can be reached by clicking on <u>data collection page</u> and then selecting one of the "Details" links. Here, the information is divided into three parts: <u>overview</u>, and <u>search results</u>.

#### Overview

The top chart provides a brief overview of the data collection. This includes:

<u>Name</u> - name of the data collection
<u>Link out</u> - provides a direct path to the source's external website
<u>Description</u> - description of the data collection
<u>ID</u> - the internal id number of the data collection used for database management purposes
<u>Institutional Source</u> - the name of the institution that provided the data
<u>Source Type</u> – provides a cryptic description of the type of information contained in the data collection, e.g. a chemical list, an associated assay chemical- specific URLS, etc.
<u>Number of Substances</u> - the number <u>substances</u> in the data collection
<u>Number of Generic Chemicals</u> - the number of generic chemicals in the database. This number may be less than number of substance if some substances do not have <u>CAS</u> numbers or if there are multiple substances with the same CAS number.

# Search Results

The search results give a list of all the chemicals that appear in the data collection. For more information go to "<u>how to use ACToR: search results</u>".

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# Generic Chemical View (ACToR & ToxRefDB)

## ACToR View:

A19 82			U.S. ENVIRONMENTAL PROTECTIO	N AGENCY
	ACToR: Aggregated Computational Toxicology Re	source		Dista 2
502	Recent Additions   Cantast Us Search: O All EPA    This Area	Go		
and section	You are here: EPAHome = National CenterferComputational Texteelogy = ACLOR = Chemical Summa	AV 1		
TeR Home	Chamber 10			
a Collections	Chemical Summary : Bisphenol A			
arch Dy Name				
arch By CASEN		GCID	336203	
arch Dy Structure	H <sub>3</sub> C CH <sub>3</sub>		xencestrogen; RN given refers to parent cpd;	
owse Assays by xicity		MESH DESCRIPTION	structure : Air Pollutants, Occupational : Estrogens, Non-Steroidal : Free Radical	
owse Assays by			Scavengers	
tegory		CASRN	80.05-7	
lemai Links		FORMULA	C15H16U2	
writed	OH OH	CMI EQ	200 2003	
xRefDB		SMILES	Cu(c)(crebe(cer)O)czeec(cez)O	
	Substances			
	Name	Data Collection		^
	.beta., beta.1-Bisgo-hydroxypheny()propane	PubChen		
	.betaQi-(p-hydroxypheny()propane	PubChen		
	.betaDi-(p-hydroxypheny()propane	NCI-Open_09-03		
	137005-53-1	PubChen		
	2,2-(4,4-Dihydroxydipheny()propene	PubChen		
	2,2-Bis(4-hydroxypheny(propen = 4,4'-isopropylidenediphenol = Bisphenol A	EUROPA Endocrine Candidate		
	2,2-Dis(4-hydroxypheny(propene	PubChen		
	2,2-Bis(4-hydroxypheny(propane	EUROPA Food Contact Monomers		
	2,2-Bis(4-hydroxypheny()propane	EUROPA Food Contact Additives		
	2,2-Bis(hydroxypheny(propane	PubChen		
	2,2-Bis(p-hydroxypheny(propane	Publishen		
	2,2-Bis-41-hydroxyfenylpropan	Publiken		
	2,2-Bis-41-hydroxyfenylpropan (Czech)	PubChen		~
				>
	Synonyms			
	beta beta Vitrio-betro-obero/incosere			^

## ToxRefDB View:

110 8210			U.S. ENVIRONMENTAL PROTECTION AGENC
	ToxRefDB: Toxicity Reference Database		State 2
	Recent Additions   Contact Us Search: O All EPA  This Area	Go	
ALL PROTECTION	You are here: <u>CPA Home</u> > <u>National Center for Computational Texture logy</u> > <u>Texture 0</u> > Chemical Sum	may:	
formation	Chemical Summany Biophonal A		
By Endpoint	Chemical Summary : Bisphenol A		
		GCID	336203
	H <sub>3</sub> C CH <sub>3</sub>		xencestrogen; RN given refers to parent cpd;
	$\sim \sim \sim$	MESH DESCRIPTION	structure : Air Pollutants, Occupational : Estrogens, Non-Steroidal : Free Radical
			Scavengers
		CASRN	80-05-7
		FORMULA	C15H16O2
	HO OH	MWY Chill ED	228.2963
		SMILES	CC(C)(e1ece(ee1)O)e2ece(ee2)O
	Substances		
	Name	Data Collection	
	Jeta "Jeta.' Bis(p-hydroxypheny(propane	PubChem	
	.beta -Di-(p-hydroxypheny(propane	PubChem	
	Joeta -Di-(p-hydroxypheny(propane	NCI-Open_09-03	
	137085-53-1	PubChem	
	2,2-(4,4*-Dihydroxydipheny()propane	PubChem	
	2,2-Bis(4-hydroxypheny()propan = 4,4'-isopropylidenediphenol = Bisphenol A	EUROPA Endocrine Candidate	
	2,2-8is(4-hydroxypheny()propane	PubChem	
	2,2-Bis(4-hydraxypheny(propane	EURCPA Food Contact Monomers	
	2,2-Bis(4-hydroxypheny()propane	EUROPA Food Contact Additives	
	2,2-Bis(hydroxypheny(propane	PubChem	
	2,2-Bis(p-hydroxypheny()propane	PubChem	
	2,2-Bis-41-hydroxyfenylpropan	PubChem	
	2,2-8is-4"-hydroxyfeny(propan (Czech)	PubChem	
	<u>(1)</u>		2
	Synonyms		
	Zeta "Zeta : Bis(p-hydroxypheny0propane		

This page is accessed by clicking on "Details" for a specific chemical and provides links to all the information relating to this chemical i.e. from all data collections in the ACToR database and all study information from ToxRefDB. Data has been aggregated from all substances with a specific CASRN from all data collections. This page is divided into five main sections: <u>Chemical Summary</u>, <u>Substances</u>, <u>Synonyms</u>, <u>Toxicology Data</u>, Category Data.

## **Chemical Summary**

**<u>GCID</u>**- Generic Chemical ID- an internal chemical ID within in ACToR <u>Mesh Description</u>- When available, a brief description of the chemical that came from the <u>MESH</u> Database from the US Nation Library of Medicine <u>CASRN</u>- The CAS (Chemical Abstracts Service) Registration Number <u>Formula</u>- The chemical formula <u>MW</u>- Molecular weight <u>SMILES</u> - (<u>Simplified Molecular Input Line Entry System</u>) is a line notation used for representing molecules

## Substance Data

The substance box provides a list of all the data collections that contain the chemical. Chemicals are aggregated by CASRN. The substance chart has the following categories:

Name- the chemicals proper name

**Data Collection**- the name of the data collection in which in appears

## Synonyms

The synonyms box contains a list of all the <u>CAS</u> numbers and names used to describe the <u>generic chemical</u>.

# Toxicology Data

The Chemical data is organized into different boxes. Each box has its own label and contains a list of <u>assays</u> and a summary of their results.

<u>**ToxRefDB Data**</u> – Detailed toxicological data available directly from ToxRefDB in a structured format. Information on toxicological outcomes are linked directly to the dose groups and studies (more detailed information below).

<u>**Hazard**</u> – Information on basic harm that can be caused by a chemical. Information under this category includes workplaces safety and first aid in case of exposure.

<u>Acute Toxicity</u> – Information on health effects due to short term exposure. **Subchronic Toxicity -** Information on health effects due to intermediate term

#### exposure.

<u>Chronic Toxicity</u> - Information on health effects due to long term exposure.

<u>**Carcinogenicity**</u> – Information from studies of cancer-causing ability of chemicals.

<u>Genetic Toxicity</u>- Information on the ability of chemicals to cause DNA damage. <u>Reproductive Toxicity</u>- Information on the ability of a chemical to damage an organism's reproductive ability.

<u>Neurotoxicity</u> - Information on the ability of a chemical to damage nerve cells or tissues.

<u>**Developmental Neurotoxicity**</u> – Information on chemicals that cause neurological deficits during development

**Immunotoxicity** - determines how a chemical affects the immune system **Dermal Toxicity**- includes studies about chemicals and what level of toxicity results from the substances being applied through the skin. May or may not have the skin as a target organ.

<u>**Respiratory Toxicity-**</u> contains data on how the chemicals that affect the respiratory system

**<u>Nephrotoxicity</u>**- measures to what degree that the chemical that affect the kidneys

**Endocrine Effects-** contains data about if and how the chemical affect hormone signaling and downstream processes

<u>Cardiotoxicity-</u> contains data bout how the chemical affects the heart <u>Ecotoxicity-</u> includes data about how chemicals affect non-human species such as fish and amphibians

<u>Food Safety</u>- includes data that determines if the food can be safely used as an ingredient, additive or food wrapper

Toxicity other- contains other information about a chemical's toxicity

## **Category Data**

The Chemical "Category" data is organized into different boxes. Each box has its own label and contains a list of <u>assays</u> and a summary of their results. These categories along with the "Toxicology Data" have been mapped to a taxonomy for accurate and consistent representations of specific data types.

**<u>Physico-Chemical Data</u>** – this is largely computed data on solubility, melting point, etc. based on chemical structure.

<u>In Vitro</u> – Primarily in vitro screening/profiling data coming out of the EPA's ToxCast research program, but will include processed data from Tox21 (an interagency research program for screening thousands of chemicals)

<u>Chemical Manufacturing and Use Levels</u> – This is data compiled by the EPA on industrial chemicals that are subject to <u>TSCA</u> (Toxic Substances Control Act)

<u>**Descriptive Data**</u> – a variety of tabulated descriptive data, for instance on intended use of the compound

<u>**Risk Management**</u> – This is a listing of international, U.S. Federal and state regulations and standards to which this chemical is subject.

<u>Material Safety Data Sheet</u> – if available, a link to the International Chemical

Safety Card, which summarizes information from the Material Safety Data Sheet. <u>Chemical Categories</u> – these are chemical structure categories used, for instance, to make initial predictions of toxicity of a new compound based on similarity with compounds which have already been tested.

<u>**Pesticidal Mode of Action**</u> – If the compound is a pesticidal active ingredient, this will provide the intended biological mode of action

**<u>PubMed via MESH</u>** – If available, a link to the literature in PubChem based on the <u>MESH</u> term.

Notes – notes provided on the chemical for and of the data collections.

**External Searches by NAME or CAS**- this is a list of pre-computed URL links to search external, on-line databases based on the CASRN and preferred name of the chemical

#### How to move through the chart



The assay names are green and underlined. Clicking on the assay names will take you to the assay view page. Clicking on the box next to the assay name will expand or collapse the result group. The result group has two columns:

<u>**Component Name-**</u> the assay component name <u>Value</u>- includes number, names, text and URLs.

Each "assay" is initially collapsed for quicker viewing across large numbers of components. To expand a single assay component, click on the "+" to view the next level of information. Click "Expand All" to view all of the data under the specific category.

#### ToxRefDB Data

All other result groups are formatted and presented in a consistent fashion. Due to the unique structure of the data stored in ToxRefDB the information is being presented in three layers. For any given chemical with ToxRefDB data, there will be a collapsed view of the study design information for each study.

oxRefDB Da	ita	
Collapse All Expand	All Driveload CSV Data	-
Study Type:	SUB	
Species:	rat	
Year:	1979	
MRID:	58606	
Study Deficiences:		
Citation:	Sachese, K.; Suter, P.; Luetkemeier, H.; et al. (1979) CGA 64250 Techn. Three Months Toxicity Study on Rate: Project No. 790014. Final rept. (Unpublished study received Jan 28, 1981 under 100-618, prepared by Ciba-Geigy Ltd., Switzenland, submitted by C	
Data Quality:	Acceptable Guideline (pre-1998)	
Guideline No:	870.3100	
Guideline Name:	Subchronic oral toxicity in rodents	
Strain	[Other]	
Admin Method:	Feed	
Admin Route:	Oral	
Start:	0	
Start Unit:	day	
End	3	
End Unit	month	
Lot/Batch No:	53/1 p1	
Punty:	90.0	
<b>Duration Comments:</b>		
Animal/Dosing Comments:	Strain SPF	
Study Type:	SUB	
Species:	mouse	
Year.	1991	
MRID	42050501	
Study Deficiences:		
Citation:	Potrepka, R.; Turnier, J. (1991) Subchronic Dietary Toxicity Study with CGA-64250 in Mice: Lab Project Number: F-00099. Unpublished study prepared by Ciba-Geigy Corp. 302 p.	
Data Quality:	Acceptable Guideline (pre-1998)	
Guideline No:	870.3100	
Guideline Name:	Subchronic oral toxicity in rodents	
Strain	Crt:CD-10CRJBR	
Admin Method:	Feed	
Admin Route:	Oral	
Start	0	
Start Unit:	day	
End	17	
End Unit:	week	1

Like the other sections, to display all of the information for a given chemical press the "Expand All" button. To browse a particular study, select the "+" box and a view of the treatment groups and their associated treatment-related effects will be displayed. If the treatment group was not assigned any treatment-related effects then the text "No Effect Data Found" will be displayed. To DOWNLOAD all of the ToxRefDB data for a given chemical, select the "Download CSV Data" link and you will be able to download a zipped-up comma-separated file. This file will contain a flattened version of the data displayed in the browser. The table below provides a listing of all fields displayed with a short description.

Field Name	Description
CASRN	Chemical Abstract Service registry number
Chemical Name	Preferred chemical name
Study ID	ToxRefDB study identifier
Citation	Study citation (primarily based on EPA's OPPIN system)
MRID	OPP's unique study identifier
Year	Study Year (primarily year of study report)
Data Quality	Data quality (primarily assessed by adherence to guideline)
Study Deficiencies	Study-level deficiencies and comments (free-text; primarily as stated in review of study)
	Study type short name
Study Type	(CHR='Chronic';MGR='Reproductive',DEV='Development';SUB='Subchronic')
Guideline No	EPA/OPPTS harmonized guideline number
Guideline Name	EPA/OPPTS harmonized guideline name
Species	Species tested in study
Strain	Strain tested in study
Admin Method	Dose administration method (e.g., gavage, feed, water, etc.)
Admin Route	Dose administration route (e.g., oral, inhalation, etc.)
Start	Start of study dosing
Start Unit	Start of study units

End	End of study dosing
End Unit	End of study units
Lot/Batch No	Test material lot and batch number
Purity	Test material purity (%)
Duration Comments	Comments specific to the duration of the study (free-text)
Animal/Dosing	
Comments	Specifies test animal strain and dosing information
Treatment Group ID	ToxRefDB treatment group id
Generation	Generation or life-stage of treatment group
Dosing Period	Dosing period (e.g., initial-to-terminal, interim sacrifice, second mating, etc.)
Gender	Gender of treatment-group
Dose Level	Dose level for set of treatment groups
Dose	Administered dose (primarily mg/kg-bw/day)
Dose Unit	Dosing units (primarily mg/kg-bw/day)
Dosing Duration	Duration of dosing
Duration Unit	Dosing duration units
N	Number of animals per treatment group
Effect ID	ToxRefDB effect id
	Type or Class of Effect (e.g., organ weight, gross pathology, neoplastic pathology,
Effect Type	etc.)
Effect Target	Target of effect (e.g., organ, analyte, system, etc.)
Effect Description	Description of effect based on effect type and target
Direction	Direction of effect: Increase or Decrease
Target Site	Specific site of effect (e.g., cell type, region, etc.)
Effect Description	
(Free-Text)	Detailed description of effect (where not exact with standard vocabulary)
LOAEL	Assigned study-level LOAEL
Endpoint Category	High-level categories specific to each study type

# Search by Name (ACToR Only)

ITED STAL				U.S. ENVIRON	MENTAL	PROT	естіо	N AGE	NCY			
a un a se	ACToR: Ag	gregated Comp	utational To	xicology Resource				🎴 <u>Sha</u>	re			
	Recent Additions   Co	ntact Us Search: O Al	I EPA 💿 This Area	Go								
PROTECTION	You are here: EPA Ho	ome » National Center for Com	putational Toxicology ×	ACToR » Search By Name								
ACToR Home												
Basic Information	Search B	v Name										
Data Collections	Couron D	y runno										
Search By Name	Chemical Name:	bisphenol A										
Search By CASRN	Type of Match:	○ Exact										
Search By Structure		Any										
Browse Toxicity Assays	Search Search Resu	ilts										
External Links							city		tal			
Help							eni	icity	E	,Š	fety	
					Ē	Ë	ing	tox	ē	ā	S	2 IIIS
	Details	Image	CASRN	Preferred Name	Haza	chra	Card	Geno	Deve	Repr	Food	Expo
		5										
		н <sub>3</sub> с Сн3										
		$( \land )$			На	Cr	Са	G	D	R	FS	Ex
		но										
	325914		80-05-7	BisphenolA								

To search for a chemical, type in the full or partial name in the text box. Select either "exact match" or "any match". Exact match will find the chemical whose name matches what you typed in. "Any" match will find matches that are similar to what you typed in. The search is performed against all of the synonyms that have been compiled for each generic chemical. When one clicks the search button, a chemical list chart appears with the results. Note that the search by name program does not accept <u>SMILES</u> or <u>InCHI</u> notation. To use SMILES or InCHI see the <u>Search by Structure</u> page.

# Search Results

See "How to use ACToR: Search Results".

After conducting a search, one can go back and edit what they entered. To do this, DO **NOT** CLICK ON THE BACK BUTTON. Clicking on the back button will erase all of your data. Instead re-click on the "Search by Name" button on the left navigation bar.

# Search by CAS Number (ACToR Only)

ATTED STAD				ι	J.S. EN	VIRON	MENT	AL PRO	тесті	ON AC	GENCY	
	ACToR: Ag	gregated Comp	utational	Toxicology	/ Res	ource				2	<u>Share</u>	)
	Recent Additions I Co	ontact Us Search: O All	EPA 💿 This A	rea		Go						
WHAL PROTECTION	You are here: EPA H	ome » National Center for Com	putational Toxicol	ogy » <u>ACToR</u> » Se	arch By CA	SRN						
ACToR Home												
Basic Information	Search B											
Data Collections		<b>,</b>										
Search By Name	Enter CASRN's	80-05-7		<u>~</u>								
Search By CASRN												
Search By Structure												
Browse Toxicity Assays												
External Links												
Help												
	Cooreb											
	Search Res	ulte										
	Search Kest	2013					≥		-			
							i <u>e</u>	ž	ente	,Ž	2	
					_	U	aŭo	ŭ.	Ē	벌	afe	2
				Preferred		5	ġ	đ	륃	ĕ	5	20
	Details	Image	CASRN	Name	Ē	ē	0	8	De	Rel	Ē	E E
		H <sub>3</sub> C CH <sub>3</sub>							_			_
		$\sim$			На	Cr	Са	G	п	R	ES	F
					-114		-04					
		но Он	80-									
	<u>325914</u>		05-7	BisphenolA								

Using <u>CAS numbers</u> is another way of locating and identifying chemicals. To find a chemical using a CAS number, type in one or more CAS numbers in the text box, separated by either commas or new lines. After search is completed, a standard chemical chart will appear.

Some examples of number in CAS format are: 7439-92-1 7440-50-8 79-34-5 39001-02-0

# Search Results

See "How to use ACToR: Search Results".

A search may be edited after being submitted. To do this, DO **NOT** CLICK ON THE BACK BUTTON. Clicking on the back button will erase all of your data. Instead re-click on the "Search by CAS" button on the left navigation bar.

# Search by Structure (ACToR Only)

SHITLD STATES	U.S. ENVIRONMENTAL PROTECTION AGENCY											
	Recent Additions I Go You are here: EPA H	ontact.Us Search: O A	NI EPA  This Area	» AGTOR » Search By St	Go							
ACTOR Home Basic Information Data Collections Search By Hame Search By Ame Search By Structure Browse Tosicity Assays Enternal Links Help	Search B	y Structure										
	Details	Image	CASRN	Preferred Name	Hazard	Chranic	Carcinogenicity	Genoloxi city	Developmental	Reproductive	Food Safety	Exposure
					На	Cr	Са	G	D	R	FS	Ex
	325914	но~~~~он -,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	80-05-7	BisphenolA								

## **Drawing Board**

#### There are two major ways to construct a molecule

1. The typical way to construct a molecule is to select a template (see 1), bonds (arrows 2), and atoms (see 3 and 4). First, select a template then click on the canvas (see 1). Then, click on button 2 and select the bond type. To attach a bond, place the cursor over the molecule until a purple circle appears. If there is a need to connect two molecules, then click and hold the left mouse button and drag the other end of the bond to the other molecule until another purple circle appears before letting go of the left mouse button. To add atoms, either click on one of the "quick add" buttons (3) or select button 4. Button 4 causes a small window to appear with the periodic table on it. Select an element and then click close. Clicking on the "Query" tab, gives some more options that do not appear on the periodic table.

**2.** The fastest way to make molecules is to copy the molecule's <u>SMILES</u> or <u>InCHI string</u> and click on button 5.

For a more in-depth tutorial for this program, click on button 6 on the upper right hand corner. This takes you to the ChemAxon Help Site.

# Search Results

See <u>"How to use ACToR: Search Results</u>".

After conducting a search, one can go back and edit what they entered. To do this, DO **NOT** CLICK ON THE BACK BUTTON. Clicking on the back button will erase all of your data. Instead re-click on the "Search by Structure" button on the left navigation bar.

TOP

# **Browsing Assays**

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a un o to	ACTo	Share				
PROTECTO	<u>Recent Ad</u> You are he	Iditions   Contact Us Search: O All EPA ere: EPA Home » National Center for Computati	• This Area	Go Toxicity Assa	/5	
oR Home						
ic Information a Collections	Brov	wse Toxicity Assays				
rch By Name	Detai	Is SourceNameAid 🛓	Name	Substa	nces Compoi	nents DataCollection
irch By CASRN irch By Structure wse Toxicity	<u>Details</u>	AIHA_WEEL_AID_1	Workplace Environmental Exposure Levels (WEELs) (2007)	114	2	<u>AIHA WEEL</u>
ays ernal Links	<u>Details</u>	ATSDR_CEP_2007_AID_1	ATSDR Completed Exposure Pathways	100	3	ATSDR CEP 2007
)	<u>Details</u>	ATSDR_HSEES_2006_AID_1	Acute Release of Hazardous Substances (ATSDR 2006-2008)	40	12	ATSDR HSEES 2006
	<u>Details</u>	ATSDR_Interactions_AID_1	ATSDR Chemical Interaction Profiles	58	3	ATSDR Interactions
	<u>Details</u>	ATSDR_Interactions_AID_1	ATSDR Chemical Interaction Profiles	58	3	ATSDR Interactions
	<u>Details</u>	ATSDR_Interactions_AID_1	ATSDR Chemical Interaction Profiles	58	3	ATSDR Interactions
	<u>Details</u>	ATSDR_Interactions_AID_1	ATSDR Chemical Interaction Profiles	58	3	ATSDR Interactions
	Details	ATSDR_MMG_AID_1	ATSDR Medical	76	1	ATSDR MMG

The browse assay page can be found by clicking on "Browse Toxicity Assay" in the left navigation button.

U.S. ENVIRONMENTAL PROTECTION AGENCY

Phenotype Hazard

Hazard Hazard

CardioTox Hazard HepatoTox NeuroTox Hazard

This page contains a collection of all the assays on the ACToR database. Assays are classified under one category but may have multiple phenotypes. Assays are organized alphabetically by assay name. Assays differ from data collections in that a data collection is all the information from a single source, while an assay is a collection of data arranged into a chart. So a single source can carry multiple assays.

**Details**- a link to a page that contains more details about a particular assay **Source Name AID**- the location of the assay **Name**- the name of the assay **Substances**- the number of substances in the data **Components**- the number of assay components **Data Collection**- the name of the Data Collection **Category**- The name of the <u>Assays Categories</u> **Phenotype**- The name of the <u>Assay Phenotype</u>s

# **Assay View**

TED STAD				U	.S. ENVIR	ONMENTAL	PROTECTION	AGENCY
	ACToR: Aggregated Computational Toxicology Resource							
	Recent Additions Conta	ct Us Search:	🔿 All EPA 💿 Thi	s Area	Go			
WTAL PROTECTION	You are here: EPA Home	» National Center f	or Computational Tox	icology » <u>ACToR</u> » Asse	ay :			
ACToR Home								
Basic Information	Assay : Wo	orkplace E	Environm	ental Expos	sure Le	vels (WE	ELs) (2007	)
Data Collections	-	•		•		•		
Search By Name	Source Name Aid	AIHA_WEEL_A	ND_1					
Search By CASRN	Name	Workplace Env	ironmental Exposi	ure Levels (WEELs) (	2007)			
Search By Structure	Description	AIHA workplace	exposure levels					
Browse Toxicity Assays	External URL	Link Out EXIT	Disclaimer					
External Links	Phenotype	Hazard						
Help	Category	Exposure limits	, Occupational					
	Substance Count	114						
	Component Count	2						
	Data Collection	AIHA WEEL						
	Source ID Nar	ne Des	cription		Ur	nits Value T	ype Compone	nt Type
	1 8-hr	TWA 8-hrt	ime-weighted aver	age exposure		TEXT	Primary	
	2 Shor	t-term TWA Ceilir	ig or short-term tin	ne-weighted average	exposure	TEXT	Primary	
	Show Assay Data P	age						
		_					-	
			EPA Home	Privacy and Security N	otice Contac	<u>t Us</u>		

The assay view gives a more in depth view of each assay. One can find this page by clicking on the "Details" link on the <u>browse assay page</u>. There are two sections to this page: the overview and the assay component chart.

#### Overview

**Source Name AID**- the location of the assay **Name**- the name of the assay **Description**- a brief summary of what the data entails **External URL**- a link to the source **Components Count**- the number of components **Data Collection**- the name of the data collection

The above may be repeated if the assay has multiple phenotypes.

#### Assay Component Chart

Source ID	Name	Description	Units Value	Type Component Type
1	8-hr TWA	8-hr time-weighted average exposure	TEXT	Primary
2	Short-term TWA	A Ceiling or short-term time-weighted average exposure	e TEXT	Primary
Show Assay [	)ata Page			

This section gives information about the type of data in the assay data. The assay component chart includes:

**Source ID**- the number assigned to the assay component within the assay **Name**- the name of the assay component

Description - text description of the assay component

<u>Units</u>- what units are used for the assay component

Value Type- the type of values. Values include

*<u>Float</u>*- numbers with decimals. This includes standard decimal notation,

exponential notation and scientific notation. <u>Intege</u>r- whole numbers such as -2, 0, 1, 2 <u>Categorical</u>- contains categories such as colors <u>Boolean</u>- true or false <u>URL</u>- contains the URL from a hyperlink <u>Text</u>- is in text form but is not a category, URL or True or False

**Component type**- tells whether this is a primary or a secondary value. The values include

<u>Primary-</u> a number that one would computer with <u>Modifier</u>- includes Variance and SD <u>Variance</u>- the distribution of a sample (Statistics) <u>SD</u>- standard deviation (Statistics) <u>Annotation</u>- additional comments

## Show Assay Data Page

This section contains a link that takes one to the Assay Data Page.

# Assay Data Page



This page contains the <u>assay</u> data. In this chart, the columns headers are the <u>assay</u> <u>components</u> and the rows are the <u>substance</u>. The cells of this table are the <u>assay results</u>. The assay table can have more than one row or entry for the same substance, and elements in the data matrix can be empty.

One can find this page by clicking the link "Show Assay Data" on the Assay View page.

The charts vary with every assay. However, all of them contain the following:

<u>Name</u>- the name of the chemical

<u>Substance ID</u>- the substance ID number

Assay ID- the ID number for the assay within the data collection

The Remaining column headings are assay components. The component names can also be found on the Assay View Page's assay component chart.

Sometime, is the assay table is very long, there will be multiples "pages". One can learn how to navigate through the chart by going to <u>here.</u>

# **External Links**

STED STA		U.S. ENVIRONMENTAL P	ROTECTION AGENCY
2 Junio - Fa	ACToR: Ag	gregated Computational Toxicology Resource	Share Share
PROTECTION	Recent Additions   Co You are here: EPA He	Contact Us Search: O All EPA  This Area Go Ome  National Center for Computational Toxicology  ACTOR  External Links	
ACToR Home			
Basic Information	External	l inks	
Data Collections	External	Linko	
Search By Name	Category	Name	URL
Search By CASRN	External Data	The PubChem Project	Link Out
Search By Structure	Source		EXIT Disclaimer
Browse Toxicity Assavs	External Data Source	International Agency for Research on Cancer	Link Out EXIT Disclaimer
External Links	External Data Source	National Library of Medicine Superlist - Regulatory and Other Lists of Chemicals	Link Out EXIT Disclaimer
Help	External Data Source	NLM Toxline	Link Out EXIT Disclaimer
	External Data Source	Proposition 65 Current List of Chemicals	Link Out EXIT Disclaimer
	External Data Source	Silent Spring Institute - Researching the Environment and Women's health	Link Out EXIT Disclaimer
	External Data Source	Environmental Information Exchange Network	Link Out EXIT Disclaimer
	External Data Source	Drug-induced Arrythmias	Link Out [EXIT Disclaimer]
	External Data Source	PDSP Ki database	Link Out EXIT Disclaimer
	External Data	National Toxicology Program (NTP)	Link Out

This page contains a link to other large databases that contain information about chemicals.

**Category**: are all external data sources **Name**: name of the website **URL**: the hyperlink to the data

# Search By Endpoint (ToxRefDB Only)

In ToxRefDB, toxicity study information is organized into four main tiers, chemical, study design, treatment group (animal) dosing information, and effects (i.e., endpoints). The "Search By Endpoint" page allows for flexible querying of the database for specific effects or sets of effects of interest. Since ToxRefDB captures on the treatment-related effects, the absence of an effect in the database is assumed to be a negative. This assumption is not always true and this should be considered whenever retrieving data from ToxRefDB.

Based on the standardized vocabulary, there is a defined set of terms for capturing the effect information on any given study. This vocabulary is constantly growing and changing based on feedback from subject matter experts. The top tier is the study type which consists of subchronic (SUB), chronic/cancer (CHR), reproductive (MGR), and developmental (DEV) studies. Each of these studies has been tested in rat, mouse and/or rabbit. Each unique effect is determined based on the combination of the Effect Type, Effect Target, Effect Description, and Effect Direction.

In the example below, the Chronic/Cancer (CHR) rat studies were selected and queried for whether or not the studies observed liver tumors [Pathology (Neoplastic) | Liver | Adenocarcinoma, Adenoma, Adenoma/Carcinoma Combined, Carcinoma, Mixed Tumor Malignant, Neoplastic nodule | Increase]. As described in the legend, a blank or null value means that the selected effects were not observed in the study. If an effect was observed than the lowest effect level (LEL: Lowest Dose Any Selected Endpoint is Observed) across the study is displayed.

Search Cri	iteria							
		Additional F	ields	1				
Study Type	CHR ¥	Citation	Admin Method	Legend				
Species Effect Type	rat v Pathology (Neoplastic) v	MRID	Admin Route	Study Type: CHR = Chronic/Can	icer			
Effect Target Effect Description	Liver  Adenocarcinoma	🗹 Year	Start 2	MGR = Multigenerat DEV = Prenatal Dev SLIB = 90, day Sub-	ion Reproductive elopmental hospic			
	Adenoma Adenoma/Carcinoma Combined	Data Usability	Start Unit	ave - so day avoir	and a second sectors			
	Carcinoma Mixed Tumor Malignant	Study Deficiences	End	HDT = Low Dose Te HDT = High Dose Te LEL = Lowest Effect	isted in mgrkg/day ested in mgrkg/day I Level = Lowest Dose Any Selected En	fpoint is Observed		
* Effect Direction	Decrease	Study Type	End Unit	mg/kg/day = Dose in	n milligram per kilogram of body weight	per day		
	By Gender	Guideline No	Duration Comments	M = Male, F = Fernal	ie, m+r = male and remaie			
	By Consultan	Guideline Name	Lot/Batch No	MHID = Master Heco	ord identifier (specific ID to EPA's Office	of Pesocide Progra	ms)	
	Dy Generation	Seasies	Durity	Each chemical/stud	ly displayed has the specific study type	n ToxRefDB. A Blan	k or Null value indicates that the	
	By Endpoint Category	Depected		selected endpoint w	vas not observed in the study			
		Strain	Animal/Dosing Comment:					
earch Clear	Endpoint: CHR   rat   Pathology (Neop	lastic)   Liver   Adenocarcino	ma, Adenoma, Adenoma/Carcir	oma Combined, Carcino	oma, Mixed Tumor Malignant, Neoplast	c nodule   increase	By Gender	
CASRN 42509-80-8	Chemical Isazofos	LDT 0.0050	HDT M 15.0	LEL (mg/kg/day)	F   LEL (mg/kg/day)	Year 1987	Guideline No 870.4300	Guideline Nan Combined chro
127277-53-6	Prohexadione-calcium	18.5	1180.0			1993	870.4300	Combined chro
23031.36.9	Prallethrin	33	103.0			1989	870.4300	toxicity/carcino
Autocal Later at		0.0	100.0			1000	010.4000	toxicity/carcino
<u>96182-53-5</u>	Tebupirimfos	0.06	2.37			1990	870.4300	Combined chron
95737-68-1	Pyriproxyfen	5.42	183.0			1991	870.4300	Combined chro
148477.71.8	Snirodiclofen	20	153.0			1000	870.4300	toxicity/carcino
1404/17/110	opiloticitien	2.0	155.5			1555	0/0.4000	toxicity/carcino
199119-58-9	Trifloxysulfuron-sodium	1.89	500.0			2000	870.4300	Combined chron toxicity/carcino
57966-95-7	Cymoxanil	1.98	126.0			1994	870.4300	Combined chro
50440.000.0	Durimethanil	19	291.0			1993	870 4300	toxicity/carcino
	and the second se					1.775.5	The second second	A A REPORT OF A PROPERTY OF A

In addition to selecting the specific set of endpoints to query, the user can choose to split the endpoint out "By Gender", "By Generation" or "By Endpoint Category". This will independently evaluate the LEL for each gender, generation and endpoint category, or any combination of the three parameters. In the example above, "By Gender" is selected and therefore the LEL (in mg/kg/day) for rat liver tumors is provided for both Male (M) and Female (F). The user can also select "Additional Fields", which provide study-level details for each returned study and include:

<u>Citation</u>: Reference/citation information for the study (primarily pulled directly from the EPA's OPPIN Database)

<u>MRID</u>: Master Record Identifier (specific unique study ID to EPA's Office of Pesticide Programs)

Year: Primarily the year of the final report or publication year

<u>Data Usability</u>: Evaluation criteria of data quality based on study guideline adherence (only Acceptable-Guideline and Acceptable-Non-guideline studies are made public)

<u>Study Deficiencies</u>: Free-text explanation of any study guideline deficiencies or comments regarding the curation of the data into the database

<u>Study Type</u>: Generic study type grouped based on similar guidelines and specific study types

<u>Guideline No</u>: OPPTS Harmonized Health Effects guideline number; although many of the older studies were performed under the older guideline system, each study entered into ToxRefDB is mapped to the new guideline numbers as a unique value for representing study types.

Guideline Name: Study type name associated with the guideline number

Species: Tested species; will be same as the selected value

<u>Strain</u>: Tested strain; due to the difficulty in deriving a unique, non-redundant list of strain that can be easily mapped to legacy data many have been listed as [other] and free-text values are displayed under the "Animal/Dosing Comments"

<u>Admin Method</u>: Dose administration method used in the study, primarily in the feed, water or via gavage

Admin Route: Dose administration route, primarily oral

<u>Start & Start Unit</u>: Time point in which dosing began; for a systemic toxicity study this is usually at time 0, but for developmental studies this is usually on a specific gestation day (GD) and for reproductive study the duration start is indicated by the time-premating.

End & End Unit: Time point in which dosing ends; for a systemic toxicity study this is usually at an absolute time (e.g., 2-years), but for developmental studies this is usually on a specific gestation day (GD) and for reproductive study the duration end is indicated by the last generation (e.g., 2 generation).

<u>Duration Comments</u>: Free-text explanation of any dosing or study duration information that is unable to be captured in other fields

Lot/Batch No: Test material lot and batch number, when provided

Purity: Test material purity

<u>Animal/Dosing Comments</u>: Free-text explanation of strain information or additional explanation of the dosing regimen not captured in the available fields

Once the "Search Criteria" is selected the user can select the "Search" button. While the search is ongoing a "Search In Progress" text will display (Do not continue to hit "Search). To the right of the "Search" and "Clear" buttons, the endpoint criteria will be displayed as shown in the screenshot below. Once the data is returned from the search into the table the user can sort on any field by selecting the column header label. The "arrow" to the right of the column header when 'up' means the data has been sorted in ascending order and when 'down', descending order.

ASRN	Chemical	LDT	HDT	M   LEL(mg/kg/day)	F   LEL(mg/kg/day)	Year	Guideline F
795-39-3	Perfuerooctanesulfonic acid (PFOS), potassium	0.025	1.0	1.0		2002	870.4300
1700.03.C	Chierdana Aachaical	0.045	1.41	1.17		1003	970 4100
702-02-0	arada)	0.045	1.41	1.17		1903	0/0.4100
12.75.6	1 3 Dichloropropene	25	25.0	12.5	25.0	1995	870.4300
The Just of Market	(Telone II)	a	2010	12.0	4,0,0	1,000	0.0.4000
19168-77-3	Tebufenovrad	0.21	17.0	13.4		1992	870 4300
825-26-1	Perfuorooctanoic acid (PEOA) ammonium salt	15.0	15.0	15.0		2001	870.4300
1738.27.3	Diciofoo-methyl	0.23	79.0	25.0	32.0	1996	870.4300
49979.41.9	Terrelovedim	60	273.0	29.0	02.0	1997	970 4300
22.34.9	Similar	0.41	63.1	45.0		1908	870 4300
ABCICLX 90001-301-9	Ovadiation	0.6	193.0	60.9		1981	870 4300
7601.63.4	Lastafan	20	76.0	76.0	75.0	1005	970 4300
7574.68.8	Dimethenamid	51	109.0	00.0	10.0	1990	870.4300
655A AA.D	Instali	27	169.0	136.0		1999	870 4300
104 55 5	Dishlahasi	24	184.0	163.0	194.0	1000	970 4300
0471.44.8	Visciozolio	70	267.0	221.0	104.0	1900	970.4300
1007.001	Asstables	22.0	207.0	221.0		1004	070.4100
11112.20.0	horafidala	22.0	600.0	200.0 600.0	£00.0	1903	970 4300
41112-29-0	Plotte (hourd shift shift	200.0	500.0	500.0	500.0	1995	870.4300
17-81-7	(DEHP)	300.0	600.0	500.0	600.0	1902	870.4300
12697-71-0	Clofencet	4.7	1290.0	909.0		1994	870.4300
36-45-8	2.5-Pyridinedicarboxylic acid, dipropyl ester	65.0	1000.0	1000.0	1000.0	1991	870.4300
2509-80-8	Isazofos	0.0050	15.0			1987	870.4300
27277-53-6	Prohexadione-calcium	18.5	1180.0			1993	870.4300
73031-36-9	Prallethrin	3.3	103.0			1989	870.4300
6182-53-5	Tebupirimfos	0.06	2.37			1990	870.4300
6737-68-1	Pyriproxyfen	5.42	183.0			1991	870.4300
48477-71-8	Spirodiclofen	2.0	153.0			1999	870.4300
199119-58-9	Trifloxysulfuron-sodium	1.89	500.0			2000	870.4300
7966-95-7	Cymoxaril	1.98	126.0			1994	870.4300
3112-28-8	Pyrimethanil	1.3	291.0			1993	870.4300
61050-58-4	Methoxylenozide	10.0	1350.0			1998	870.4300
19515-38-7	lcaridin	50.0	200.0			1996	870.4300
8587-05-0	Hexythiazox	3.0	207.0			1985	870.4300
7-71-4	2,4-imidazolidinedione, 5.5-dimethyl-	100.0	1000.0			1994	870.4300
7-71-4	2,4-imidazolidinedione, 5.5-dimethyl-	100.0	1000.0			1996	870.4300
22224-92-6	Fenamiphos	0.098	3.36			1986	870.4300
22-39-4	Diphenylamine	7.5	302.0			1994	870.4300
8967-40-9	Flumetsulam	100.0	1000.0			1991	870.4300
9607-70-2	Acetic scid, ((5-chloro- 8-quinolinyf)oxy)-,	0.36	81.5			1992	870.4300

The hyperlinked CAS numbers allow the user to go directly to the "Generic Chemical" page and look in more detail at the effects and additional data on the chemical. As with other section of ACToR and ToxRefDB, if the user would like to return to the "Search By Endpoint" page with returned search information use the "Search By Endpoint" link on the sidebar and do NOT press the back button.

# Glossary

# Active ingredients

An active ingredient is a substance in a drug which has some pharmaceutical or pesticide values. This is the opposite for inactive ingredients, which are only carriers that allow that body to processes the active ingredients better.

# ACToR

(Aggregated Computational Toxicology Resource) is a collection of databases collated or developed by the EPA National Center for Computational Toxicology

# Assay

An assay is a collection of data for substances from one data collection. Currently, an assay can be thought of a simple table. An assay falls into one data type category but may have multiple phenotypes. An assay can have more than one row or entry for the same substance, and elements in the data matrix can be empty.

# Assay category

Assays are organized into a number of categories that describe the broad type of data presented. Several of these categories describe the level of biological organization being probed, while others describe the class of information being presented. The current sets of categories are:

**PhysicoChemical**- physical and chemical properties (in vitro and/or in silico) **Biochemical**- chemical processes in living organisms that are non-cell based **Genomics**- gene expression values or signatures **Cellular**- cell-based assay **Tissue**- tissue slice assay **Organ**- focus on organs **Organism**- focus on organisms (animal testing) In vivo toxicology (tabular primary)- tabulated results from primary animalbased studies of chemical effects In vivo toxicology (study listing primary)- primary studies are available but have not been tabulated In vivo toxicology (tabular secondary)-tabulated data from secondary sources for in vivo toxicology studies **In vivo toxicology (summary calls)**- derived summary determinations of risk In vivo toxicology (summary report via URL)- links to text reports on the web for which specific data values are not directly accessible in tabular form General Descriptive information- a brief description of the chemical **Regulation**- listings of chemicals that fall under specific environmental laws, government mandates, or standards

# **Chemical Category**

Chemical category is a listing of structural or uses categories, often intended for prioritization efforts

<u>Chemical Summary URL</u>- link to chemical summaries <u>Chemical Use Level</u>- the amount of chemicals produced or used <u>Pesticidal mode of action (MoA)</u>- explains how to drug or pesticide works and what the chemical targets

## Assay component

An assay component defines one column or element of an assay. A component has a unique ID, a name, a description, a data type, and optionally units.

# Assay phenotype

Some assays are characterized by toxicology phenotypes. This allows one to organize the data in ACToR into broad toxicity areas. The current set of phenotypes are:

Hazard – Information on basic harm that can be caused by a chemical.

Information under this category includes workplaces safety and first aid in case of exposure.

<u>Acute Toxicity</u> – Information on health effects due to short term exposure. <u>Subchronic Toxicity</u> - Information on health effects due to intermediate term exposure.

<u>Chronic Toxicity</u> - Information on health effects due to long term exposure. <u>Carcinogenicity</u> – Information from studies of cancer-causing ability of chemicals.

<u>Genetic Toxicity</u>- Information on the ability of chemicals to cause DNA damage. <u>Reproductive Toxicity</u>- Information on the ability of a chemical to damage an organism's reproductive ability.

<u>Neurotoxicity</u> - Information on the ability of a chemical to damage nerve cells or tissues.

**Developmental Neurotoxicity** – Information on chemicals that cause neurological deficits during development

**Immunotoxicity** - determines how a chemical affects the immune system

**Dermal Toxicity**- includes studies about chemicals and what level of toxicity results from the substances being applied through the skin. May or may not have the skin as a target organ.

<u>**Respiratory Toxicity-**</u> contains data on how the chemicals that affect the respiratory system

<u>Nephrotoxicity</u>- measures to what degree that the chemical that affect the kidneys

**Endocrine**- contains data about if and how the chemical affect hormone signaling and downstream processes

<u>Cardiotoxicity-</u> contains data bout how the chemical affects the heart

**Ecotoxicity-** includes data about how chemicals affect non-human species such as fish and amphibians

<u>Food Safety</u>- includes data that determines if the food can be safely used as an ingredient, additive or food wrapper <u>Toxicity other</u>- contains other information about a chemical's toxicity <u>PK/metabolism</u>- Information on pharmacokinetics and metabolism of xenobiotic chemicals

#### Assay result

An assay result is one data point for a single substance and a single assay component.

#### Assay types

There are two main types of assays: phenotypes and categories.

## CAS

CAS (Chemical Abstract Services) Registry Number (for more information)

Some examples of number in CAS format are: 7439-92-1 7440-50-8 79-34-5 59325 39001-02-0 59001050

# Chemical

A chemical is defined by a unique chemical ID in the database and can be either a substance or a compound.

## **Chemical structure**

Diagram of a chemical- can be used to search for information about chemicals.

# Compound

A compound is an entity with a chemical ID and chemical structure information, which may be a 2 or 3 dimensional molfile or a string representation. This can be SMILES or InCHII.

## Data collection

A data collection is at minimum a set of substances with corresponding CAS registry numbers and names. Additional information may include chemical structures and assays. As mentioned above, a <u>generic chemical</u> links together data from many <u>data collections</u> on all <u>substances</u> that share a common <u>CAS</u> registry number. All data is initially compiled as part of a set of Data Collections.

# Exposure data

Exposure studies, measure the amount of a substance that people and animals are exposed to. This data does not explain how the person was exposed to it or if it causes health problems.

## Generic chemical

A generic chemical aggregates all data from all data collections for substances with a single given CAS number. It will have links to one or more substances and all of their related assay data, as well as all synonyms derived from the substances.

# HPV and MPV

HPV stands for High Production Volume industrial chemicals and MPV for Medium Production Volume industrial chemicals

Includes the chemical structure and calculated physical chemical properties of compounds produced or imported into the United States

# InCHI

The IUPAC International Chemical Identifier (InChI<sup>TM</sup>) is a non-proprietary identifier for chemical substances (for more information).

# Inert ingredient

An inert ingredient means any substance other than an active ingredient. Inert ingredients tend to be carriers for the active ingredients. (<u>for more information</u>)

# In vitro

An experiment that is performed outside of a living organisms (for examples test tubes)

# In vivo

Experimentation done on or inside of living organisms- other wise known as animal testing

# MESH

is the U.S. National Library of Medicine's controlled vocabulary used for indexing articles for MEDLINE/ PubMed. MESH terminology provides a consistent way to retrieve information that may use different terminology for the same concepts.

# SMILES

SMILES (Simplified Molecular Input Line Entry System) is a *line notation* (a typographical method using printable characters) for entering and representing molecules and reactions. (for more information)

## Substance

A substance is an entity with a chemical ID, one or more names (including a CAS number) and potentially a URL pointing to primary data. One special name for the substance is the "source name sid" which is a unique alphanumeric label from the source, which allows a unique link back to the source.

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