Chemical-disease inference using Comparative Toxicogenomics Database

童俊維

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Genomics data grows

Where are the data?

- Literatures
  - Chemical A interacts with gene G
  - Chemical A affects the expression of gene G
  - Chemical A increases the expression of gene G
  - Chemical A decreases the expression of gene G
  - Chemical A is associated with disease D
  - etc.

Where are the data?

- Databases
  - Pathway database
    - Chemicals (A, B, C, ...) and genes (G, H, I, ...) are in the same pathway

  - Disease database
    - Genes (A, B, C, ...) are associated with the disease D

  - Gene Ontology database
    - Genes (A, B, C, ...) are associated with the function F

  - Drug database
    - Genes (A, B, C, ...) are targets of drug X

All those data are stored in different ways
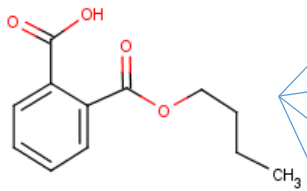
THRB (literature A, Rat)

AR (literature B, Human)

PPARA (Literature C, Human and Rat)

.

.

.

RBMX (Database D)

Kidney Disease

Carcinoma

PPAR signaling pathway

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.

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Fatty acid metabolic process

OMIM

KEGG REACTOME

Chemical

Gene

Function and Disease

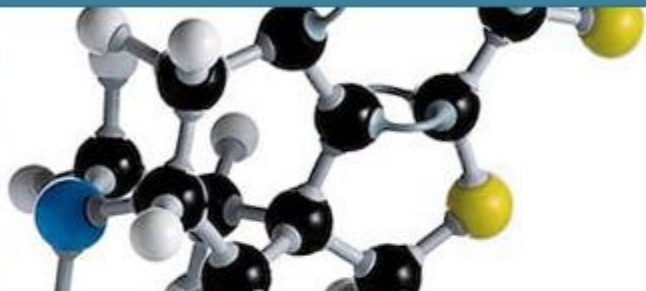# How to integrate these information?

- Manually check each interacting genes and find associated diseases
  - Requiring professional skills
  - Difficult to infer the global influence of a chemical

- A curated database built by expert curators will be valuable!!
  - The global influence can be inferred by statistical methods
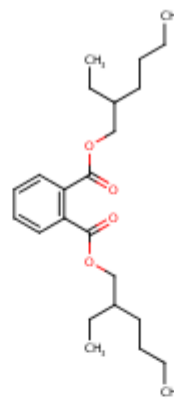 - Comparative Toxicogenomics Database (CTD)

CLICK TO HIDE

Diethylhexyl Phthalate

CASRN: 117-81-7

FULL RECORD DISPLAY

Displays all fields in the record.

For other data, click on the Table of Contents

Substance Identification:

Chemical Name:

Diethylhexyl Phthalate

CAS Registry Number:

117-81-7

Genetic Information:

Related Genes:

Gene: ABCA1 [Link to main CTD database]

Organism: Mus musculus

Interaction Type: affects cotreatment | increases expression | increases reaction

Interaction: [Tetrachlorodibenzodioxin co-treated with bisphenol A co-treated with 2,4,5,2',4',5'-hexachlorobiphenyl co-treated with Diethylhexyl Phthalate] promotes the reaction [Dietary Fats results in increased expression of ABCA1 mRNA]

Synonyms: ABC1 | ABC-1 | ATP-binding cassette 1 | ATP-binding cassette, subfamily A (ABC1), member 1 | ATP-binding cassette sub-family A member 1 | ATP-binding cassette, sub-family A member 1 | ATP-binding cassette transporter | ATP-binding cassette transporter 1 | ATP-binding cassette transporter A1 | BOS_9308 | CERP | cholesterol efflux regulatory protein | HDLDT1 | membrane-bound | RP23-95M14.8 | TGD

PubMed References: (1)23756648

Gene: ABCA2 [Link to main CTD database]

Organism: Mus musculus

Interaction Type: decreases expression

Interaction: Diethylhexyl Phthalate results in decreased expression of ABCA2 mRNA

Synonyms: Abc2 | ATP-binding cassette 2 | ATP-binding cassette, subfamily A (ABC1), member 2 | ATP-binding cassette sub-family A member 2 | ATP-binding cassette, sub-family A, member 2 | ATP-binding cassette transporter 2 | BOS_12279 | D2H0S1474E | DKEY-266H7.1 | RP11-229P13.8 | RP23-47P18.8

PubMed References: (1)19850644

Comparative Toxicogenomics Database (CTD)

- A freely available database that is dedicated to promoting the exploration and development of testable hypotheses about the effects of the environment on human health

- Manually curated and cross-species information

- http://ctdbase.org/

- Davis et al. (2013) Nucleic Acids Res.

ctd™
Giving insight into how chemicals affect our health.
Comparative Toxicogenomics Database
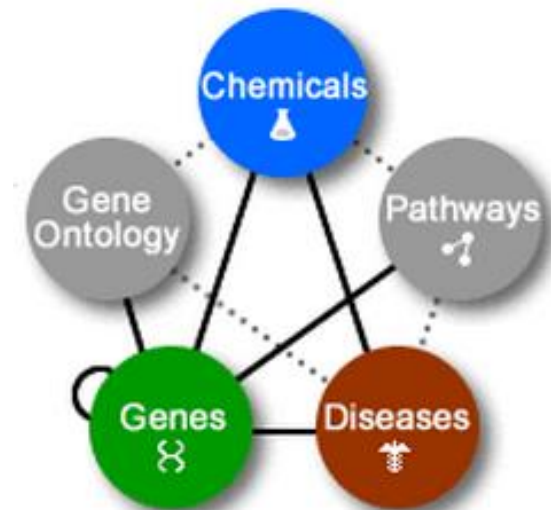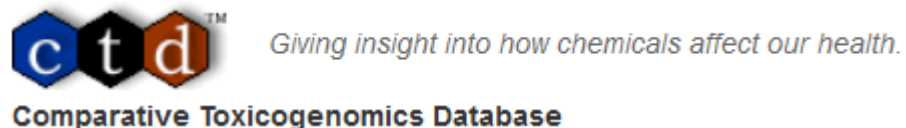
Data curation and integration
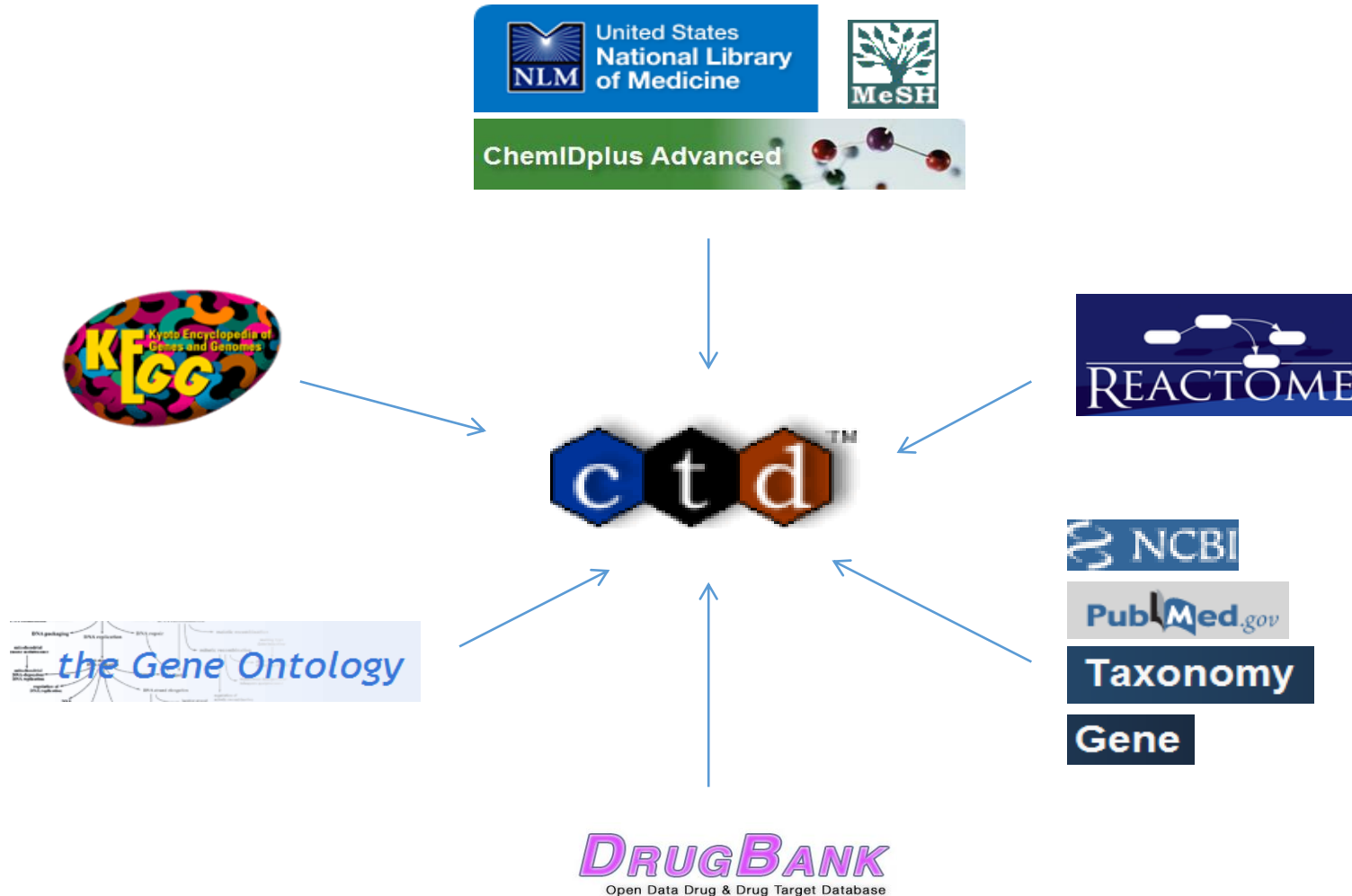
Data Status: 八月 2014

These statistics reflect our latest monthly data release.

Chemical–gene interactions (curated)	1,002,333
Unique chemicals	10,766
Unique genes	35,399
Unique organisms	521
Gene–disease associations	15,307,651
Curated[1]	29,717
Unique genes	7,480
Unique diseases	4,924
Inferred[2]	15,277,934
Unique genes	35,236
Unique diseases	3,007
Chemical–disease associations	1,663,911
Curated[1]	192,164
Unique chemicals	8,537
Unique diseases	3,056
Inferred[2]	1,471,747
Unique chemicals	10,501
Unique diseases	4,206

Chemical–GO associations (enriched)	3,393,110
Chemical–pathway associations (enriched)	264,254
Disease–pathway associations (inferred)	55,564
Gene–gene interactions	287,678
Gene–GO annotations	1,080,513
Gene–pathway annotations	63,623
GO–disease associations (inferred)	651,223
Chemicals with curated data	13,607
Diseases with curated data	6,351
Via OMIM curation	3,426
Genes with curated data	36,489
Via OMIM curation	3,425
Curated references	110,142

Phthalates

- Phthalates are a group of similar diesters of phthalic acid used as plasticizers to soften and increase the flexibility in polyvinyl chloride (PVC) plastics

- Since phthalates are not covalently bound to plastics, they can leach into the surrounding environment

- Human exposure to phthalates mainly occurs through foods, because of the use of PVC in wrapping materials and food processing

- Phthalates are also found in meat, fish, milk products, and other foods with a high fat content

Singh and Li (2011) Genomics

Inferring human diseases

- There is sufficient evidence in rodents that phthalate exposure causes developmental and reproductive toxicity
  - but not yet in humans
- The Comparative Toxicogenomics Database has been established to analyze the impact of environmental chemicals on human health
- The top three phthalate toxicity categories were found to be cardiotoxicity, hepatotoxicity and nephrotoxicity, and the top 20 diseases included cardiovascular, liver, urologic, endocrine and genital diseases

Singh and Li (2011) Genomics

c t d ™

Illuminating how chemicals affect human health.

Comparative Toxicogenomics Database

Connect. Compare.

CTD illuminates how environmental chemicals affect human health. *More...*

Discover.

1. What human diseases are associated with a gene/protein? (Example)
2. What human diseases are associated with a chemical? (Example)
3. What genes/proteins interact with a chemical? (Example)
4. What chemicals interact with a gene/protein? (Example)
5. What references report a chemical–gene/protein interaction? (Example)
6. What cellular functions (GO terms) are affected by a chemical? (Example)

News
▸ *2014年8月11日*
New data available!

▸ *All changes...*

Subscribe to CTD's mailing list
[Email address] [Subscribe]

Our Latest Publication
▸ Davis AP, Wiegers TC, Roberts PM, King BL, Lay JM, Lennon-Hopkins K, Sciaky D, Johnson R, Keating H, Greene N, Hernandez R, McConnell KJ, Enayetallah AE, Mattingly CJ.
A CTD-Pfizer collaboration: manual curation of 88,000 scientific articles text mined

23,769,860 *TOXICOGENOMIC RELATIONSHIPS!*

Keyword Search

All ▾

DEHP ✕

[Search] ? *Advanced searches*

▾ 🧪 **Updated Chemicals**

2,2',4,4'-tetrabromodiphenyl ether Acrolein
Benzo(a)pyrene bisphenol A
decabromobiphenyl ether
Dermatophagoides pteronyssinus antigen p 1 Cisplatin
Dietary Fats enterotoxin B, staphylococcal Erythromycin
Estolate Ethanol furan Isoproterenol
lipopolysaccharide, E coli O55-B5 Lipopolysaccharides
Lutein myristicin Nanotubes, Carbon Nitrogen Dioxide
Particulate Matter Plant Extracts Soot
Tetrachlorodibenzodioxin tris(2-butoxyethyl) phosphate
Vehicle Emissions

▸ 🜋 **Updated Diseases**

▸ 🧬 **Updated Genes**

🔍 Keyword Query

140 items matched your keywords:

🧪 **Chemicals**	**2**
⚕ Diseases	0
🧬 Genes	0
GO **GO Terms**	**1**
🧫 Organisms	0
⚙ Pathways	0
📋 **References**	**137**

2 results.

	🔀 ⚕	**Chemical**
1.	⚕	4-hydroperoxydechlorocyclophosphamide [Equivalent Term: <mark>DEHP-CP</mark>]
2.	🔀 ⚕	Diethylhexyl Phthalate [Equivalent Term: <mark>DEHP</mark>]

2 results.

Download: ✅ **CSV** | 📊 **Excel** | ◇ **XML** | 📋 **TSV**

Basics	**Gene Interactions**	**Genes**	**Diseases**	**Comps**	**Pathways**	**GO**	**References**

Name ?	**Diethylhexyl Phthalate**
CAS Type 1 Name ?	1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester
Equivalent Terms ?	Bis(2-ethylhexyl)phthalate | DEHP | Di 2 Ethylhexylphthalate | Di-2-Ethylhexylphthalate | Dioctyl Phthalate | Phthalate, Diethylhexyl | Phthalate, Dioctyl
CAS Registry Number ?	117-81-7
Definition ?	An ester of phthalic acid. It appears as a light-colored, odorless liquid and is used as a plasticizer for many resins and elastomers.
Structure ?	
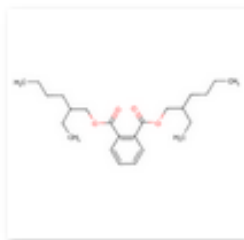
Top Interacting Genes ?

PPARA
PPARG
CYP3A4
NR1I2
CYP19A1
STAR
CASP3
MMP2
AKT1
CAT

MeSH® ID ?	D004051
External Links	*CCRIS* ?
	117-81-7

Ancestors ? — Top ↑

Chemicals ← Organic Chemicals ⚕ ← Carboxylic Acids ⚕ ← Acids, Carbocyclic ⚕ ← Phthalic Acids ⚕ ← *Diethylhexyl Phthalate* ⚕

Descendants ? analogs & derivatives — Top ↑

Diethylhexyl Phthalate ⚕

DAF-789

metaplast

mono-(2-ethylhexyl)phthalate ⚕

	Interacting Gene	Interactions	Organisms
1.	PPARA	514	4
2.	PPARG	28	4
3.	CYP3A4	21	3
4.	NR1I2	20	5
5.	CYP19A1	18	3
6.	STAR	16	3
7.	CASP3	14	2
8.	MMP2	14	2
9.	AKT1	13	3
10.	CAT	11	3
11.	TIMP2	11	3
12.	CYP4A14	10	1
13.	INSL3	10	2
14.	NR1I3	10	3
15.	ESR1	9	3
16.	CYP11A1	8	2
17.	CYP2C9	8	1
18.	FSHB	8	4
19.	VIM	8	2
20.	ACOX1	7	2

1–50 of 3,119 results.

◀ First ◀ Previous 1 2 3 4 5 6 7 8 ▶ Next ▶ Last

	Interacting Chemical	Interacting Gene	Interaction	References	Organisms
1.	Diethylhexyl Phthalate	ABCA1	[Tetrachlorodibenzodioxin co-treated with bisphenol A co-treated with 2,4,5,2',4',5'-hexachlorobiphenyl co-treated with Diethylhexyl Phthalate] promotes the reaction [Dietary Fats results in increased expression of ABCA1 mRNA]	1	1
2.	mono-(2-ethylhexyl)phthalate	ABCA12	mono-(2-ethylhexyl)phthalate results in increased expression of ABCA12 mRNA	1	1
3.	Diethylhexyl Phthalate	ABCA2	Diethylhexyl Phthalate results in decreased expression of ABCA2 mRNA	1	1
4.	Diethylhexyl Phthalate	ABCA2	PPARA protein promotes the reaction [Diethylhexyl Phthalate results in decreased expression of ABCA2 mRNA]	1	1
5.	mono-(2-ethylhexyl)phthalate	ABCA4	mono-(2-ethylhexyl)phthalate results in increased expression of ABCA4 mRNA	1	1
6.	mono-(2-ethylhexyl)phthalate	ABCA7	mono-(2-ethylhexyl)phthalate results in decreased expression of ABCA7 mRNA	1	1
7.	Diethylhexyl Phthalate	ABCB1	Diethylhexyl Phthalate promotes the reaction [NR1I2 protein results in increased expression of ABCB1 mRNA]	1	1
8.	Diethylhexyl Phthalate	ABCB1	Diethylhexyl Phthalate results in increased expression of ABCB1 mRNA	1	1
9.	Diethylhexyl Phthalate	ABCB11	Diethylhexyl Phthalate results in decreased expression of ABCB11 mRNA	1	1

1–50 of 3,119 results.

◀ First ◀ Previous 1 2 3 4 5 6 7 8 ▶ Next ▶ Last

Download: ⤵ CSV | ⊞ Excel | ⟨⟩ XML | 🔖 TSV

- Reference and Organisms

[Tetrachlorodibenzodioxin co-treated with bisphenol A co-treated with 2,4,5,2',4',5'-hexachlorobiphenyl co-treated with Diethylhexyl Phthalate] promotes the reaction [Dietary Fats results in increased expression of ABCA1 mRNA]

✓	Reference	Organisms
1. ✓	Naville D, et al. Low-dose food contaminants trigger sex-specific, hepatic metabolic changes in the progeny of obese mice. FASEB J. 2013 Sep;27(9):3860-70.	Mus musculus

Diethylhexyl Phthalate results in increased expression of ACADVL mRNA

1–3 of 3 results.

✓	Reference	Organisms
1. ✓	Posnack NG, et al. Phthalate exposure changes the metabolic profile of cardiac muscle cells. Environ Health Perspect. 2012 Sep;120(9):1243-51.	Rattus norvegicus
2. ✓	Hayashi Y, et al. Hepatic peroxisome proliferator-activated receptor α may have an important role in the toxic effects of di(2-ethylhexyl)phthalate on offspring of mice. Toxicology. 2011 Oct 28;289(1):1-10.	Homo sapiens
3. ✓	Ren H, et al. Characterization of peroxisome proliferator-activated receptor alpha--independent effects of PPARalpha activators in the rodent liver: di-(2-ethylhexyl) phthalate also activates the constitutive-activated receptor. Toxicol Sci. 2010 Jan;113(1):45-59.	Mus musculus

Chemical-disease inference
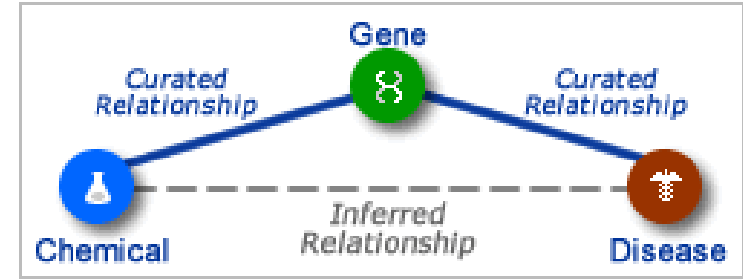
Creating inferred chemical-disease relationships.

Chemical-gene interactions	Gene-disease associations		Inference score
THRB	Kidney Disease		2.28
AR	Hypertension		16.21
PPARA	Carcinoma, Hepatocellular		63.70
.	.		.
.	.		.
.	.		.
TGFB1	Fatty liver		14.04

Chemical → Gene → Disease

| Basics | Gene Interactions | Genes | **Diseases** | Comps | Pathways | GO | References |

❓

These diseases are associated with *Diethylhexyl Phthalate* or its descendants. Each association is *curated* (M *marker/mechanism* and/or T *therapeutic*) and/or *inferred* (via a curated gene interaction).

Disease categories [Show chart]
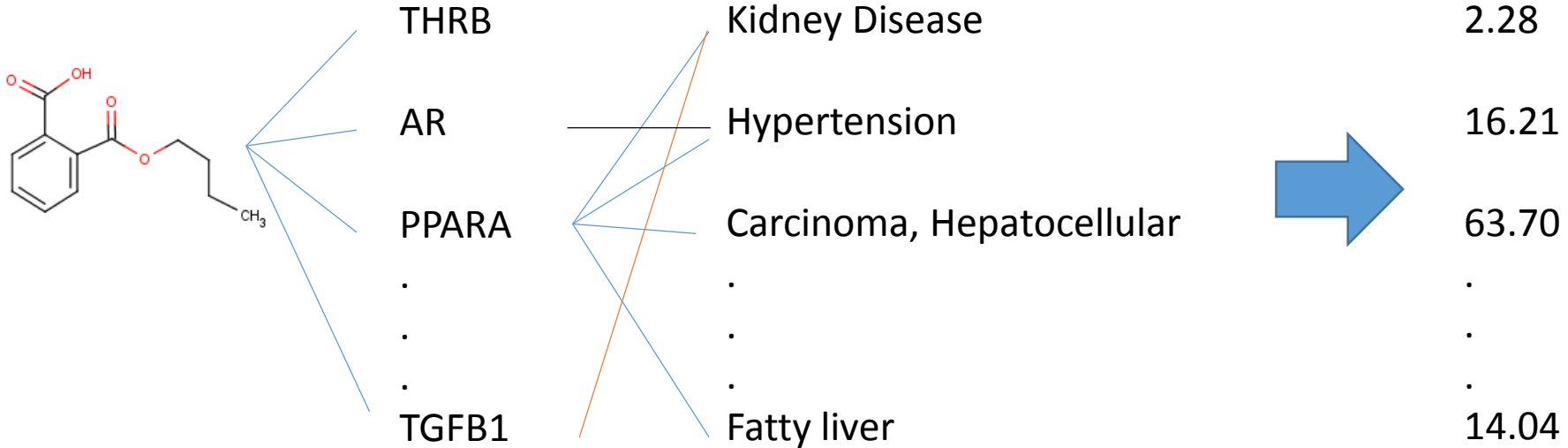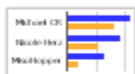

Filter by

Disease category
ALL ▼

Association type
ALL ▼

Filter

1–50 of 2,073 results.

|◄ First | ◄ Previous | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | ► Next | ►| Last

	Chemical	Disease	Direct Evidence	Enrichment Analysis	Inference Network	Inference Score	References
1.	Diethylhexyl Phthalate	Carcinoma, Hepatocellular	M	🔱 GO 🔵	❄ *59 genes:* ABCB1 | ABCB4 | ACLY | ACOX1 | ACTB | AFP | AR | ATP5H | C9 | CASP8 | CCNA1 | CCND1 | CD276 | CEBPA | CTNNB1 | CXCL8 |	63.70	45
48.	Diethylhexyl Phthalate	Weight Loss	T		*1 gene:* ADIPOQ	4.20	2
50.	Diethylhexyl Phthalate	Diabetes Mellitus, Experimental		🔱 GO 🔵	❄ *53 genes:* ACOT1 | ACOX1 | ACSL1 | ADRA1A | AGT | ATF3 | ATP2A2 | BAX | BCL2 | CAT | CHRM2 | CPT1A | CPT1B | CYP1A1 | CYP2B10 | CYP2B9 | CYP3A11 | CYP4A10 | CYP4A14 | EDN1 | ESRRA | FAS | FGF21 | GCK | GPX1 | HMOX1 | HSD11B1 | ID1 | IFNG | INS1 | INSR | IRS1 | MMP2 | MMP9 | NQO1 | PCK1 | PDK4 | PKLR | PPARA | PPARG | PPARGC1A | REN | SLC2A2 | SLC2A4 | SOD1 | SOD2 | SREBF1 | TGFB1 | TIMP2 | TNF | TRP53 | UCP2 | VEGFA	90.46	37

🔵 Diethylhexyl Phthalate ↔ 🔵 Weight Loss

This chemical–disease association may be inferred in part via curated interactions between *Diethylhexyl Phthalate* and any genes listed below, and a curated association between those genes and *Weight Loss*.

		Association type			
Filter by	ALL ▼	Filter			

1–2 of 2 results.

	✔	Reference		Association
1.	✔	Madsen EL, et al. Weight loss larger than 10% is needed for general improvement of levels of circulating adiponectin and markers of inflammation in obese subjects: a 3-year weight loss study. Eur J Endocrinol. 2008 Feb;158(2):179-87.		*Inferred via 1 gene:* ADIPOQ
2.	✔	Tomaszewski KE, et al. Modulation of 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicity in F344 rats by di(2-ethylhexyl)phthalate. Chem Biol Interact. 1988;65(3):205-22.		**T**

Modulation of 2,3,7,8-tetrachlorodibenzo-p-dioxin toxicity in F344 rats by di(2-ethylhexyl)phthalate.

Basics | Chemical–Gene Interactions | Gene–Gene Interactions | **Diseases**

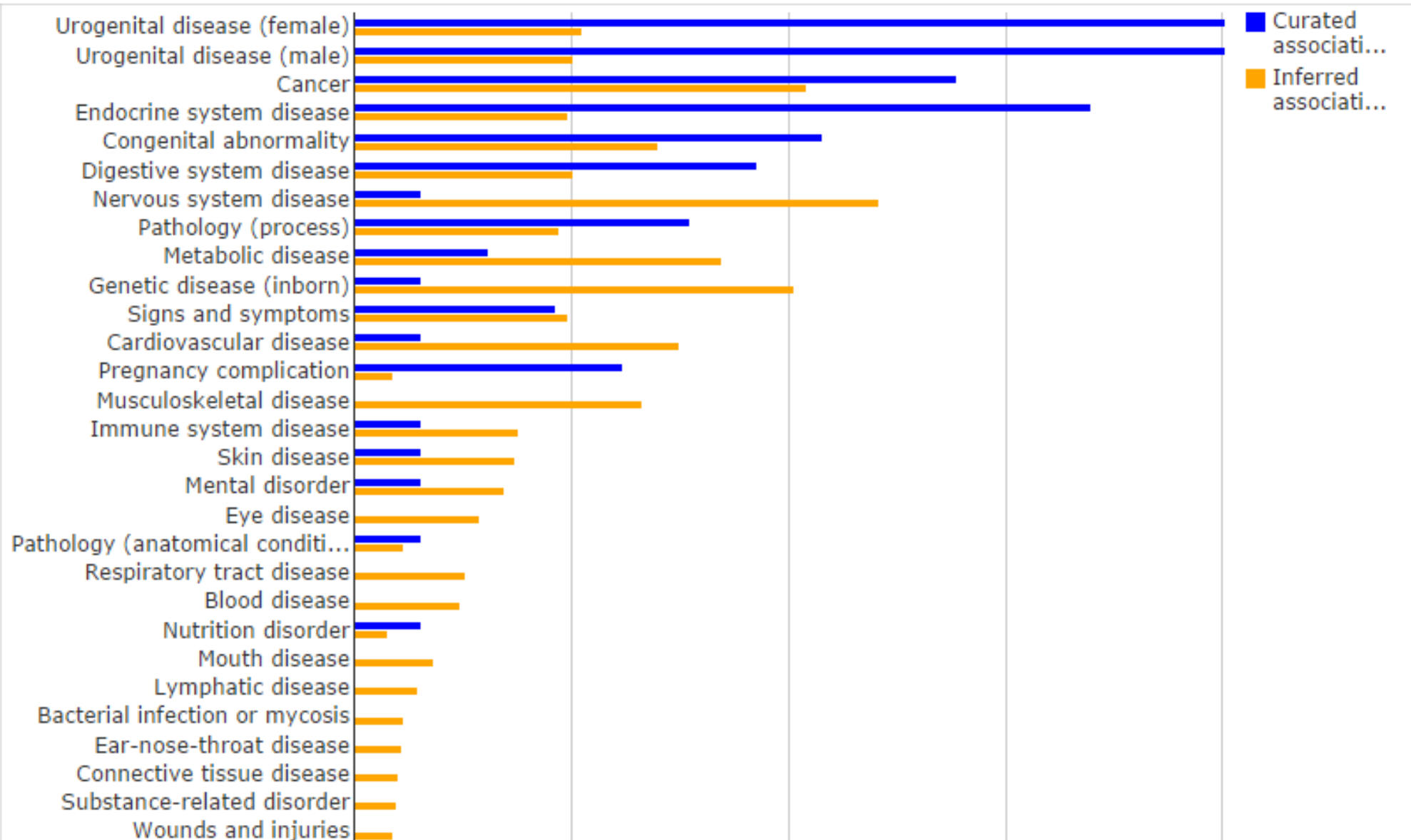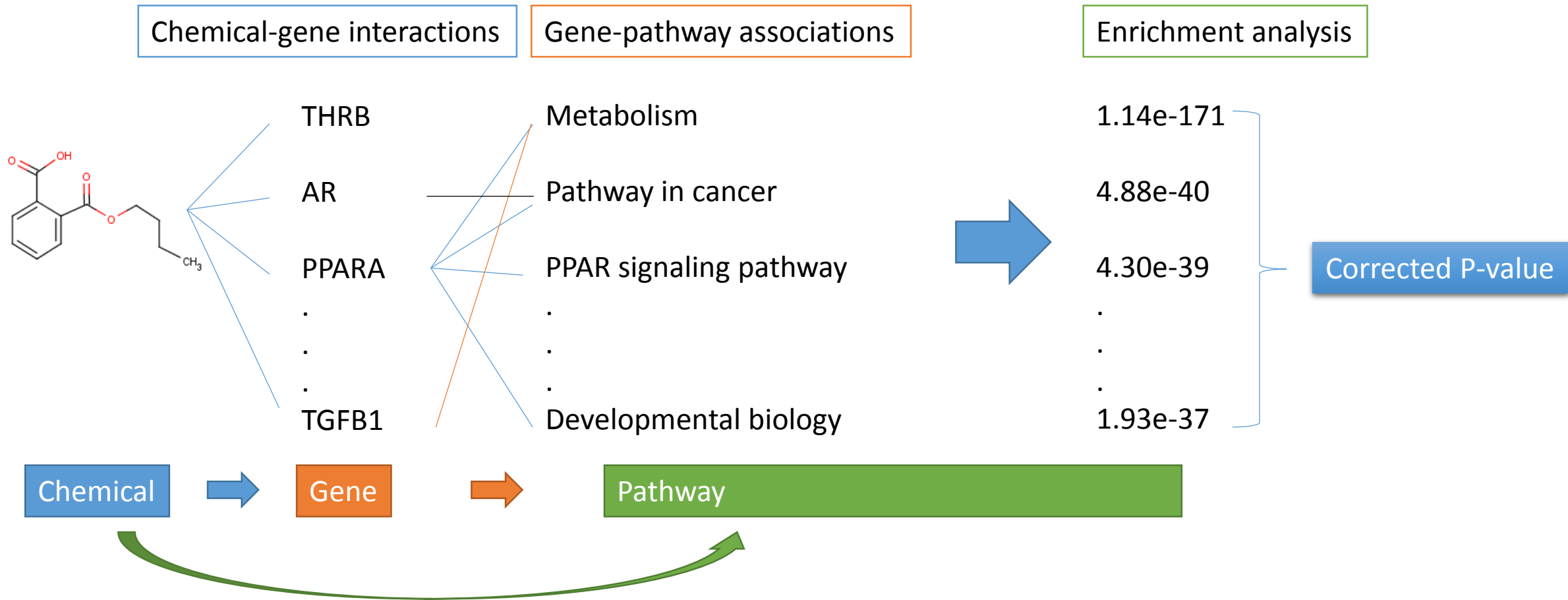|	
Authors ?	Tomaszewski KE, Montgomery CA, Melnick RL.
Institution ?	National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709.
Citation ?	Chem Biol Interact. 1988;65(3):205-22.
PubMed® ID ?	3378278
Review Status ?	✓ Curated.
Abstract ?	The effects of cotreatment with a hyperlipidemic chemical, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), and a hypolipidemic agent, di(2-ethylhexyl)-phthalate (DEHP), on lipid metabolism and toxicologic responses were studied in F344 rats. Treatment with TCDD alone (160 micrograms/kg) caused an increase in serum triglycerides and cholesterol while treatment with DEHP alone (2 g/kg/day) caused a decrease in triglycerides and cholesterol versus untreated controls. When administered before or after TCDD, DEHP caused a decrease in TCDD-induced hyperlipidemia. This change was attributed to enhanced hepatic peroxisomal beta-oxidation and decreased hepatic lipid synthesis resulting from treatment with DEHP. TCDD treatment produced a fatty liver, as determined by gravimetric analysis of extracted lipid and microscopic examination of liver sections which revealed extensive cytoplasmic vacuolization that stained positive with Oil Red 0, but did not induce peroxisomal beta-oxidation. Thus, an increase in hepatic or serum lipid levels is not sufficient for induction of peroxisome proliferation. Neither TCDD nor DEHP treatment affected mitochondrial beta-oxidation. Pretreatment of rats with DEHP, followed by daily exposure to this hypolipidemic agent after treatment with TCDD, had a partial protective effect against TCDD-induced fatty liver, body weight loss and mortality. Microscopic examination of liver sections confirmed the suppression of TCDD-induced fatty liver by pretreatment with DEHP. When DEHP treatment was initiated after the TCDD dose, there was less protection against the above parameters of TCDD toxicity. This study demonstrates that TCDD-induced fatty liver, hyperlipidemia and mortality can be antagonized by treatment with a hypolipidemic agent such as DEHP.

Disease categories [Hide chart]

Legend:
- ■ Curated associati…
- ■ Inferred associati…

Categories (top to bottom):
- Urogenital disease (female)
- Urogenital disease (male)
- Cancer
- Endocrine system disease
- Congenital abnormality
- Digestive system disease
- Nervous system disease
- Pathology (process)
- Metabolic disease
- Genetic disease (inborn)
- Signs and symptoms
- Cardiovascular disease
- Pregnancy complication
- Musculoskeletal disease
- Immune system disease
- Skin disease
- Mental disorder
- Eye disease
- Pathology (anatomical conditi…
- Respiratory tract disease
- Blood disease
- Nutrition disorder
- Mouth disease
- Lymphatic disease
- Bacterial infection or mycosis
- Ear-nose-throat disease
- Connective tissue disease
- Substance-related disorder
- Wounds and injuries

Chemical-pathway inference

These pathways are **enriched** significantly among genes that interact with *Diethylhexyl Phthalate* or its descendants. We show only terms with a corrected p-value <0.01.

1–50 of 166 results.

Pathway	Pathway ID	P-value	Corrected P-value	Annotated Genes	Genome Frequency
1. Metabolism	REACT:111217	4.21e-174	1.14e-171	295	1497/36904 genes: 4.06%
2. Metabolic pathways	KEGG:01100	5.18e-89	1.40e-86	189	1218/36904 genes: 3.30%
3. Disease	REACT:116125	2.45e-60	6.62e-58	156	1232/36904 genes: 3.34%
4. Immune System	REACT:6900	7.41e-60	2.00e-57	150	1146/36904 genes: 3.11%
5. Signal Transduction	REACT:111102	1.48e-57	4.00e-55	191	1916/36904 genes: 5.19%
6. Pathways in cancer	KEGG:05200	1.81e-42	4.88e-40	71	334/36904 genes: 0.91%
7. PPAR signaling pathway	KEGG:03320	1.59e-41	4.30e-39	39	74/36904 genes: 0.20%

Diethylhexyl Phthalate → PPAR signaling pathway Enrichment

Diethylhexyl Phthalate (or a descendant) interacts with these genes, which are associated with the enriched pathway, *PPAR signaling pathway*.

1–39 of 39 results.

	Gene
1.	ACADL
2.	ACADM
3.	ACOX1
4.	ACSL1
5.	ACSL3

Chemical-GO term inference
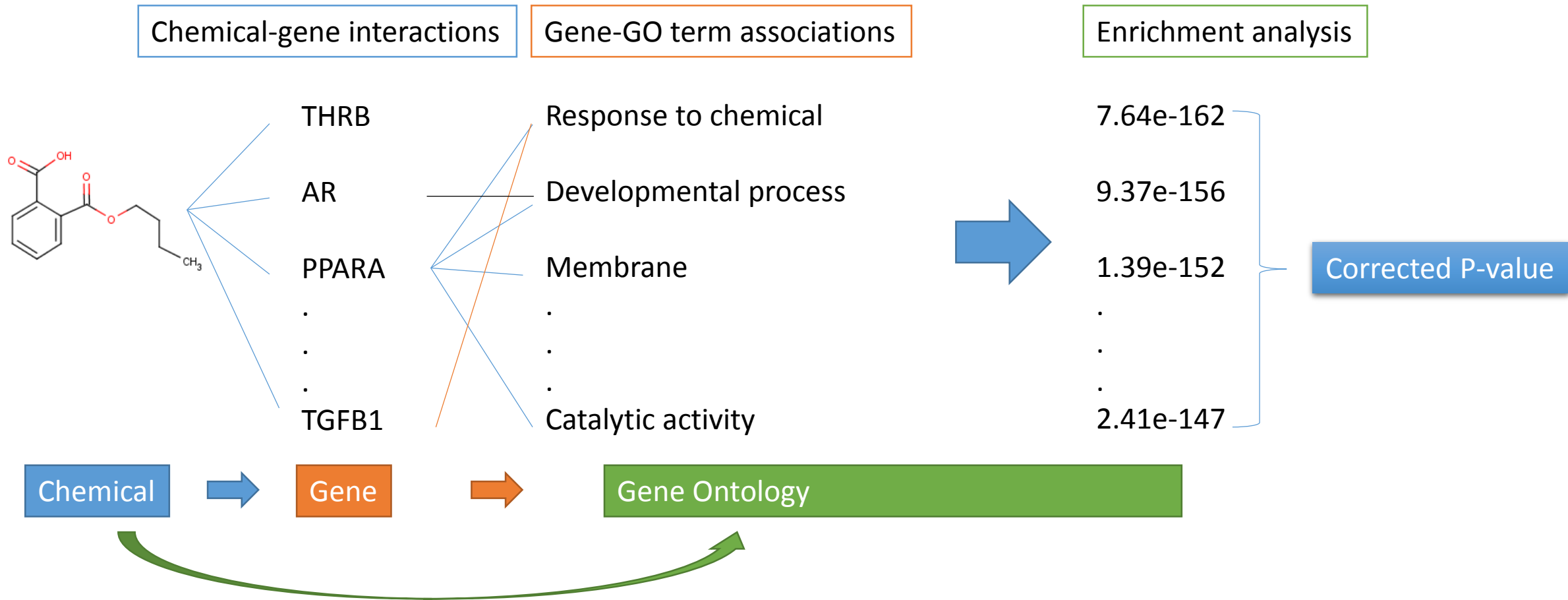
Gene Ontology (GO) terms

- The Gene Ontology project provides a controlled vocabulary of terms for describing gene product characteristics and gene product annotation data

- Many of genes/proteins have Gene Ontology (GO) annotations that provide information about their associated **biological processes**, **molecular functions**, and **cellular components**

- The significance of enrichment was calculated by the hypergeometric distribution and adjusted for multiple testing using the Bonferroni method

- http://geneontology.org/

These GO terms are **enriched** significantly among genes that interact with *Diethylhexyl Phthalate* or its descendants. We show only terms with a corrected p-value <0.01.

Filter by | Ontology: ALL ▼ | Highest GO level: 1 ▼ | Filter

1–50 of 2,050 results.

|◀ First | ◀ Previous | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | ▶ Next | ▶| Last

	Ontology	Highest GO Level	GO Term	P-value	Corrected P-value	Annotated Genes	Genome Frequency
1.	BP	1	cellular process	0	0	1,278	13978/36904 genes: 37.88%
2.	BP	2	single-organism cellular process	0	0	1,165	11359/36904 genes: 30.78%
3.	BP	1	single-organism process	0	0	1,256	12672/36904 genes: 34.34%
4.	CC	1	cell	0	0	1,295	14909/36904 genes: 40.40%
5.	CC	1	cell part	0	0	1,295	14907/36904 genes: 40.39%
6.	BP	1	metabolic process	4.65e-306	4.85e-302	1,114	11072/36904 genes: 30.00%
7.	MF	1	binding	2.22e-286	2.31e-282	1,151	12464/36904 genes: 33.77%
8.	CC	2	intracellular	4.54e-282	4.73e-278	1,155	12682/36904 genes: 34.36%
9.	BP	2	organic substance metabolic process	1.52e-278	1.59e-274	1,041	10144/36904 genes: 27.49%
10.	CC	2	intracellular part	8.14e-277	8.49e-273	1,144	12555/36904 genes: 34.02%

These chemicals have comparable sets of interacting genes to *Diethylhexyl Phthalate*.

Filter by interaction type ?

☐ *increases*
☐ *decreases*
☐ *affects (degree unspecified)*

ALL
activity
binding
expression

Filter

Pathway view of top 10 Comps: ⬚ XGMML ?

	Similarity Index	Common Interacting Genes
perfluorooctanoic acid	0.15234	388
perfluorooctane sulfonic acid	0.14593	278
Clofibrate	0.13146	486
Dietary Fats	0.12789	487
rosiglitazone	0.12736	283
Dexamethasone	0.12577	327
Fenofibrate	0.12536	174
Phenobarbital	0.1213	627
Diethylnitrosamine	0.12109	430
troglitazone	0.1189	256
Pregnenolone Carbonitrile	0.11693	210
Dibutyl Phthalate	0.11472	604
1,4-bis(2-(3,5-dichloropyridyloxy))benzene	0.11348	218
Carbon Tetrachloride	0.11324	354
propiconazole	0.10675	280
Doxorubicin	0.1051	233
pirinixic acid	0.10508	838
Ozone	0.10437	222
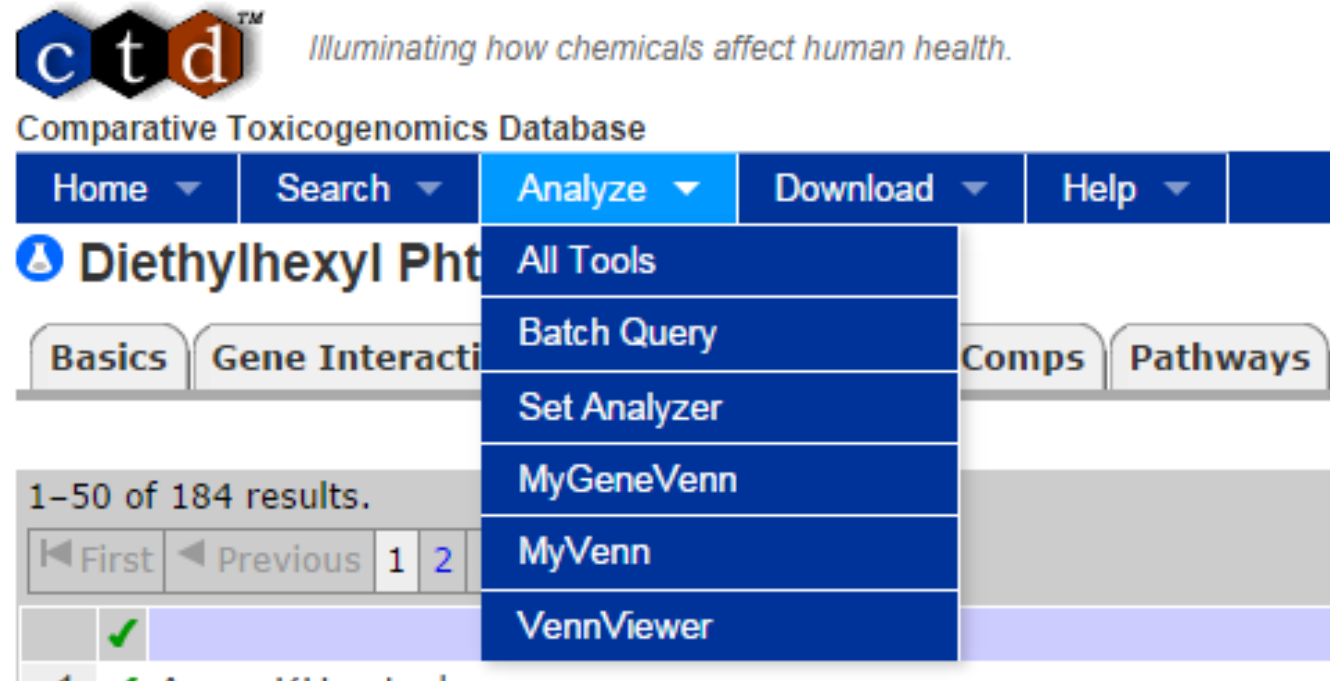
✓	Reference ⬍	Cited Chemicals	Cited Genes	Cited Diseases
1. ✓	Aung KH, et al. Involvement of hemeoxygenase-1 in di(2-ethylhexyl) phthalate (DEHP)-induced apoptosis of Neuro-2a cells. J Toxicol Sci. 2014;39(2):217-29.	Diethylhexyl Phthalate	CASP3 | HMOX1	
2. ✓	Kolšek K, et al. Molecular docking revealed potential disruptors of glucocorticoid receptor-dependent reporter gene expression. Toxicol Lett. 2014 Apr 21;226(2):132-9.	2,2'-methylenebis(ethyl-6-tert-butylphenol) | 3-hydroxy-2-naphthoic acid o-anside | cypermethrin | dicumyl peroxide | Diethylhexyl Phthalate | tetramethrin	NR3C1	
10. ✓	Guo J, et al. The increased number of Leydig cells by di(2-ethylhexyl) phthalate comes from the differentiation of stem cells into Leydig cell lineage in the adult rat testis. Toxicology. 2013 Apr 5;306:9-15.	Diethylhexyl Phthalate		Cryptorchidism | Hypospadias | Leydig Cell Tumor | Neoplasms, Experimental | Prenatal Exposure Delayed Effects
11. ✓	Manikkam M, et al. Plastics derived endocrine disruptors (BPA, DEHP and DBP) induce epigenetic transgenerational inheritance of obesity, reproductive disease and sperm epimutations. PLoS One. 2013;8(1):e55387.	bisphenol A | Dibutyl Phthalate | Diethylhexyl Phthalate	ABCC4 | ABCC6 | ACAP3 | ACOXL | ACTG2 | ACTL6A | ACTN3 | ADRA1A | AKAP17A | ALDH6A1 | AMN1 | AMZ2 | ANP32A | ANP32E | AP2A1 | ARMCX2 | ASMT | ASMTL | ATF3 | B4GALT2 | BATF | BCAT2 | BCL9L | BEST2 | BIRC6 | BROX | C4A | CABLES1 | CALCA | CALCOCO1 | CRLN4 | CCDC17 |	Kidney Diseases | Ovarian Diseases | Prenatal Exposure Delayed Effects | Prostatic Diseases | Testicular Diseases

Analysis tools

- Batch Query
- Set Analyzer
- MyGeneVenn
- MyVenn
- VennViewer

Batch Query

- The Batch Query tool allows you to download data for up to 4,000 chemicals, diseases, genes, GO terms, pathways, or references simultaneously

- Enter or paste your query terms into the text box (return-, tab- or |- delimited), or upload a tab-separated-values (TSV) file containing the terms

- E.g.

- DEHP|MEHP|DINP|DIDP

Batch Query

1 Select your input type

- ● Chemicals (MeSH® names, synonyms, or IDs, or CAS RNs) ❓
- ○ Diseases (MeSH or OMIM names, synonyms, or IDs) ❓
- ○ Genes (NCBI symbols or IDs) ❓
- ○ Gene Ontology terms (GO names, synonyms, or IDs) ❓
- ○ Pathways (KEGG or REACTOME names or IDs) ❓
- ○ References (PubMed® IDs or DOIs) ❓

2 Provide query terms (up to 4,000)

Return-, tab- or |-delimited

```
DEHP|MEHP|DINP|DIDP
```

Or **uplo**

選擇檔

Identifi

3 Choose data to download

Data

Chemical–gene interactions ❓
- ● Curated
  - Type(s):
    - ANY
    - abundance
    - activity
    - binding
    - cotreatment

Chemical associations ❓

Gene associations ❓
- ○ Curated

Disease associations ❓
- ○ All
- ○ Curated
- ○ Inferred

Pathway associations ❓
- ○ Inferred
- ○ Enriched *(recommended)*

Gene Ontology associations ❓
- ○ Enriched *(recommended)*
- ○ All

Format
- ● TSV (tab-separated values)
- ○ CSV (comma-separated values)
- ○ JSON
- ○ XML

Download   Clear

The CSV file can be opened by EXCEL

	A	B	C	D	E	F	G	H	I	J	K
1	# Input	ChemicalN	ChemicalII	CasRN	GeneSymb	GeneID	Organism	OrganismII	Interaction	InteractionActions	PubMedIDs
2	dehp	Diethylhex	D004051	117-81-7	ABCA1	19	Mus muscu	10090	[Tetrachlorodibenz	affects^cotreatmentline	23756648
3	dehp	Diethylhex	D004051	117-81-7	ABCA2	20	Mus muscu	10090	Diethylhexyl Phtha	decreases^expression	19850644
4	dehp	Diethylhex	D004051	117-81-7	ABCA2	20	Mus muscu	10090	PPARA protein pro	decreases^expressionI	19850644
5	dehp	Diethylhex	D004051	117-81-7	ABCB1	5243	Homo sapi	9606	Diethylhexyl Phtha	increases^expressionli	17003290
6	dehp	Diethylhex	D004051	117-81-7	ABCB1	5243	Homo sapi	9606	Diethylhexyl Phtha	increases^expression	17003290
7	dehp	Diethylhex	D004051	117-81-7	ABCB11	8647	Mus muscu	10090	Diethylhexyl Phtha	decreases^expression	19245819
8	dehp	Diethylhex	D004051	117-81-7	ABCB1B	18669	Mus muscu	10090	Diethylhexyl Phtha	increases^expression	19850644
9	dehp	Diethylhex	D004051	117-81-7	ABCB1B	18669	Mus muscu	10090	PPARA protein pro	increases^expressionli	19850644
10	dehp	Diethylhex	D004051	117-81-7	ABCB4	5244	Mus muscu	10090	Diethylhexyl Phtha	increases^expression	9210621
11	dehp	Diethylhex	D004051	117-81-7	ABCC2	1244	Rattus norv	10116	Diethylhexyl Phtha	increases^expression	11752103
12	dehp	Diethylhex	D004051	117-81-7	ABCC3	8714	Mus muscu	10090	[Diethylhexyl Phth	affects^bindinglincrea	15833929
13	dehp	Diethylhex	D004051	117-81-7	ABCC3	8714	Mus muscu	10090	Diethylhexyl Phtha	increases^expression	15833929I
14	dehp	Diethylhex	D004051	117-81-7	ABCC4	10257	Rattus norv	10116	[bisphenol A co-tre	affects^cotreatmentlaff	23359474

Set Analyzer

- Perform analyses such as set-based enrichment for collections of chemicals or genes, and pathway generation for collections of genes

- What diseases, GO terms and pathways are most related to a given set of chemicals?

- What diseases, GO terms and pathways are most related to a given set of genes/proteins?

Query by chemicals

Set Analyzer

Perform analyses such as set-based enrichment for collections of chemicals or genes, and pathway generation for collections of genes. ❓

1 **Select your input type**

⦿ Chemicals (MeSH® names, synonyms, or IDs, or CAS RNs) ❓
◯ Genes (NCBI symbols or IDs) ❓

2 **Enter your data set**

Return-, tab- or |-delimited

```
Diallyl phthalate
Di-n-pentyl phthalate
Dicyclohexyl phthalate
DEHP
MEHP
```

3 **Choose the analysis**

◉ Enriched diseases **?**
○ Enriched GO functional annotations **?**

Ontology
○ All
○ Biological Process
○ Molecular Function
○ Cellular Component

○ Enriched pathways **?**
○ Common gene–gene interactions **?**

4 **Configure the analysis**

P-value **?**

Threshold: 0.01 (0–1.0)

◉ Corrected *(recommended)*
○ Raw

Submit   Clear

Chemical Set Analyzer: Enriched diseases

⊞ Your chemical set (5)

P-value
Threshold: 0.01 ● Corrected ○ Raw

Disease category
ALL ▼

Filter   **Revise analysis**

539 results.

	Disease	Disease Categories	P-value	Corrected P-value	Annotated Genes	Genome Frequency
1.	Neoplasms	○ Cancer	1.98e-264	4.02e-261	433	2778/36904 genes: 7.53%
2.	Neoplasms by Site	○ Cancer	2.54e-219	5.15e-216	348	2012/36904 genes: 5.45%
3.	Digestive System Diseases	○ Digestive system disease	3.60e-207	7.31e-204	307	1565/36904 genes: 4.24%
4.	Pathological Conditions, Signs and Symptoms		4.36e-197	8.85e-194	336	2130/36904 genes: 5.77%
5.	Cardiovascular Diseases	○ Cardiovascular disease	5.22e-179	1.06e-175	253	1163/36904 genes: 3.15%
6.	Neoplasms by Histologic Type	○ Cancer	4.49e-178	9.10e-175	277	1490/36904 genes: 4.04%
7.	Nutritional and Metabolic Diseases		3.11e-170	6.30e-167	256	1295/36904 genes: 3.51%
8.	Metabolic Diseases	○ Metabolic disease	4.35e-166	8.81e-163	245	1197/36904 genes: 3.24%
9.	Congenital, Hereditary, and Neonatal Diseases and Abnormalities		3.92e-164	7.95e-161	317	2334/36904 genes: 6.32%
10.	Nervous System Diseases	○ Nervous system disease	2.49e-161	5.06e-158	321	2457/36904 genes: 6.66%

🔗 MyGeneVenn

Create a [Venn diagram](#) to compare *your* gene list to genes associated with up to two chemicals or diseases.

---

1 **Enter your gene list**

NCBI symbols or IDs (return-, tab- or |-delimited) ❓

```
THRB|AR|PPARA|TGFB1
```

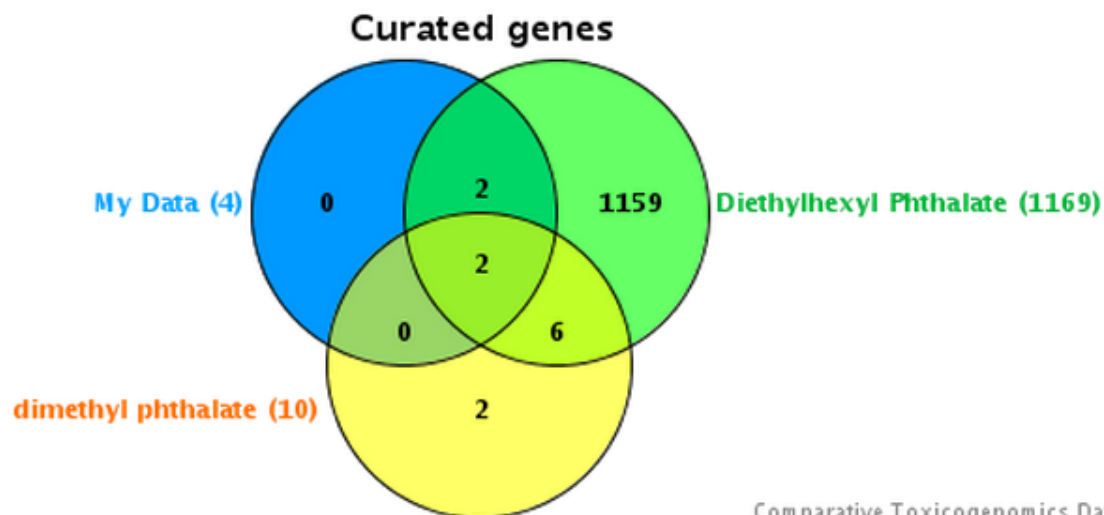Data set name: ❓ `My Data`

---

2 **Choose the data sets to compare**

- ⦿ Genes that interact with these chemicals: ❓
- ○ Genes with *curated* associations to these diseases: ❓
- ○ Genes with *inferred* associations to these diseases: ❓

Chemical 1: `DEHP`

Chemical 2: `Dimethyl phthalate` (optional)

MeSH® names, synonyms, or IDs, or CAS RNs.

Submit **Clear**

MyGeneVenn: Curated genes

Curated genes

My Data (4)   0   2   1159   Diethylhexyl Phthalate (1169)

2

dimethyl phthalate (10)   0   6

2

Comparative Toxicogenomics Database, 2014 Sep 1.

Click a region to expand/collapse its data set.

⊞ Genes only in My Data (0)   Top ↑

⊞ **Genes related only to Diethylhexyl Phthalate (1,159)**   Top ↑

⊞ **Genes related only to dimethyl phthalate (2)**   Top ↑

⊞ **Genes common only to My Data and Diethylhexyl Phthalate (2)**   Top ↑

⊞ Genes common only to My Data and dimethyl phthalate (0)   Top ↑

⊞ **Genes common only to Diethylhexyl Phthalate and dimethyl phthalate (6)**   Top ↑

⊞ **Genes common to all (2)**   Top ↑

⊞ **All genes in My Data (4)**   Top ↑

⊞ **All genes related to Diethylhexyl Phthalate (1,169)**   Top ↑

⊞ **All genes related to dimethyl phthalate (10)**   Top ↑

MyVenn

Create a Venn diagram to view relationships among your lists of CTD chemicals, diseases, genes, GO terms or pathways, or any other data.

1 Select your input type

- ● **Chemicals** (MeSH® names, synonyms, or IDs, or CAS RNs) ❓
- ○ **Diseases** (MeSH or OMIM names, synonyms, or IDs) ❓
- ○ **Genes** (NCBI symbols or IDs) ❓
- ○ **Gene Ontology terms** (GO names, synonyms, or IDs) ❓
- ○ **Pathways** (KEGG or REACTOME names or IDs) ❓
- ○ **Other** ❓

2 Enter your data sets ❓

Set 1

Terms (return-, tab- or |-delimited)

```
ZCCHC18
ZFAT
```

Name

```
DEHP
```

Set 2

Terms (return-, tab- or |-delimited)

```
HSD17B11
HSD17B12
```

Name

```
Dimethyl phthalate
```

Set 3 (optional)

Terms (return-, tab- or |-delimited)

```
GALR2
GRM7
HTR1B
```

Name

```
Dicyclohexyl phthalate
```

Submit   **Clear**

Genes

DEHP (1668)   1650   8   1   Dimethyl phthalate (10)

1

Dicyclohexyl phthalate (13)   9   0

3

Comparative Toxicogenomics Database, 2014 Sep 1.
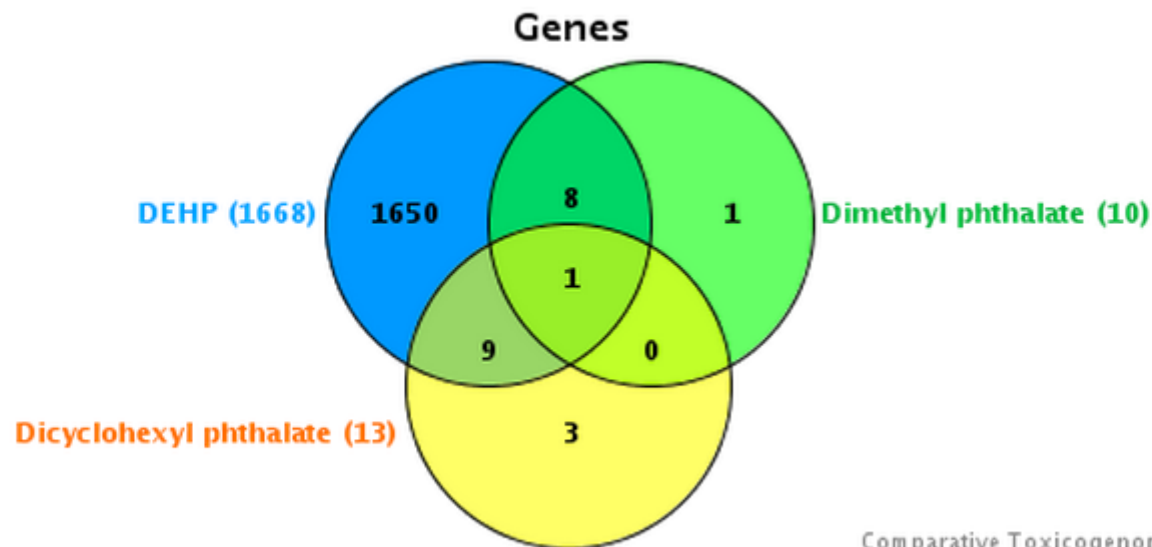
Click a region to expand/collapse its data set.

⊞ **Genes only in DEHP (1,650)**   Top ↑

⊞ **Genes only in Dimethyl phthalate (1)**   Top ↑

⊞ **Genes only in Dicyclohexyl phthalate (3)**   Top ↑

⊞ **Genes common only to DEHP and Dimethyl phthalate (8)**   Top ↑

⊞ **Genes common only to DEHP and Dicyclohexyl phthalate (9)**   Top ↑

⊞ Genes common only to Dimethyl phthalate and Dicyclohexyl phthalate (0)   Top ↑

⊞ **Genes common to all (1)**   Top ↑

⊞ **All genes in DEHP (1,668)**   Top ↑

⊞ **All genes in Dimethyl phthalate (10)**   Top ↑

⊞ **All genes in Dicyclohexyl phthalate (13)**   Top ↑

VennViewer

Create a Venn diagram to compare associated data sets for up to three chemicals, diseases, or genes.

1 Select your input type

● **Chemicals** (MeSH® names, synonyms, or IDs, or CAS RNs) **?**
○ **Diseases** (MeSH or OMIM names, synonyms, or IDs) **?**
○ **Genes** (NCBI symbols or IDs) **?**

2 Enter your chemicals

Chemical 1: `dehp`
Chemical 2: `dimethyl phthalate`
Chemical 3: `dicyclohexyl phthalate`

3 Choose the data sets to compare

Chemical associations **?**

Gene associations **?**
● Curated

Disease associations **?**
○ Curated
○ Inferred

Pathway associations **?**
○ Enriched *(recommended)*
○ Inferred

Gene Ontology associations **?**
○ Enriched *(recommended)*
○ All

VennViewer: Curated genes

Revise query   Download results: 📊 **CSV** | 📑 **TSV** ● 🔴 **Enlarge diagram**

Curated genes

Diethylhexyl Phthalate (1169)   1153   7   2   dimethyl phthalate (10)

1

dicyclohexyl phthalate (13)   8   0

4

Comparative Toxicogenomics Database, 2014 Sep 1.
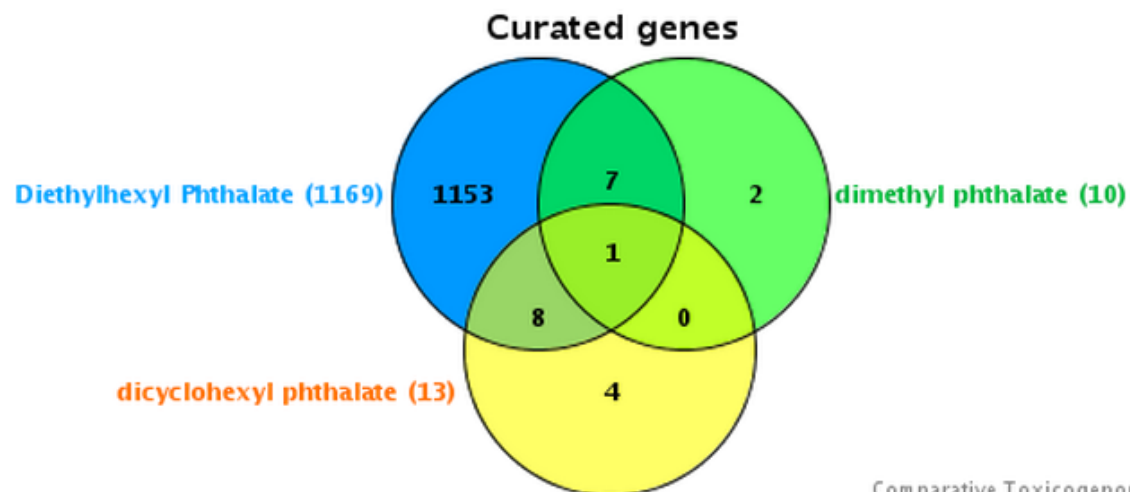
Click a region to expand/collapse its data set.

⊞ **Genes related only to Diethylhexyl Phthalate (1,153)**	Top ↑
⊞ **Genes related only to dimethyl phthalate (2)**	Top ↑
⊞ **Genes related only to dicyclohexyl phthalate (4)**	Top ↑
⊞ **Genes common only to Diethylhexyl Phthalate and dimethyl phthalate (7)**	Top ↑
⊞ **Genes common only to Diethylhexyl Phthalate and dicyclohexyl phthalate (8)**	Top ↑
⊞ Genes common only to dimethyl phthalate and dicyclohexyl phthalate (0)	Top ↑
⊞ **Genes common to all (1)**	Top ↑
⊞ **All genes related to Diethylhexyl Phthalate (1,169)**	Top ↑
⊞ **All genes related to dimethyl phthalate (10)**	Top ↑
⊞ **All genes related to dicyclohexyl phthalate (13)**	Top ↑