

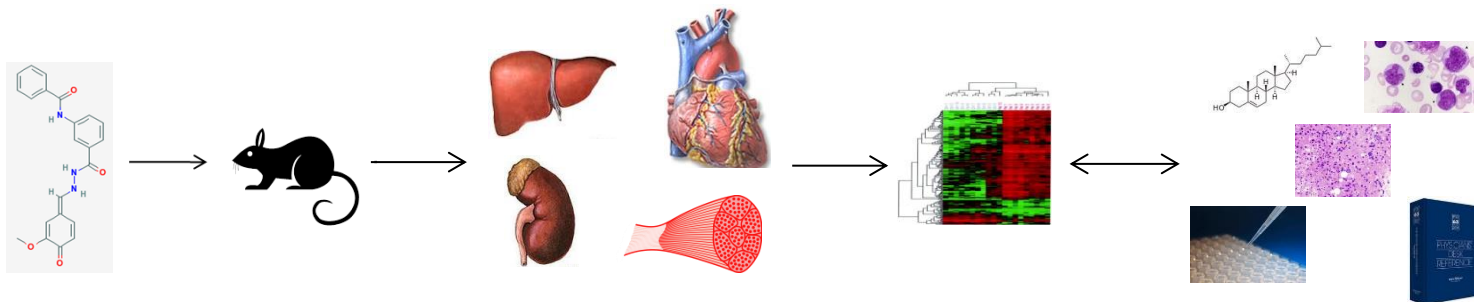


# The DrugMatrix® (DM) Database

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RTP, NC





# Disclaimer

The statements, opinions or conclusions contained herein do not necessarily represent the statements, opinions or conclusions of NTP, NIEHS, NIH or the United States government.



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NIEHS/NTP



NIEHS/NTP

*Photo courtesy of Steve McCaw*

# Acknowledgments – Iconix and Entelos

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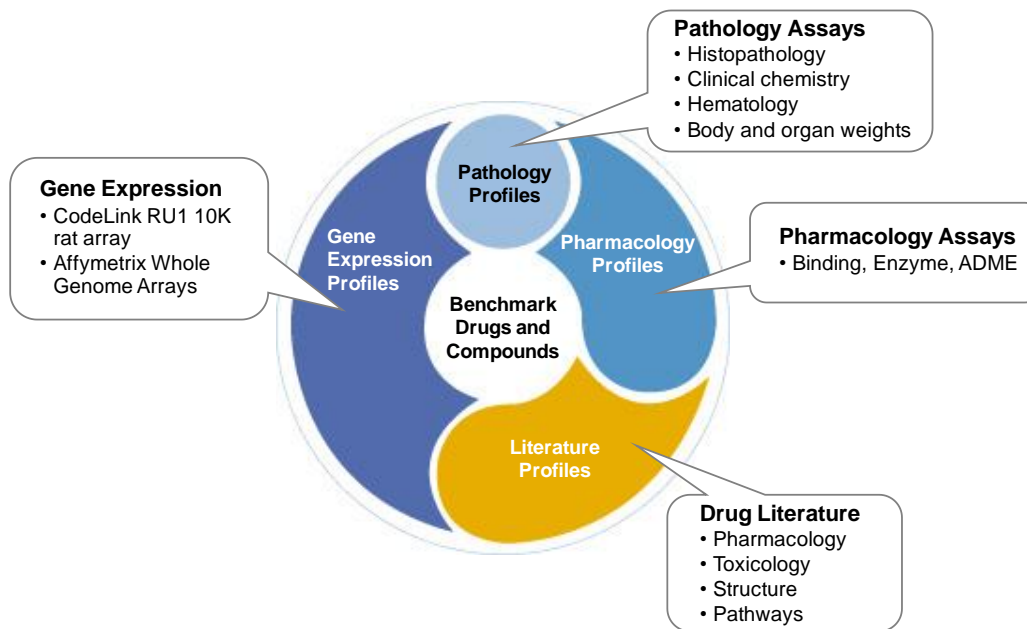


# Outline

- Data
- Interface
- Example Application



# DrugMatrix Data



## DrugMatrix

- DrugMatrix
  - Large-scale Rat Toxicogenomics Database and Analysis Tool
  - <https://ntp.niehs.nih.gov/drugmatrix/index.html>
- Originally owned by Iconix Pharmaceuticals and Entelos, Inc.
  - No data for these resources were generated by NTP
- Acquired by NTP in late 2010





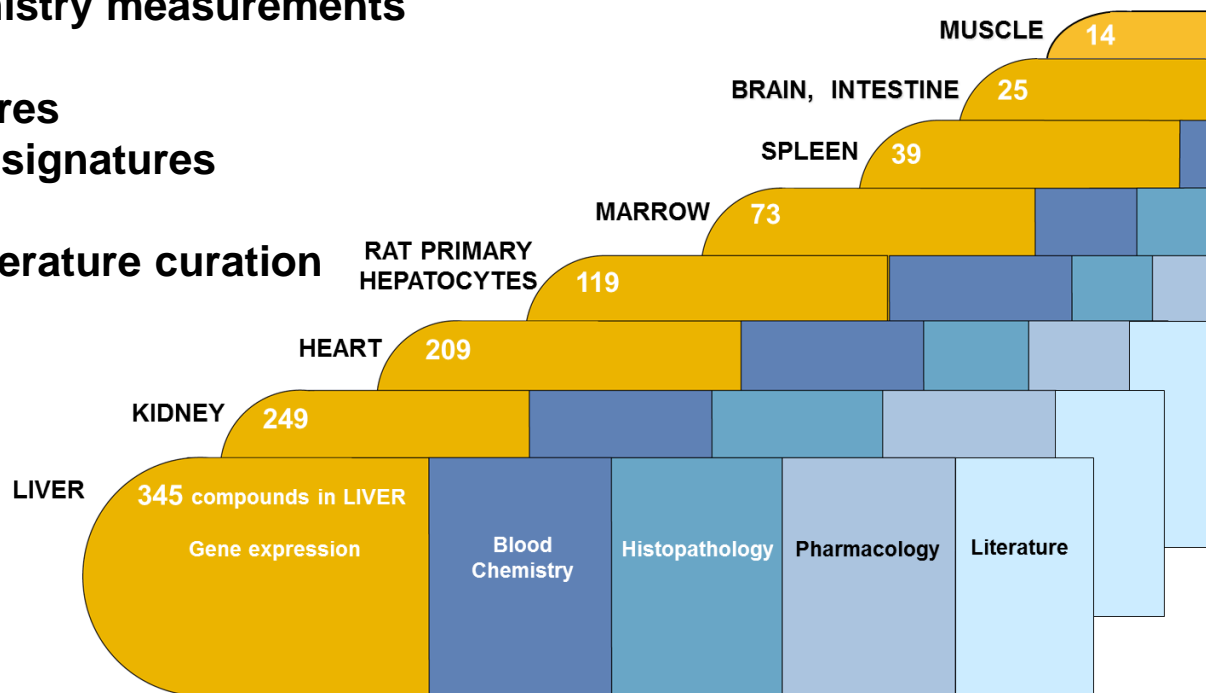
## Goals of Acquisition

- Make the computational and data resources **open to the public** **(no fee)**
- Facilitate the **integration** of toxicogenomics into hazard characterization
- **Build a bridge** between traditional toxicology and Tox21



# DrugMatrix Database Content

- ~ 700 Short-term toxicity studies (0.25 to 5 days) in male SD rats
- ~ 637 compounds studied at multiple doses, time points and tissues
- ~ 5600 drug-treatment transcript profiles
- ~ 13,000 Codelink RU1 Microarrays
- ~ 5,000 Affymetrix RG230-2 Arrays
- ~ 127,000 histopathology measurements
- ~ 150 histopathology diagnoses over 7 tissues
- ~ 100,000 hematology and chemistry measurements
- ~ 138 hand annotated pathways
- ~ 290 scorable genomic signatures
- ~ 2500 pathway-based scorable signatures
- ~ 130 in vitro assays
- ~ 900 chemicals with detailed literature curation
- ~ 8000 chemical structures
- ~ 60,000 literature facts
- ~ 123,000 frozen samples





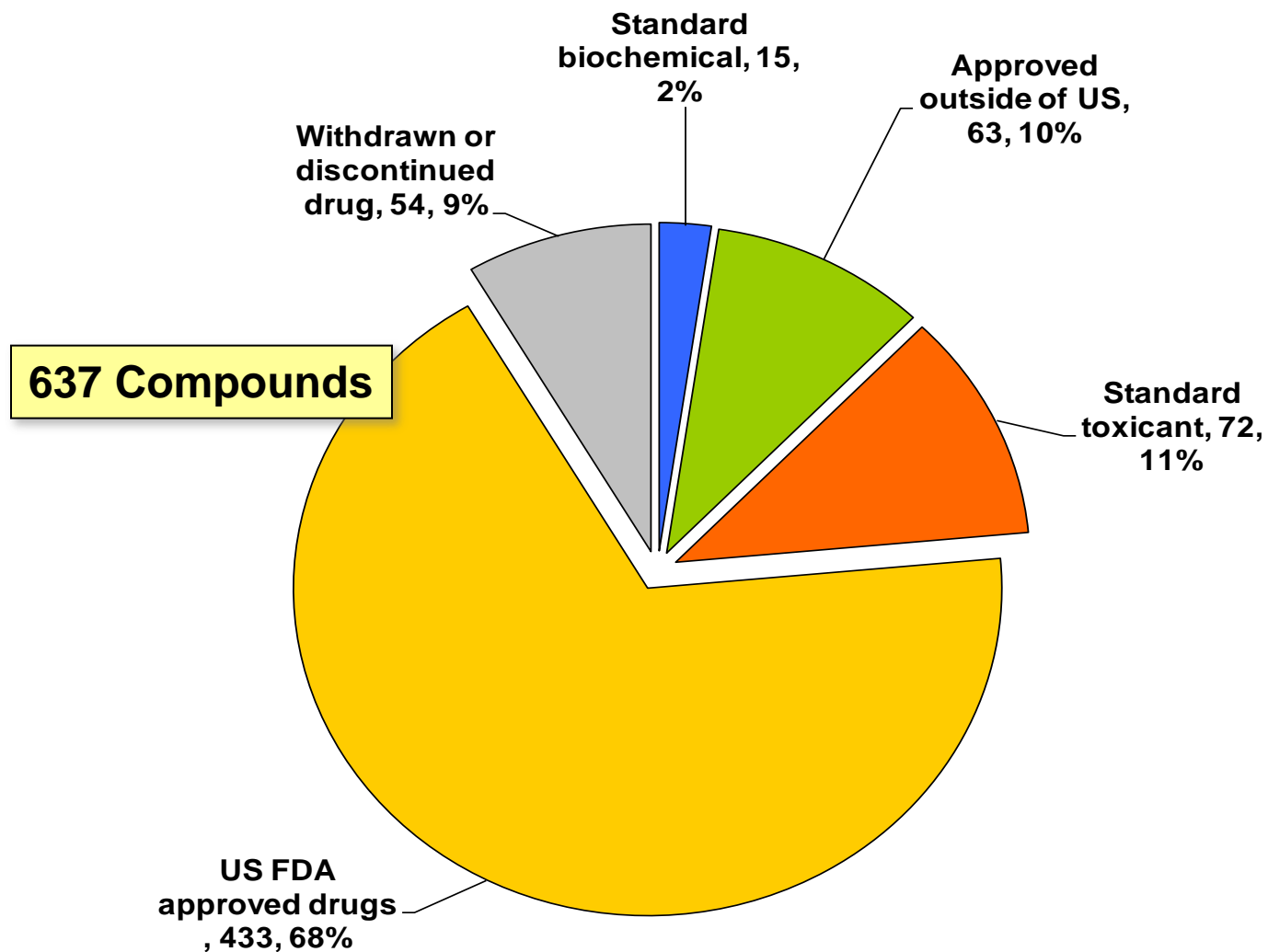
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# In vivo Studies

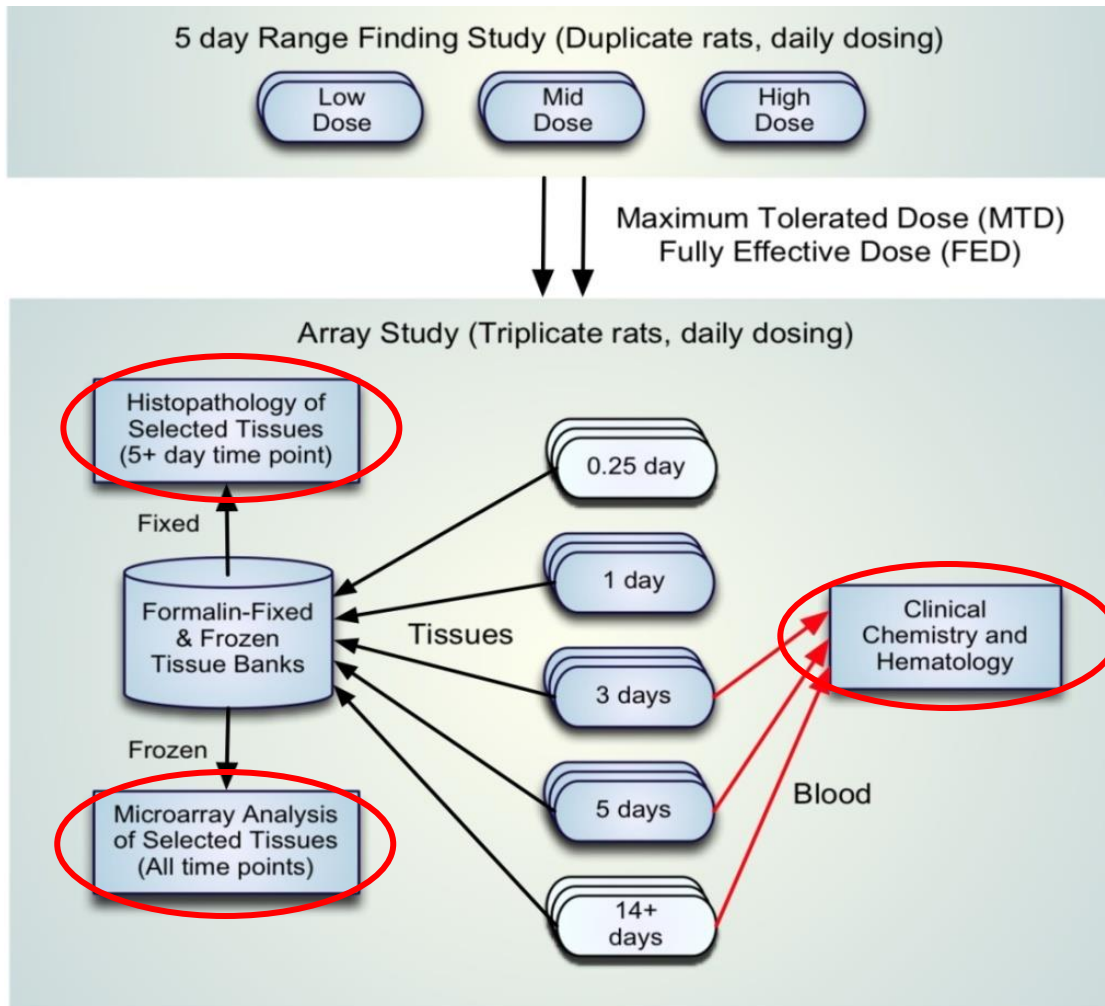




# DrugMatrix Chemical Diversity



## Standardized DrugMatrix *in vivo* Experimental Protocol



- Two doses
  - MTD
  - FED
- Four time points
  - 0.25
  - 1
  - 3
  - 5, 7, or 14
  - 3 rats/time point
- Daily dosing every morning at ~ same time
- Sacrifice in morning at ~ same time (except 0.25d)
- Tissues collected
  - Punches flash frozen
  - Part fixed in formalin



## Frozen Samples from In vivo Studies

Tissue	Compounds	Treatments	Organism	Treatments/ Compound
Liver	661	5301	Sprague Dawley Male	8.0
Whole Blood	152	778	Sprague Dawley Male	5.1
Plasma	661	4665	Sprague Dawley Male	7.1
Heart	661	4510	Sprague Dawley Male	6.8
Kidney	661	5358	Sprague Dawley Male	8.1
Thigh Muscle	653	2892	Sprague Dawley Male	4.4
<b>Total</b>	<b>661</b>	<b>5622 unique</b>		

- Treatments could include: 2 dose levels (MTD/FED), 4 time points (1, 3 and 5 days + 4<sup>th</sup> (7, 14, 30 or 90 day)) = up to 8 treatments
- Gene arrays run on liver, heart, kidney, thigh muscle, bone marrow, spleen, brain, intestine, and primary hepatocytes.
- Snap frozen tissues retained for organs/fractions in table above.
- Histopathology (100 endpoints) read on all tissues for which gene arrays were run, and for most of the remaining tissues. (Rat Atlas of Histopathology). Histology slides and FFPE sections no longer available.
- RNA likely available for most tissues for which gene arrays were run, for most of the remaining tissues, and for most rat primary hepatocyte cultures.
- Clinical chemistry and hematology available on many samples

## Dose Justification

DOSE JUSTIFICATION

Note: The final low array dose choice was based on a rat model for gastric ulcer formation and motor co-ordination.

**High Array Dose Recommendation**  
At the high RF dose (54mg/kg/day), weight gain was 21.3%. No clinical signs were displayed by any animals at any of the doses. Animals gained 21.4% body weight at the mid (32mg/kg/day) and 19.2% body weight at the low (16mg/kg/day) RF doses. It has been decided to use the high RF dose as the high array dose.

**Low Array Dose Recommendation**  
Phenobarbital is indicated for gastrointestinal disturbances such as cramps, spasms, diarrhea, nausea, vomiting and peptic ulcer. It is also indicated as a treatment for irritable bowel syndrome and is a potent anesthetic/anti-convulsant. Human dose is 125mg/day (PDR). This scales to 7mg/kg/day in the rat. 50mg/kg/day for 10 days was administered to rats with chronic gastric ulcer. This dose significantly increases cytochrome P-450 in the gastric mucosa, which results in the stimulation of mucosal barrier protective glycoproteins (PMID 9206565 - abstract only).

Gastric ulcers were induced in rat glandular stomach by the cold-restraint method. The fore and hind limbs are tied together with metallic wire and the rats are left in a 40C incubator for 2 hours. An oral dose of 50mg/kg gave 78% protection against ulcer formation under these conditions. 20mg/kg resulted in 33% protection and 10mg/kg resulted in 11% protection. Rats are also trained to walk on a rotating rod. The reduction in locomotor activity caused by Phenobarbital administration is reflected in the % of animals that fall off the rod in 2 minutes. 100mg/kg Phenobarbital will cause 100% of the rats to fall off the rod; 50mg/kg cause 70% to fall; 25mg/kg causes 40% to fall (PMID 2860988). 25mg/kg/day administered in the rat diet for 2 weeks resulted in significant induction of hepatic cytochrome P450 (PMID 1554380 - article retrieved).

I recommend that we use 25mg/kg/day as the low array dose, which would protect against gastric ulcer formation (50mg/kg/day) is too close to the high array dose. Floater tissue should be the brain.

All recommendations were accepted at the dose-setting meeting 12-17-01.



# Pathology Lab Report

PHENOBARBITAL-RATM-20020115

TIME COURSE DOSE RESPONSE **PATHLAB REPORT**

EXPERIMENTS HISTOPATHOLOGIES

EXPRESSION EXPERIMENTS

EXPERIMENT	TYPE	TISSUE	TIME	D
<input checked="" type="checkbox"/> PHENOBARBITA-5d-54ma/ka...	BIOCHIP	LIVER	5.0d	5
<input checked="" type="checkbox"/> PHENOBARBITA-5d-54ma/ka...	GENECHIP	LIVER	5.0d	5
<input checked="" type="checkbox"/> PHENOBARBITA-3d-54ma/ka...	BIOCHIP	LIVER	3.0d	5
<input checked="" type="checkbox"/> PHENOBARBITA-3d-54ma/ka...	GENECHIP	LIVER	3.0d	5
<input checked="" type="checkbox"/> PHENOBARBITA-1d-54ma/ka...	BIOCHIP	LIVER	1.0d	5
<input checked="" type="checkbox"/> PHENOBARBITA-1d-54ma/ka...	GENECHIP	LIVER	1.0d	5
<input checked="" type="checkbox"/> PHENOBARBITA-1d-25ma/ka...	BIOCHIP	LIVER	1.0d	2
<input checked="" type="checkbox"/> PHENOBARBITA-1d-25ma/ka...	GENECHIP	LIVER	1.0d	2
<input checked="" type="checkbox"/> PHENOBARBITA-.25d-25ma/...	BIOCHIP	LIVER	0.25d	2
<input checked="" type="checkbox"/> PHENOBARBITA-.25d-25ma/...	GENECHIP	LIVER	0.25d	2

## PHENOBARBITAL

### Histopathology and Clinical Pathology Report





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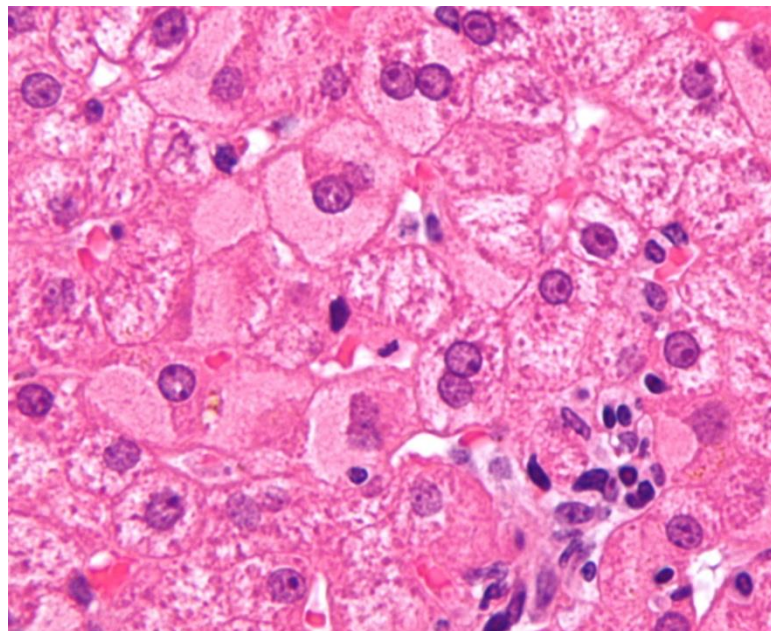
## In vitro Studies





## Rat Hepatocyte Genomics

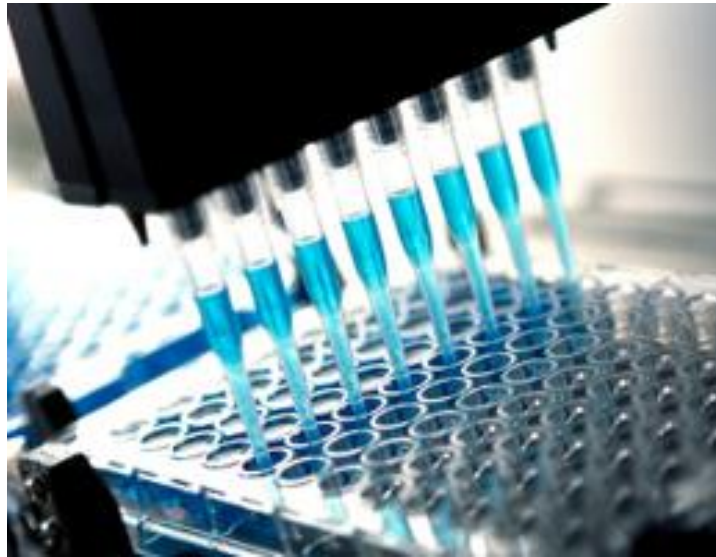
- Male Sprague Dawley Rats
- 16 and 24 hr treatments
- Codelink
  - 119 chemicals
  - 244 treatments
- Affymetrix
  - 126 chemicals
  - 279 treatments





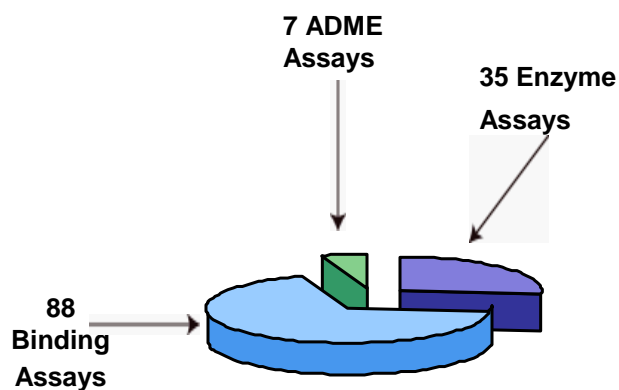
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# Pharmacology Assays



## Molecular Pharmacology Profiles

- Over 870 compounds profiled across 130 *in vitro* pharmacology assays



**DOXORUBICIN**

> SMILES    > SYNONYMS    > IDENTIFIERS    > PHYSICAL PROPS.

SIMILAR    INDUCED    REPRESSED    EXPERIMENTS    ACTIVITIES    LITER.    TARGET    MOTIF

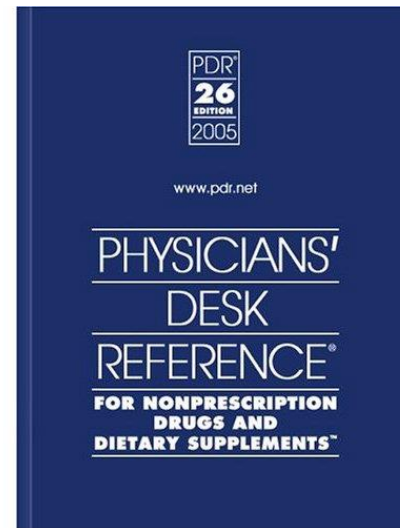
> I MENU    BIO-ACTIVITIES

ASSAY		INHIBITION	IC50	KI
<a href="#">Protein Tyrosine Kinase, HER2 Receptor</a>	<input checked="" type="checkbox"/>	100.0%	2.485uM	
<a href="#">Protein Tyrosine Kinase, Fyn</a>	<input checked="" type="checkbox"/>	98.0%	5.147uM	
<a href="#">Serotonin 5-HT4</a>	<input checked="" type="checkbox"/>	82.0%	12.468uM	2.078uM
<a href="#">Sodium Channel, Site 2</a>	<input checked="" type="checkbox"/>	75.0%	15.245uM	13.668uM
<a href="#">Protease, Caspase 1</a>	<input checked="" type="checkbox"/>	73.0%	12.192uM	
<a href="#">Lipoxygenase 15-LO</a>	<input checked="" type="checkbox"/>	73.0%	13.59uM	
<a href="#">Protein Tyrosine Kinase, Lck</a>	<input checked="" type="checkbox"/>	61.0%	31.913uM	
<a href="#">Muscarinic M1</a>	<input checked="" type="checkbox"/>	53.0%	15.336uM	3.693uM
<a href="#">Serotonin 5-HT1B</a>	<input checked="" type="checkbox"/>	52.0%	34.464uM	15.666uM



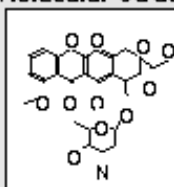
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# Literature and Structure Curation



## Literature and Structure Curation

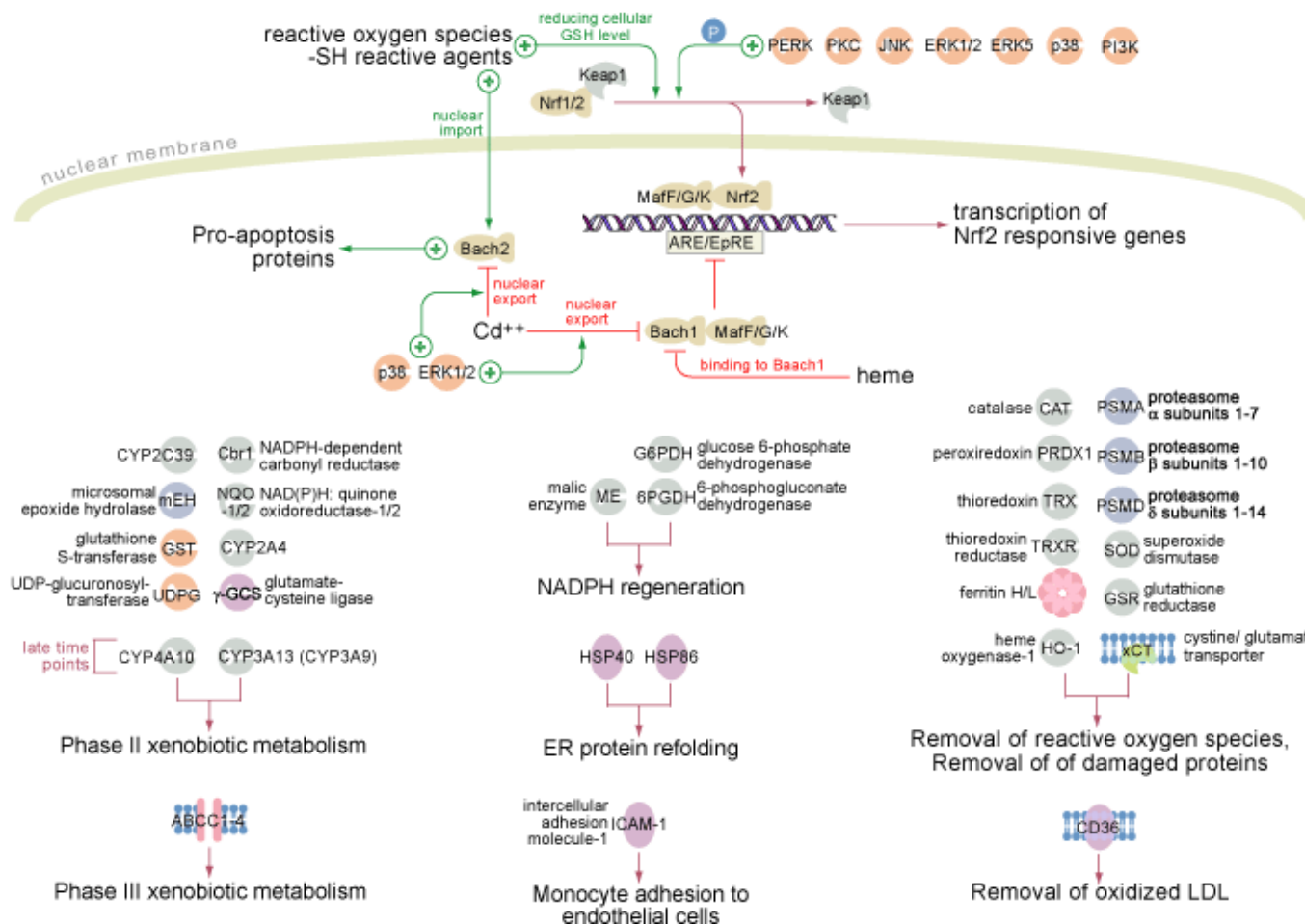
- Clinical literature
  - indication, mechanism, toxicity
- Pharmacology literature
  - ED50, LD50, IC50
- Pharmacokinetic literature
  - CMax, half-life, AUC, Clearance
- Physical properties
  - MW, logP, logS, pKa
- Structure files
  - .mol files

DETAIL	CURATION	PHARMA.	PATH
<b>DETAIL</b>			
<b>Compound:</b> DOXORUBICIN			
<b>Molecular Structure:</b>			
			
<b>Molecular Weight:</b> 544			
<b>Formula:</b> C27 H29 N O11			
<b>Development Status:</b> US FDA Approved			
DETAIL	CURATION	PHARMA	PATH
<b>COMPOUND CURATION</b>			
<b>Mechanism:</b> Inhibit DNA synthesis, repair, and function			
<b>Mode Class:</b> Distorts /blocks macromolecular synthesis scaffold			
<b>Known Toxicity:</b> Carcinogenicity Mutagenicity Blood & Bone Marrow Toxicity Cardiovascular Toxicity			
<b>Tissue Toxicity:</b> Carcinogenicity Mutagenicity Hemorrhage Cardiomyopathy Cardiotoxicity Congestive Heart Failure Myelosuppression			
<b>Adverse Effect:</b> REP_3_Testicular Atrophy IMU_2_Urticaria XXX_1_Infection CVS_1_Cardiotoxicity CVS_1_Cardiomyopathy SKN_1_Alopecia / Hair Loss BBM_3_Acute Leukemia			
DETAIL	CURATION	PHARMA	PATH
<b>COMPOUND PHARMACOLOGY</b>			
	ANTOX, LD50		10.5 mg...
	ANTOX, LD50		16 mg/kg
	ANTOX, Observed T...		10 mg/kg
	ANTOX, Observed T...		25 mg/kg
	ANTOX, TDL <sub>0</sub> (Time...		12 mg/kg
	ANTOX, TDL <sub>0</sub> (Time...		15 mg/kg
	ANTOX, TDL <sub>0</sub> (Time...		21 mg/kg
	ANTOX, TDL <sub>0</sub> (Time...		24 mg/kg
	CLNPH, AUC		.413 mg...
	CLNPH, Clearance		71.4 L/h
	CLNPH, Cmax		.0426 m...
	CLNPH, Cmax		4.5 mg/L
	CLNPH, Effective ...		75 mg/m...
	CLNPH, Half_Life		30 h
	CLNPH, Half_Life		47 h
	VVPH, Eff Conc		4 mg/kg



# Pathways

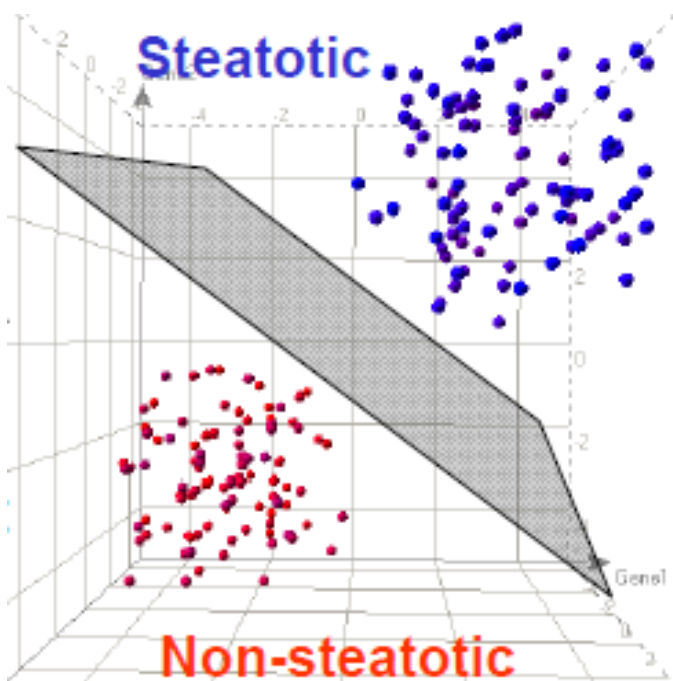
Oxidative Stress Response Mediated by Nrf2



x 138



## Signatures



Signature Types	Example Signatures*
Organ Pathology	Hepatic Necrosis, Bile Duct Hyperplasia, Renal Tubular Necrosis, Nephromegaly, Cardiac Myocyte Degeneration, Heart Weight Increase
Mechanistic Class	DNA Alkylator, PXR Activation, Peroxisome Proliferator

\*Thousands of signatures





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**Where you can get the data???**





## DrugMatrix Data

Download DrugMatrix Array Data 

- <ftp://anonftp.niehs.nih.gov/drugmatrix>
- Unprocessed microarray data
- Microarray data normalized by organ
- Individual animal toxicology data
- In vitro screening data
- Chemical Annotations



# DrugMatrix Interface



# DrugMatrix Homepage

Launch DrugMatrix® - Windows Internet Explorer

https://ntp.niehs.nih.gov/drugmatrix/index.html

File Edit View Favorites Tools Help

Favorites Launch DrugMatrix®

Home RSS Print Page Safety Tools ?

National Toxicology Program  
Department of Health and Human Services

## DrugMatrix®

DrugMatrix is the scientific communities' largest molecular toxicology reference database and informatics system. DrugMatrix is populated with the comprehensive results of thousands of highly controlled and standardized toxicological experiments in which rats or primary rat hepatocytes were systematically treated with therapeutic, industrial, and environmental chemicals at both non-toxic and toxic doses. Following administration of these compounds in vivo, comprehensive studies of the effects of these compounds were carried out at multiple time points and in multiple target organs. These studies included extensive pharmacology, clinical chemistry, hematology, histology, body and organ weights, and clinical observations. Additionally, a curation team extracted all relevant information on the compounds from the literature, the Physicians' Desk Reference, package inserts, and other relevant sources. The heart of the DrugMatrix database is large-scale gene expression data generated by extracting RNA from the toxicologically relevant organs and tissues and applying these RNAs to the GE Codelink™ 10,000 gene rat array and more recently the Affymetrix whole genome 230 2.0 rat GeneChip® array. DrugMatrix contains toxicogenomic profiles for 638 different compounds; these compounds include FDA approved drugs, drugs approved in Europe and Japan, withdrawn drugs, drugs in preclinical and clinical studies, biochemical standards, and industrial and environmental toxicants. Contained in the database are 148 scorable genomic signatures derived using MOSEK computational software that cover 96 distinct phenotypes. The signatures are informative of organ-specific pathology (e.g., hepatic steatosis) and mode of toxicological action (e.g., PXR activation in the liver). The phenotypes cover a number of common target tissues in toxicity testing (including liver, kidney, heart, bone marrow, spleen and skeletal muscle). The primary value that DrugMatrix provides to the toxicology community is in its capacity to use toxicogenomic data to perform rapid toxicological evaluations. Further value is provided by DrugMatrix ontologies that help characterize mechanisms of pharmacological/toxicological action and identify potential human toxicities. Overall, DrugMatrix allows a toxicologist to formulate a comprehensive picture of toxicity with greater efficiency than traditional methods.

**Information for getting started:**

- Software requirements: Internet Explorer
- Supported platforms and data formats for upload:

Supported microarrays	Required data format
Codelink Rat Uniset 1	Tab-delimited text files
Affymetrix Rat Genome 230 2.0	PLIER CHP files
Affymetrix Rat Genome U34A	PLIER CHP files
Affymetrix Rat Expression 230A	PLIER CHP files
Affymetrix Rat Focus Array Plate	PLIER CHP files

Local intranet | Protected Mode: Off 111%



# DrugMatrix Interface – Help Section

The screenshot displays two overlapping Internet Explorer windows. The top window is titled "DrugMatrix 8.0.0 - Windows Internet Explorer" and shows the main application interface with a navigation bar containing tabs for SEARCH, ADVANCED, and WORKSPACE. Below this are various data categories: GENE, COMPOUND, ASSAY, EXPRESSION, PATHWAY, EXPR. STUDY, NOTIF, SIGNATURE, and HISTOPATHOL. The bottom window is titled "DrugMatrix™ Help - Windows Internet Explorer" and displays the help page content.

**DrugMatrix™**

→ **DOCUMENTATION**  
**TECHNICAL SUPPORT**  
**ABOUT DRUGMATRIX**  
**NTP WEBSITE**

Documentation and white papers were provided by original developers of DrugMatrix (Iconix Pharmaceuticals and Entelos, Inc) and have not been edited to reflect current NIEHS ownership of DrugMatrix. Any questions related to DrugMatrix should be directed to [drugmatrix@niehs.nih.gov](mailto:drugmatrix@niehs.nih.gov).

**DrugMatrix Documentation**

- [DrugMatrix Release Notes](#)
- [DrugMatrix Reference Manual \(NOTE: Please see Release Notes for the latest features\)](#)
- [DrugMatrix Tutorial Manual](#)
  - [-AffyData.zip](#)
  - [-threeexp.zip](#)
- [DrugMatrix Pathway Legend](#)
- [Supported Format for Affymetrix Array Data](#)
- [DrugMatrix Data Warehouse Schema Documentation](#)

**DrugMatrix Materials and Methods White Papers**

- [Drug Signature Profile Documentation](#)
- [Blood Chemistry and Hematology Description and Incidence](#)
- [Histopathology Glossary](#)
- [DrugMatrix Calculations](#)

SERVER STATUS: COMPLETE



## DrugMatrix – Search and List Management Tools

The image shows a screenshot of the DrugMatrix 8.0.0 web application interface. The browser title bar indicates "DrugMatrix 8.0.0 - Windows Internet Explorer". The application has a top navigation bar with "SEARCH", "ADVANCED", and "WORKSPACE" tabs. The "SEARCH" tab is active, showing a search form with a "FIND TEXT" input field containing "%", a "WITHIN DOMAIN" dropdown menu set to "- Select -", and a "SEARCH" button. A red circle highlights the search form area. Below the search form is a "MENU" and "LIST DISPLAY" section. On the right side, there is a "GENE" section with a "FAVORIT" button. The bottom of the page features the NTP logo and text.

DrugMatrix 8.0.0 - Windows Internet Explorer

DrugMatrix™

SEARCH ADVANCED WORKSPACE

SEARCH

FIND TEXT  
%

WITHIN DOMAIN  
- Select -

Gene  
Compound  
Assay  
Expression  
Pathway  
Expr. Study  
Motif  
Signature  
Histopathology

>| MENU LIST DISPLAY

GENE  
>| FAVORIT

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## DrugMatrix Integrated Data Domains

- **Gene Domain** – search individual genes to find out how they behave with different treatments
- **Chemical Domain** – search individual chemicals to identify structurally similar chemicals, gene expression perturbations, assay hits, etc
- **Assay Domain** – search and display in vitro assay results and clinical chemistry/hematology results
- **Expression Domain** – view results for single expression studies
- **Pathway Domain** – explore over 130 different biological pathways
- **Expression Study Domain** – view composite results multi-day/dose toxicity/toxicogenomic studies
- **Signature Domain** – Search predefined genomic signatures in DrugMatrix
- **Histopathology Domain** – Find details on specific histopathologies annotated in DrugMatrix
- **Motif Domain** – Search DrugMatrix Motif Signatures that are based solely on genes annotated to biological pathways



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# Advanced Search Tool







## Advanced Search Tool

- Conduct a variety of sophisticated queries of the DrugMatrix data
- Filter for drug/target interactions
- Mine data relevant to your research

DrugMatrix™

SEARCH | ADVANCED | WORKSPACE

ADVANCED

FIND  
Expression

N = 812 CLEAR ALL DISPLAY

WHERE: [REMOVE](#)  
Find expression experiments which have histopathology data for findings that exactly match bile duct hyperplasia

AND: [REMOVE](#)  
Find expression experiments which have (details) for experiments run on tissues that exactly match liver

AND: [REMOVE](#)  
Find expression experiments which have histopathology data with an average severity in affected animals equal to 0

EXPERIMENT

- 1,1-DICHLORO-5d-600mg/...
- 1,1-DICHLORO-5d-600mg/...
- 17-METHYLTES-5d-2000mg...
- 17-METHYLTES-5d-2000mg...
- 1-NAPHTHYL I-.25d-30mg/...
- 1-NAPHTHYL I-.25d-30mg/...
- 1-NAPHTHYL I-.25d-60mg/...
- 1-NAPHTHYL I-.25d-60mg/...
- 1-NAPHTHYL I-1d-60mg/kg...
- 1-NAPHTHYL I-1d-60mg/kg...
- 2,3,7,8-TETR-28d-.0007mg...

ADD CRITERIA CLOSE

Find expression experiments which have histopathology data for findings that exactly match ...

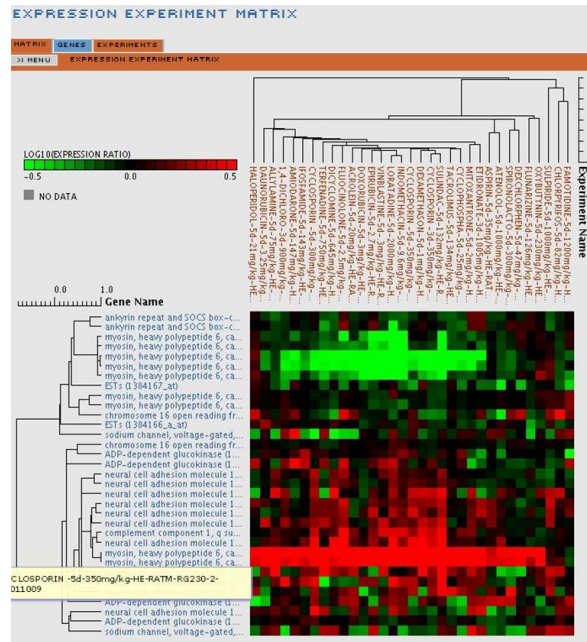
which have names	for tissues that	exactly match
which have histopathology data	for findings that	begin with
which have expression profiles similar to experiments	with an average severity in affected animals	end with
that show transcriptional responses	with a p-value	contain
which have clinical chemistry responses	with a percent incidence	
which are related to motifs		
which have (details) for		
which are related to signatures		

Bile Duct

RUN QUERY



## Analysis Tools





# DrugMatrix Functionality and Analysis Tools

- Upload your own data for analysis or mine the DrugMatrix data
  - Data you upload is private – not shared with the government or other users
- Contextualize your data relative to over 4000 expression profiles elicited by >600 well characterized, phenotypically anchored prototype agents
- Find similar expression profiles
- Determine significantly up and down regulated genes
- Perform gene ontology analysis of perturbed genes
- Visualize expression profiles on pathways
- Score expression profiles for >50 phenotypes with genomic signatures
- Construct expression patterns for putative biomarker sets
- Test the performance of biomarker sets for detecting phenotypes
- Find consistently changed genes
- Identify enriched literature annotations in groups of expression profiles
- Mine the literature

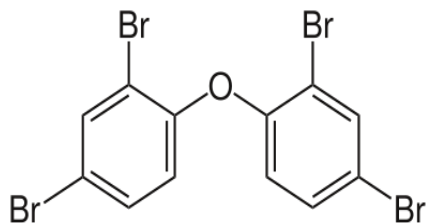


# **Example Application of DrugMatrix**

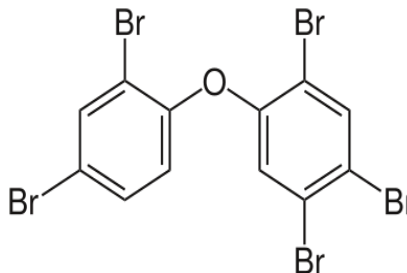
Toxicogenomic Assessment of DE-71  
(Study Scientist: Dr. June Dunnick)



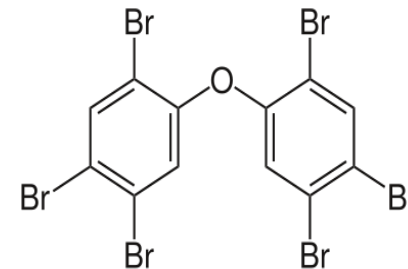
## DE-71: A mixture of polybrominated diphenyl ethers



BDE 47



BDE 99



BDE 153

- PBDEs are flame retardant components that bioaccumulate; persistent organic pollutants
- Widespread human exposure



## Gene Expression Study design

- Dose level: 0 or 50 mg/kg/day
- Route: Oral Gavage (corn oil)
- Model: Male Wistar Han rats
- Exposure period: gestational day (GD) 6 to postnatal day (PND) 21
- Euthanized: PND 22
- Tissue evaluated: Liver
- Question: What are the potential toxicological effects of DE-71 that can be identified by toxicogenomics?
- DE-71 expression studies are not included in DrugMatrix Database

# DrugMatrix Analysis of DE-71- Top DEGs (Liver)

- Cyp1a1, Cyp2b, Cyp2c

- Fgf21, Cyp17a1, Abcg8

## Induced

## Repressed

SIMILAR	INDUCED	REPPRESSED	DENDROGRAM	CLIN. PATH.	MOTIF	SPLP	TRANK	HISTOPATHOLOGY
» MENU TRANSCRIPTIONAL RESPONSES (INDUCED)								
GENE	CONFIDENCE INTERVAL	P VALUE						
<input checked="" type="checkbox"/> <a href="#">urinary protein 2 (1370396_x_at,rc_AA945585_at)</a>		2.68E-10						
<input checked="" type="checkbox"/> <a href="#">urinary protein 2 (1370349_a_at)</a>		1.41E-10						
<input checked="" type="checkbox"/> <a href="#">estrogen sulfotransferase (1368733_at,M86758_at,NM_012883_PROBE1)</a>		9.59E-8						
<input checked="" type="checkbox"/> <a href="#">cytochrome P450, family 2, subfamily A, polypeptide 3a (1369136_at)</a>		1.07E-10						
<input checked="" type="checkbox"/> <a href="#">transmembrane protein 27 (1387013_at,NM_020976_PROBE1)</a>		3.49E-9						
<input checked="" type="checkbox"/> <a href="#">CEA-related cell adhesion molecule 10 (Non-specific probe) (1370371_a_at)</a>		1.78E-11						
<input checked="" type="checkbox"/> <a href="#">urinary protein 2 (1389270_x_at)</a>		1.87E-5						
<input checked="" type="checkbox"/> <a href="#">cytochrome P450, family 2, subfamily c, polypeptide 29 (DBSS moderate) (139615...)</a>		0.00E0						
<input checked="" type="checkbox"/> <a href="#">Kruppel-like factor 2 (lung) (DBSS) (1386040_at)</a>		1.11E-12						
<input checked="" type="checkbox"/> <a href="#">CLIP associating protein 2 (1396604_at)</a>		1.50E-7						
<input checked="" type="checkbox"/> <a href="#">Iroquois related homeobox 2 (Drosophila) (1391457_a_at)</a>		1.30E-9						
<input checked="" type="checkbox"/> <a href="#">cytochrome P450, family 1, subfamily a, polypeptide 1 (1370269_at)</a>		1.63E-6						
<input checked="" type="checkbox"/> <a href="#">cytochrome P450 2c13 (1370495_s_at,M82855c s_at)</a>		7.54E-6						
<input checked="" type="checkbox"/> <a href="#">RT1 class I, CE10 (1388202_at)</a>		1.14E-4						
<input checked="" type="checkbox"/> <a href="#">Cytochrome P450 2C24 (CYP11C24) (P450-PROS2) (DBSS) (1370241_at,M18335_f...)</a>		1.14E-9						
<input checked="" type="checkbox"/> <a href="#">ESTs (1397343_at)</a>		8.82E-8						
<input checked="" type="checkbox"/> <a href="#">Transcribed locus (1380543_at)</a>		7.32E-10						
<input checked="" type="checkbox"/> <a href="#">cytochrome P450, family 2, subfamily b, polypeptide 13 (1387993_at)</a>		2.69E-8						
<input checked="" type="checkbox"/> <a href="#">leptin (1387748_at)</a>		9.76E-8						
<input checked="" type="checkbox"/> <a href="#">MGC14161 protein (DBSS) (1396720_at)</a>		1.50E-7						

SIMILAR	INDUCED	REPPRESSED	DENDROGRAM	CLIN. PATH.	MOTIF	SPLP	TRANK	HISTOPATHOLOGY
» MENU TRANSCRIPTIONAL RESPONSES (REPPRESSED)								
GENE	CONFIDENCE INTERVAL	P VALUE						
<input checked="" type="checkbox"/> <a href="#">hypothetical protein FLJ32871 (DBSS) (1394309_at)</a>		6.62E-11						
<input checked="" type="checkbox"/> <a href="#">ABO blood group (transferase A, alpha 1-3-N-acetylgalactosaminyltransfer...)</a>		3.68E-5						
<input checked="" type="checkbox"/> <a href="#">protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), beta is...</a>		3.61E-6						
<input checked="" type="checkbox"/> <a href="#">CDNA clone IMAGE:7460165 (1371298_at)</a>		5.89E-11						
<input checked="" type="checkbox"/> <a href="#">olfactory receptor 1696 (1370741_at)</a>		8.72E-5						
<input checked="" type="checkbox"/> <a href="#">fibroblast growth factor 21 (1387643_at)</a>		3.48E-6						
<input checked="" type="checkbox"/> <a href="#">N-terminal acetyltransferase 1 (DBSS) (1381204_at)</a>		6.13E-5						
<input checked="" type="checkbox"/> <a href="#">ESTs (1392613_at)</a>		9.46E-6						
<input checked="" type="checkbox"/> <a href="#">ESTs (1379156_at)</a>		2.07E-5						
<input checked="" type="checkbox"/> <a href="#">nuclear factor, erythroid derived 2 (1375040_at,BF397726_PROBE1)</a>		2.09E-6						
<input checked="" type="checkbox"/> <a href="#">low-density lipoprotein receptor-related protein 10 (Non-specific probe) (1...</a>		1.45E-6						
<input checked="" type="checkbox"/> <a href="#">F-box protein FBL2 (DBSS) (1381961_at)</a>		1.06E-2						
<input checked="" type="checkbox"/> <a href="#">Transcribed locus (1381317_at)</a>		5.61E-3						
<input checked="" type="checkbox"/> <a href="#">cytochrome P450, family 17, subfamily a, polypeptide 1 (1387123_at,M21...</a>		1.77E-7						
<input checked="" type="checkbox"/> <a href="#">sorting nexin associated golgi protein 1 (DBSS) (1390064_at)</a>		2.18E-3						
<input checked="" type="checkbox"/> <a href="#">Transcribed locus (1380306_at)</a>		3.14E-5						
<input checked="" type="checkbox"/> <a href="#">alpha-2-macroglobulin (1367794_at,J02635_PROBE1)</a>		4.14E-6						
<input checked="" type="checkbox"/> <a href="#">ATP-binding cassette, sub-family G (WHITE), member 8 (1369440_at)</a>		3.65E-5						
<input checked="" type="checkbox"/> <a href="#">hypothetical protein MGC35130 (DBSS) (1386132_at)</a>		2.10E-4						
<input checked="" type="checkbox"/> <a href="#">ESTs (1374610_at,AI599365_PROBE1)</a>		2.59E-4						

# DrugMatrix Analysis of DE-71- Signature Scoring

DE71\_21.0D\_50.0MG/KG\_LIVER

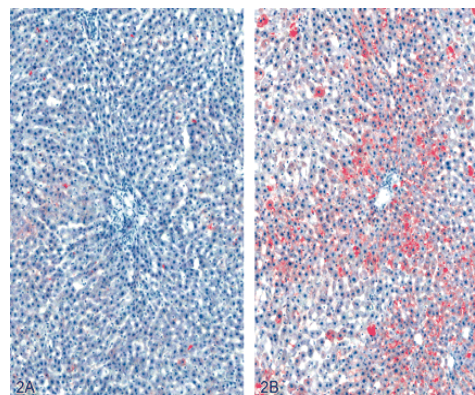
TRANSOR. RESP.

SIMILAR INDUCED REPRESSED DENDROGRAM CLIN. PATH. MOTIF SPLP TRANK HISTOPATHOLOGY

> MENU DRUG CLASSIFIER

SIGNATURE NAME	SP SCORE	POSTERIOR	LOGIT	DERIVATION
<input checked="" type="checkbox"/> <a href="#">Hepatic hypertrophy, centrilobular LIVER RG230-2 ASPLP ToxFX.1.2.4</a>	2.668	0.999835654...	6.9067547...	RG230-2
<input checked="" type="checkbox"/> <a href="#">Hepatic lipid accumulation, centrilobular LIVER RG230-2 SPLP ToxFX.1.2.4</a>	0.93	0.902890876...	2.2297663...	RG230-2
<input checked="" type="checkbox"/> <a href="#">Hepatic lipid accumulation, macrovesicular LIVER RG230-2 ASPLP ToxFX.1.2.4</a>	0.482	0.873777575...	1.9347802...	RG230-2
<input checked="" type="checkbox"/> <a href="#">Hepatic lipid accumulation, periportal LIVER RG230-2 SPLP ToxFX.1.2.4</a>	0.192	0.776136029...	1.2432892...	RG230-2
<input checked="" type="checkbox"/> <a href="#">Hepatomegaly LIVER RG230-2 ASPLP ToxFX.1.2.4</a>	0.292	0.775934833...	1.2421316...	RG230-2

Rat Liver - Oil Red O



Vehicle

DE71

Dunnick, *et al*, Tox. Path., 2012



## DrugMatrix Analysis of DE-71- Chemical Enrichment Analysis

- Chemical ontology enrichment analysis of the top 25 most similar expression studies (Hypergeometric Analysis)

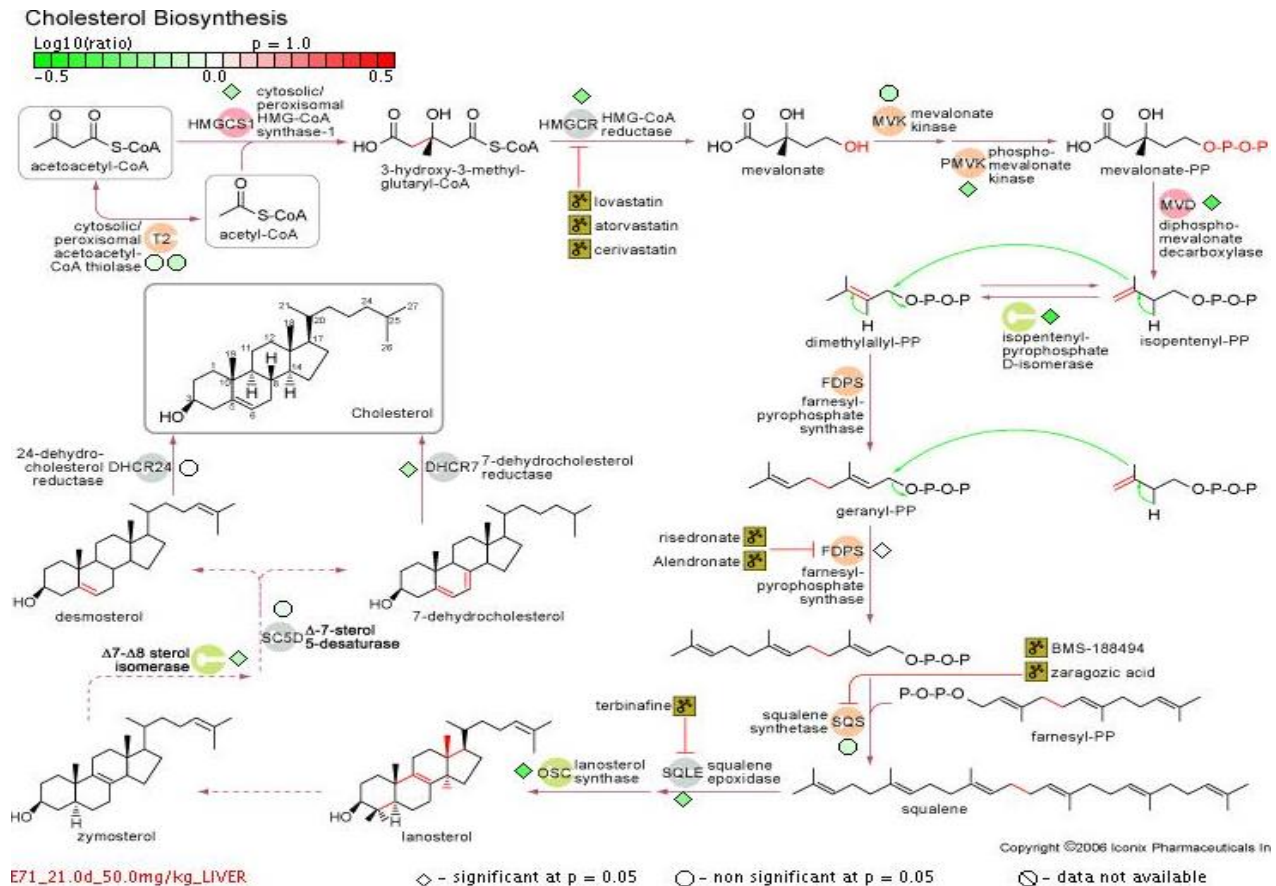
	A	B	C
1	CATEGORY	TERM	PVALUE
2	MECH_LEVEL_3	aromatase *	4.17E-06
3	MECH_LEVEL_2	Inhibit estrogen biosynthesis *	4.44E-06
4	SOLVENT	CMC .5 %	8.35E-06
5	ADVERSE_EFFECT	BBM_2_Bone Marrow Toxicity	1.07E-06
6	ADVERSE_EFFECT	NEU_1_Ataxia	3.35E-06
7	ADVERSE_EFFECT	END_2_Acute Intermittent Porphyria	1.07E-06
8	ADVERSE_EFFECT	KID_3_Acute Tubular Necrosis	1.07E-06
9	STRUCTURE_ACTIVITY	NSAID, COX-3, antipyrene like	1.07E-06
10	STRUCTURE_ACTIVITY	Estrogen antagonist, aromatase inhibitor *	6.99E-07

\* DE-71 has been shown to alter aromatase activity in number of studies

# DrugMatrix Analysis of DE-71- Pathway Analysis

Pathway	% Gene Changed in Pathway
Cholesterol Biosynthesis	75
Xenobiotic Metabolism	52
Bile Acid Synthesis	50

\*Multiple subchronic studies have observed increases in serum cholesterol following DE71 exposure





## Conclusions

- Identified 3 hepatic/non-hepatic toxicological effects of DE-71
  - Steatosis
  - Repro-related endocrine perturbations
  - Alterations in lipid homeostasis
  - Overall profile suggests DE-71 may exacerbate metabolic syndrome
- Suggestion of an AhR, CAR/PXR related MOA
- Helps focus future toxicological assessments



**NTP**  
National Toxicology Program

**QUESTIONS???**

