NTP
National Toxicology Program

The DrugMatrix® Database

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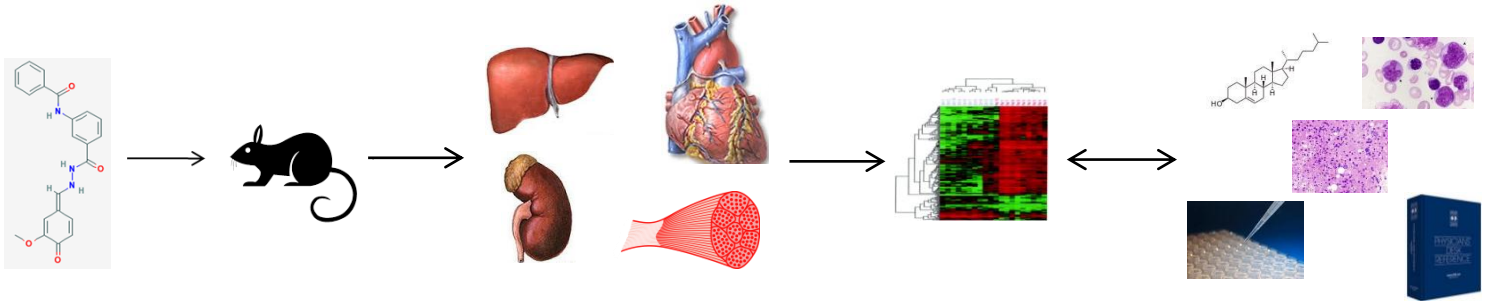
CHE Conference Call

13 December 2012



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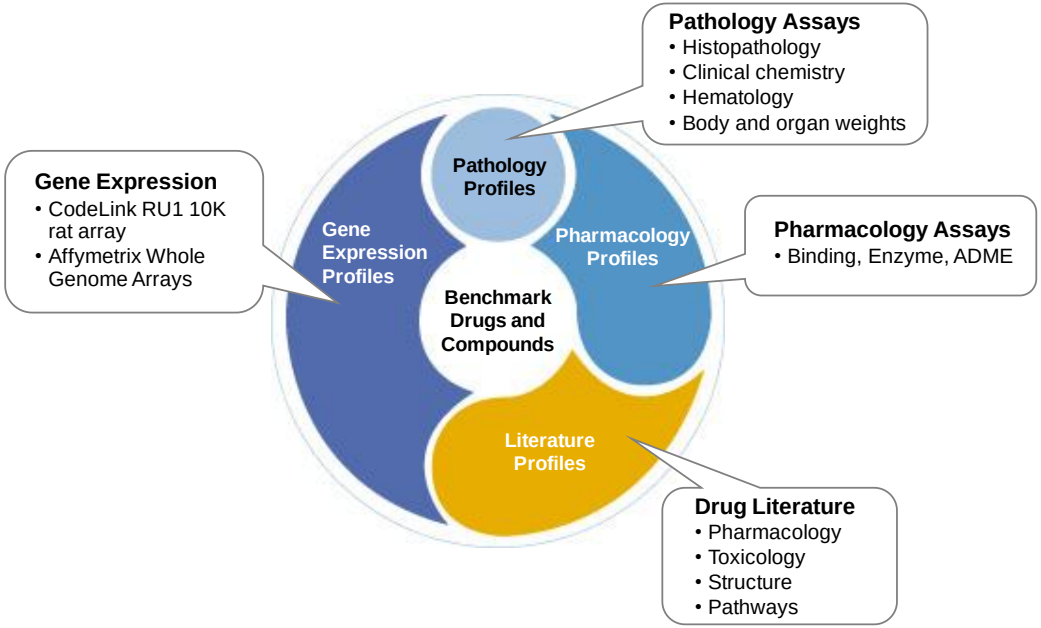
Outline

- Part 1: Overview of DM
- Part 2: Example Application of DM in a Short-term Toxicity Assessments

Part 1:
Overview of DrugMatrix



DrugMatrix

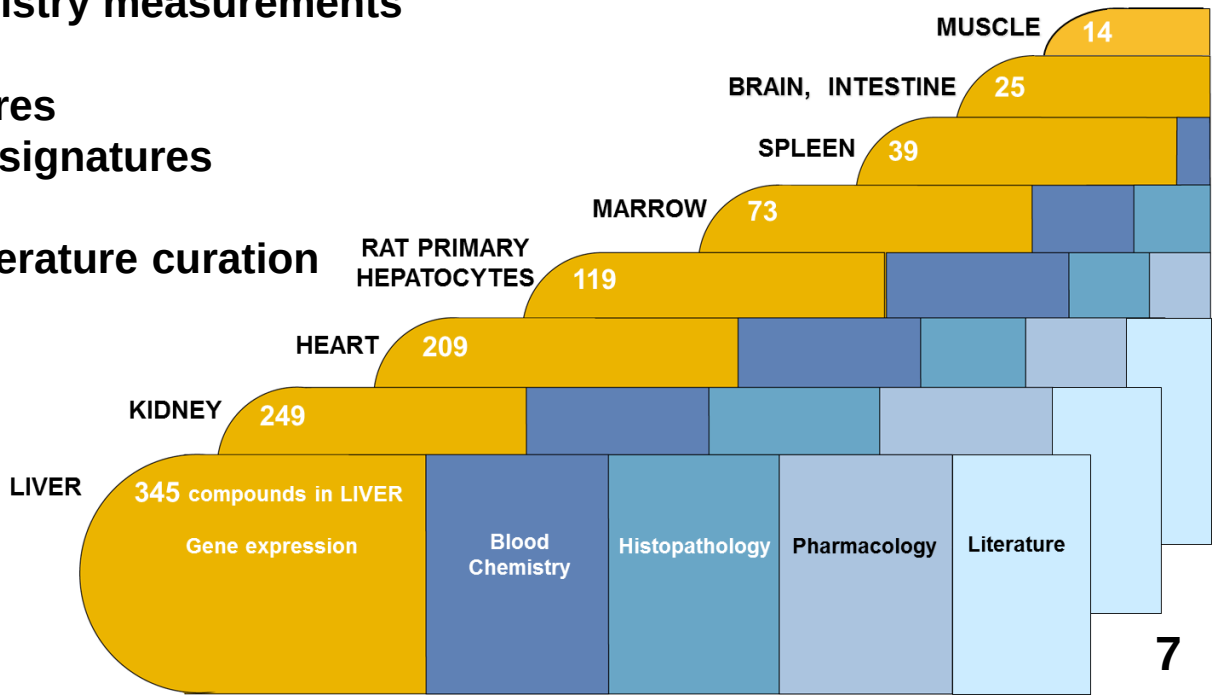
- DrugMatrix
  - Large-scale Rat Toxicogenomics Database and Analysis Tool
  - https://ntp.niehs.nih.gov/drugmatrix/index.html
- Originally owned by Iconix Pharmaceuticals and Entelos, Inc.
  - No data for these resources were generated by NTP
- Acquired by NTP in late 2010

Goals of Acquisition

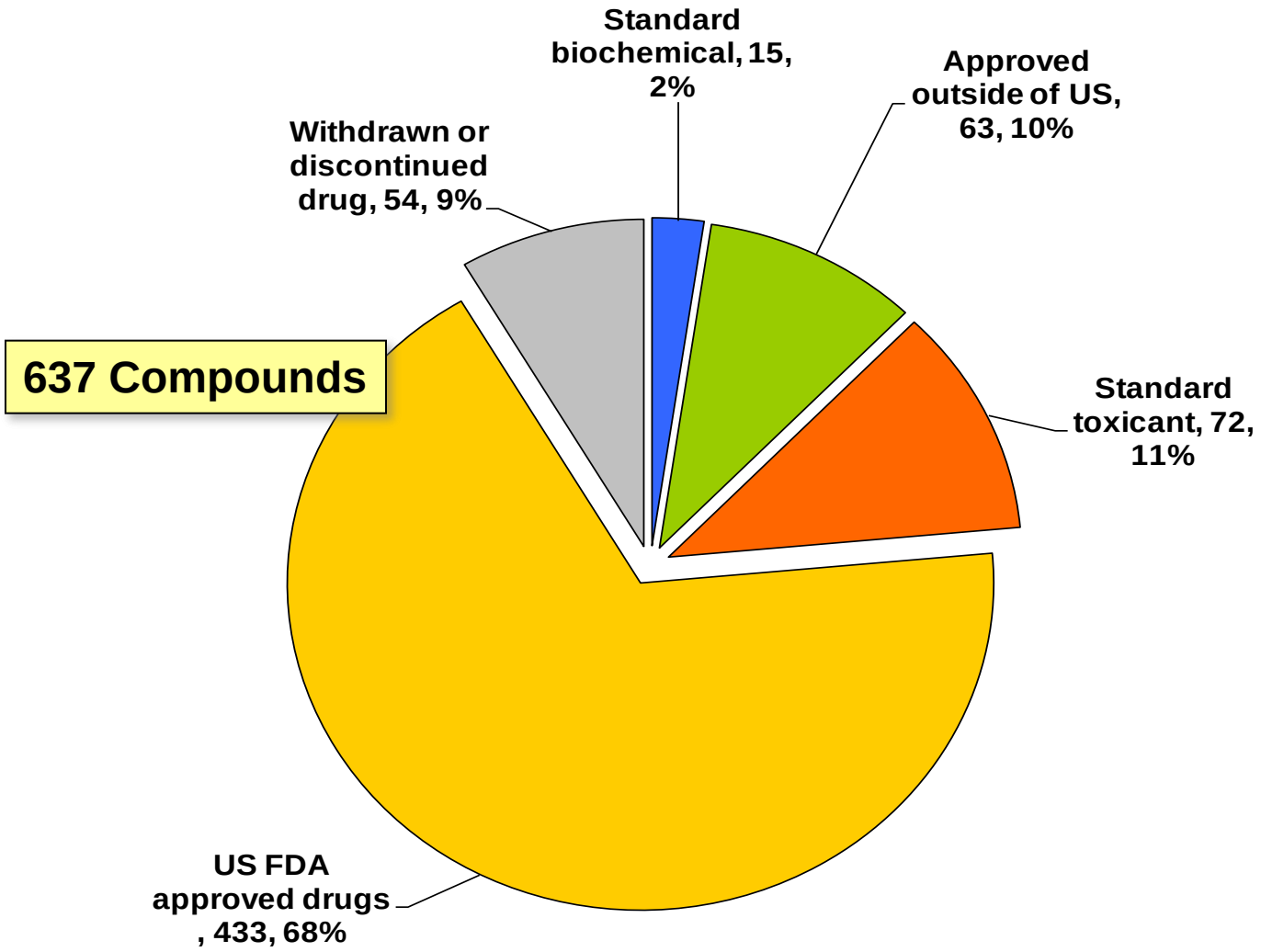
- Make the computational and data resources **open to the public (no fee)**
- Facilitate the **integration** of toxicogenomics into hazard characterization
- **Build a bridge** between traditional toxicology and Tox21

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



DrugMatrix Chemical Diversity



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 Functionality and Analysis Tools

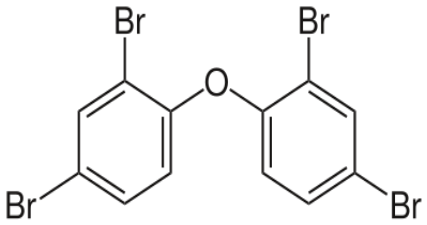
- Upload your own data for analysis or mine the DrugMatrix data
  - Data you upload is private – not shared with the government or other users
- Contextualize your data relative to over 4000 expression profiles elicited by >600 well characterized, phenotypically anchored prototype agents
- Find similar 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

Part 2:
Example Application of DrugMatrix

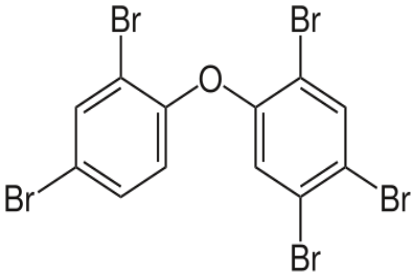
Toxicogenomic Assessment of DE-71

(Study Scientist: Dr. June Dunnick)

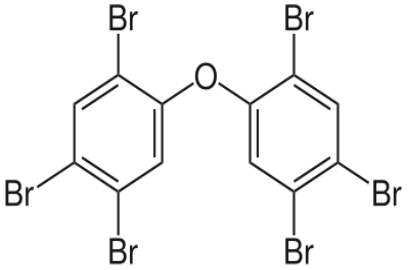
DE-71: A mixture of polybrominated diphenyl ethers



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

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

>| MENU TRANSCRIPTIONAL RESPONSES (INDUCED)

GENE	CONFIDENCE INTERVAL	P VALUE
urinary protein 2 (1370396_x_at,rc_AA945585_at)		2.68E-10
urinary protein 2 (1370349_a_at)		1.41E-10
estrogen sulfotransferase (1368733_at,M86758_at,NM_012883_PROBE1)		9.59E-8
cytochrome P450, family 2, subfamily A, polypeptide 3a (1369136_at)		1.07E-10
transmembrane protein 27 (1387013_at,NM_020976_PROBE1)		3.49E-9
CEA-related cell adhesion molecule 10 (Non-specific probe) (1370371_a_at)		1.78E-11
urinary protein 2 (1389270_x_at)		1.87E-5
cytochrome P450, family 2, subfamily c, polypeptide 29 (DBSS_moderate) (139615...		0.00E0
Kruppel-like factor 2 (lung) (DBSS) (1386040_at)		1.11E-12
CLIP associating protein 2 (1396604_at)		1.50E-7
Iroquois related homeobox 2 (Drosophila) (1391457_a_at)		1.30E-9
cytochrome P450, family 1, subfamily a, polypeptide 1 (1370269_at)		1.63E-6
cytochrome P450 2c13 (1370495_s_at,M82855cds_s_at)		7.54E-6
RT1 class I, CE10 (1388202_at)		1.14E-4
Cytochrome P450 2C24 (CYPIIC24) (P450-PROS2) (DBSS) (1370241_at,M18335_f...		1.14E-9
ESTs (1397343_at)		8.82E-8
Transcribed locus (1380543_at)		7.32E-10
cytochrome P450, family 2, subfamily b, polypeptide 13 (1387993_at)		2.69E-8
leptin (1387748_at)		9.76E-8
MGC14161 protein (DBSS) (1396720_at)		1.50E-7

Repressed

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>| MENU TRANSCRIPTIONAL RESPONSES (REPRESSED)

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

DrugMatrix Analysis of DE-71- Signature Scoring

DE71_21.OD_50.OMG/KG_LIVER

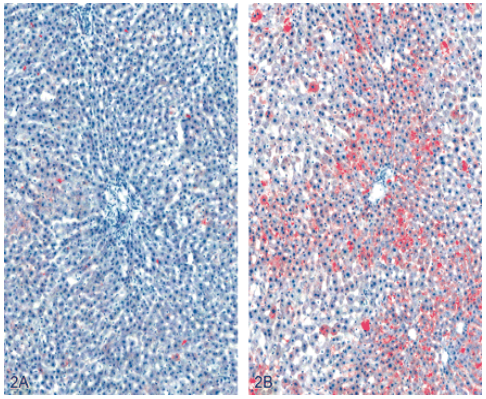
TRANSCR. RESP.

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

MENU | DRUG CLASSIFIER

SIGNATURE NAME	SP SCORE	POSTERIOR	LOGIT	DERIVATION
Hepatic hypertrophy, centrilobular LIVER RG230-2 ASPLP ToxFX.1.2.4	2.668	0.999835654...	6.9067547...	RG230-2
Hepatic lipid accumulation, centrilobular LIVER RG230-2 SPLP ToxFX.1.2.4	0.93	0.902890876...	2.2297663...	RG230-2
Hepatic lipid accumulation, macrovesicular LIVER RG230-2 ASPLP ToxFX.1.2.4	0.482	0.873777575...	1.9347802...	RG230-2
Hepatic lipid accumulation, periportal LIVER RG230-2 SPLP ToxFX.1.2.4	0.192	0.776136029...	1.2432892...	RG230-2
Hepatomegaly LIVER RG230-2 ASPLP ToxFX.1.2.4	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)

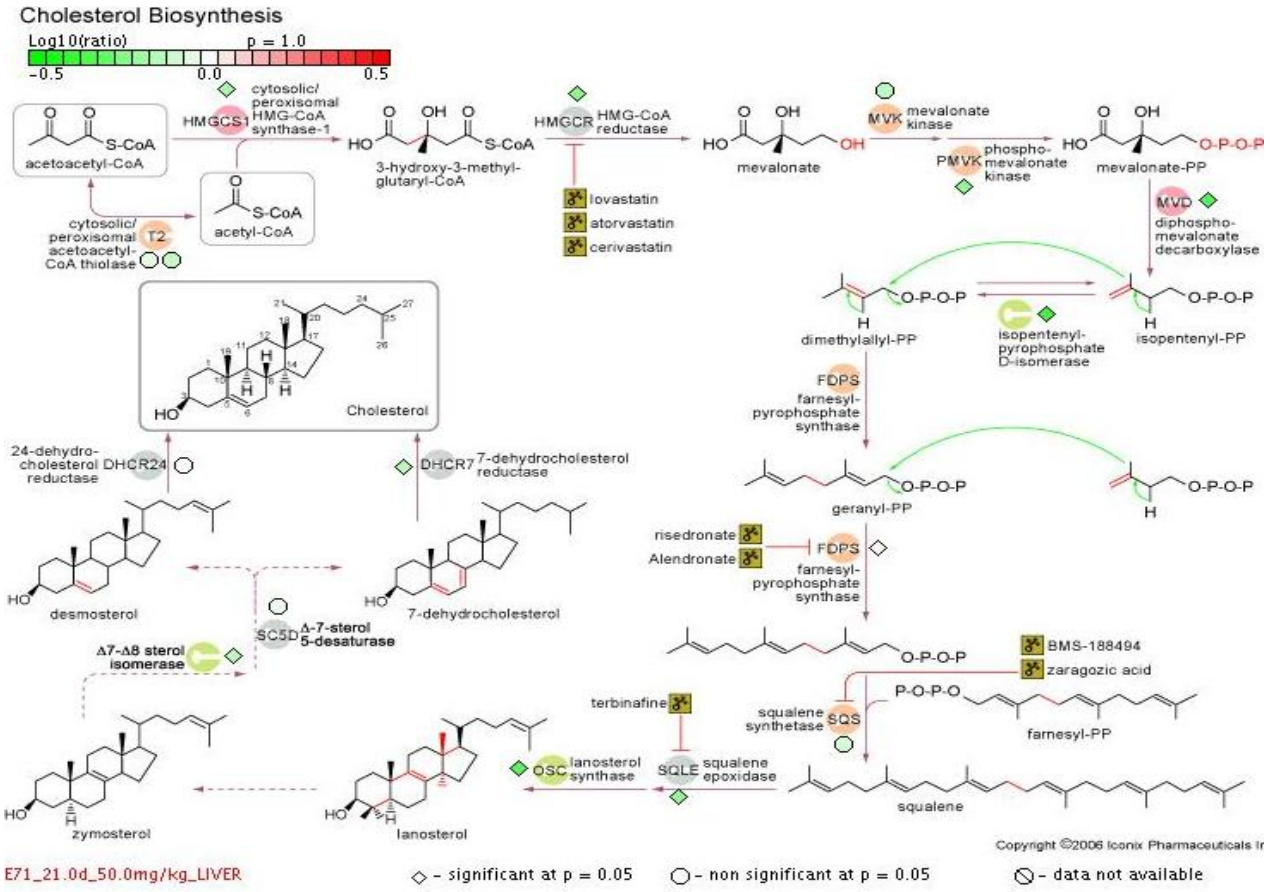
	A	B	C
1	CATEGORY	TERM	PVALUE
2	MECH_LEVEL_3	aromatase *	4.17E-06
3	MECH_LEVEL_2	Inhibit estrogen biosynthesis *	4.44E-06
4	SOLVENT	CMC .5 %	8.35E-06
5	ADVERSE_EFFECT	BBM_2_Bone Marrow Toxicity	1.07E-06
6	ADVERSE_EFFECT	NEU_1_Ataxia	3.35E-06
7	ADVERSE_EFFECT	END_2_Acute Intermittent Porphyria	1.07E-06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



Part 2: 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

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