NIEHS National Institute of Environmental Health Sciences

RISKeLearning

Computational Toxicology: New Approaches for the 21st Century

July 7th, 2009 Session 3: **Chemical Prioritization / Rapid Assay Techniques**

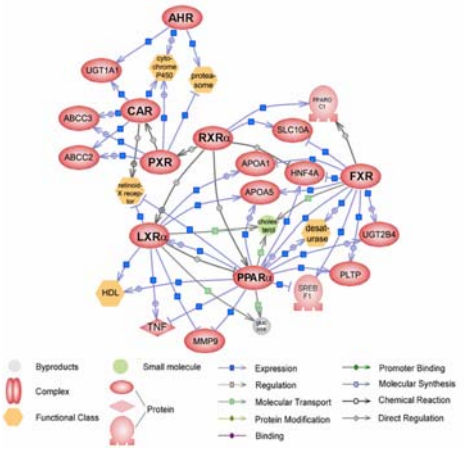
Ivan Rusyn , Ph.D., Associate Professor, Department of Environmental Sciences & Engineering, University of North Carolina at Chapel Hill

Richard Judson , Ph.D., Bioinformatician, National Center for Computational Toxicology, U.S. EPA

Srp Superfund Research Program

U.S. Department of Health and Human Services National Institute of Health National Institute of Environmental Health Services

Tools and Technologies for Pathway-Based Research



Ivan Rusyn, M.D., Ph.D.
Associate Professor
Department of Environmental Sciences & Engineering
University of North Carolina
Chapel Hill, NC, USA

1. Data collection:

•Understanding the host organism (genotyping, phenotyping, exposure assessment)

•Measuring adverse health effects of environmental agents (technologies for screening at various scales of biological organization)

•Deciphering the interactions between chemicals and molecules - building pathways

2. Data analysis:

•Issues with data acquisition/storage

•Data analysis

•Data visualization (expert-driven vs biology-driven pathways)

3. Data interpretation/applications

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•This presentation contains reference to commercial products and technologies
•The speaker declares no conflicts of interest with regards to any commercial entity referred to herein
•The images have been obtained from public sources and appropriate credits are given, where available
•This presentation should not be interpreted as endorsement, or recommendation for use of any technology, approach or method mentioned herein
•The speaker is expressing his personal views and not those of the funding agencies (NIH and EPA)

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a quick guide to...

Genomenewsnetworks.org

SEQUENCED GENOMES

The genomes of more than 180 organisms have been sequenced since 1995. The Quick Guide includes descriptions of these organisms and has links to sequencing centers and scientific abstracts.

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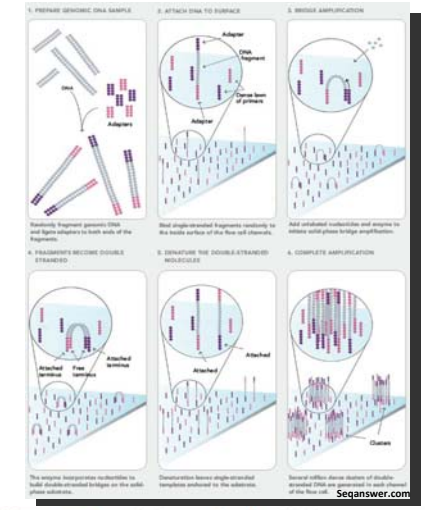
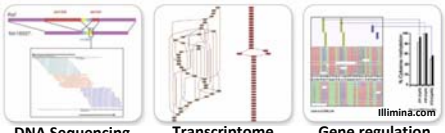
Ultra High Throughput Sequencing – Towards the "$1,000 Genome"

Illumina® "SOLEXA" Genome Analyzer





DNA Sequencing | **Transcriptome analysis** | **Gene regulation and control**

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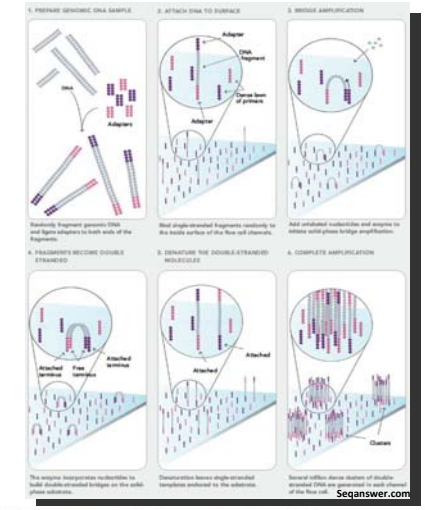
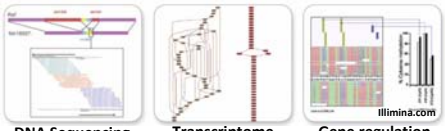
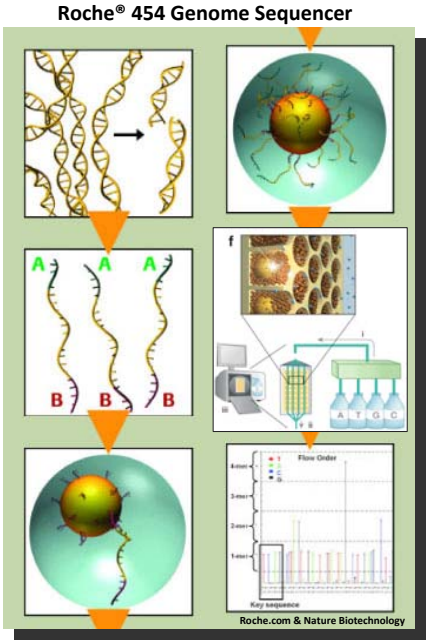




DNA Sequencing | Transcriptome analysis | Gene regulation and control

Roche® 454 Genome Sequencer



DNA Sequencing | Transcriptome analysis | Gene regulation and control

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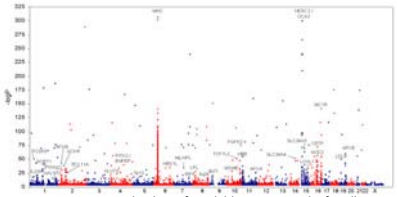
Ultra High Throughput Sequencing – Enabling GWAS Studies

Epidemiological studies: hundreds of individuals could now be genotyped for ~10^6 SNPs



Genome-wide plots of available GWAS results for all associations P = 0.0001. (*BMC Medical Genetics* 2009)

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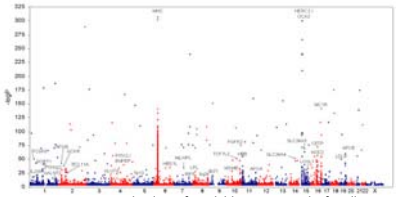

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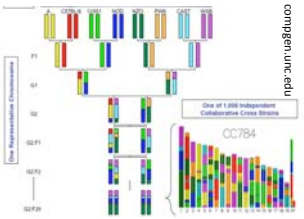
***In vivo* animal studies:** dozens of inbred mouse strains have been genotyped for ~10^7 SNPs

www.niehs.nih.gov/crg/

ornl.gov



compgen.unc.edu

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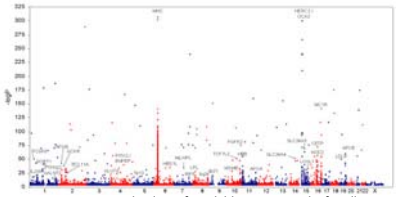

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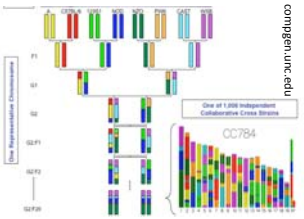

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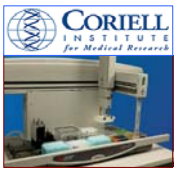
***In vitro* studies:** tens to hundreds of cell lines have been genotyped for ~10^7 SNPs



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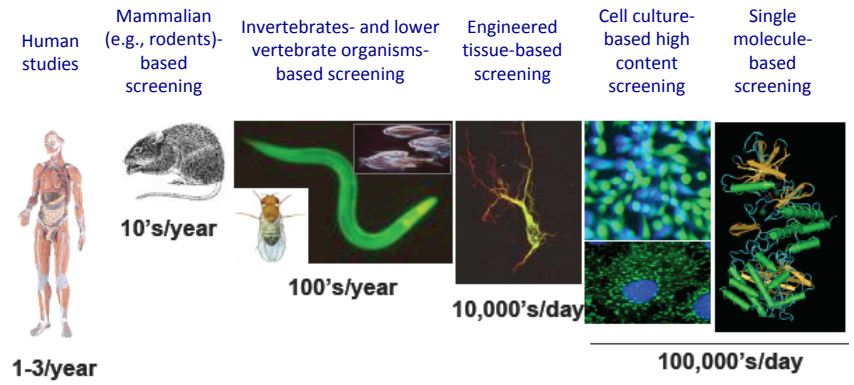
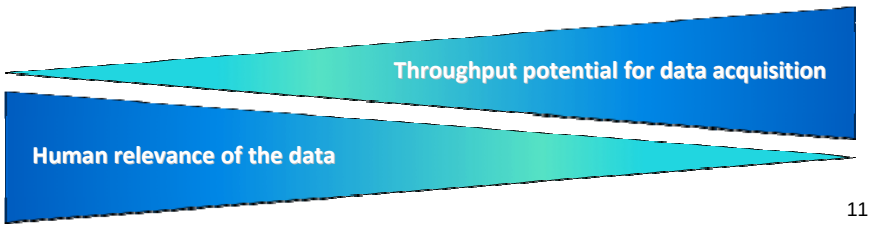
Acquiring Data for Pathway-Based Research: Scales of Biological Organization



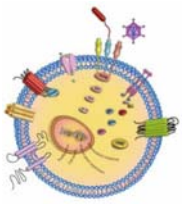


11

Image credit: R. Tice (NIEHS)

Single Molecule-Based Screening

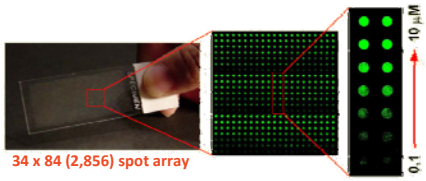
Cell-free Systems



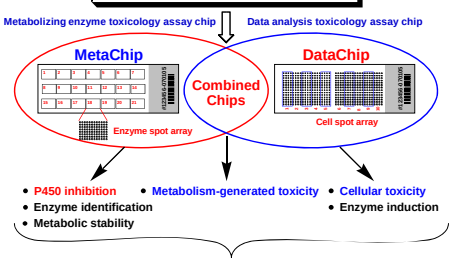
Ligand Binding Assays
- GPCRs
- Voltage- & Ligand-gated Ion channels
- Nuclear receptors
- Transporters

Enzyme Assays
- Anhydrases & Esterases
- Kinases (including protein & lipid)
- Miscellaneous (COMT, ChaT, GAD)
- Phosphatases
- Proteases (Caspase & Matrix-Metallo)
- Oxidases, Oxygenases & Reductases

Cell-based Systems



Toxicology Assay Platform



- P450 inhibition
- Metabolism-generated toxicity
- Cellular toxicity
- Enzyme identification
- Enzyme induction
- Metabolic stability

Requires active and stable human enzymes and viable human cells

Solidus Biosciences, Inc.

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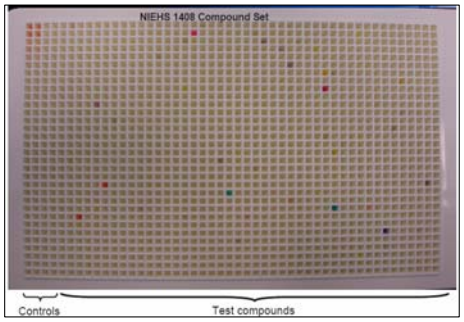
Cell Culture-Based High Content/High Throughput Screening



13

Image credit: R. Tice (NIEHS) and C. Austin (NCGC)

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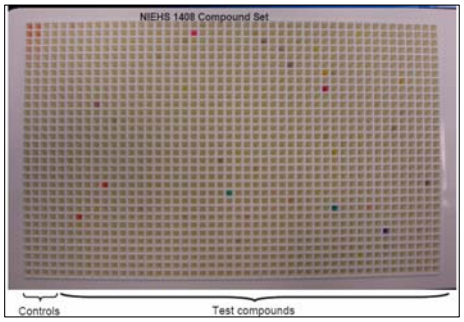

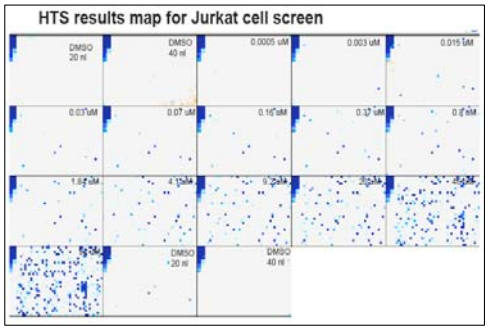

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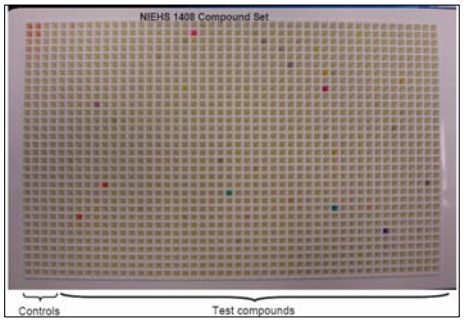

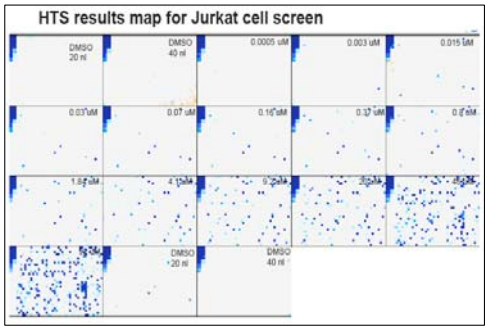

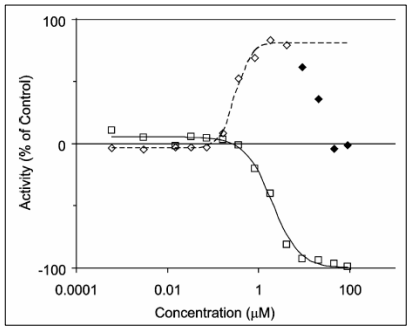

15

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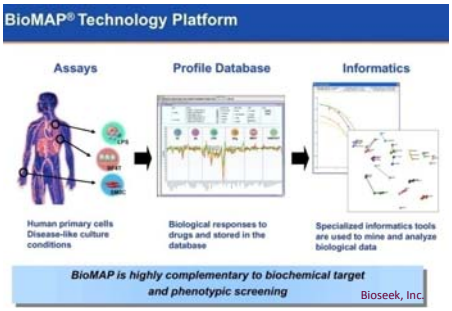
Engineered Tissue-Based Screening

Cell co-cultures and culture in presence of activators/cytokines



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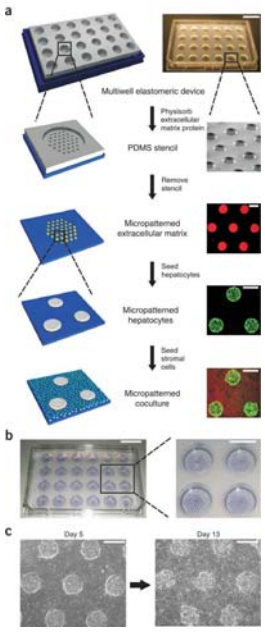
Engineered Tissue-Based Screening

Microscale liver hepatocyte cultures



Khetani & Bhatia, Nature Biotechnology (2008)

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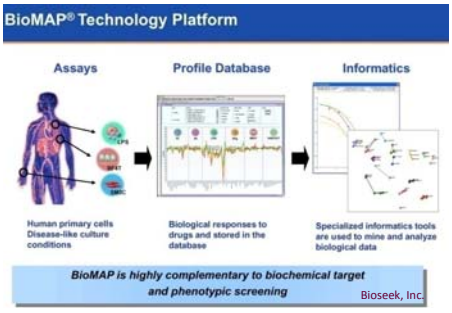

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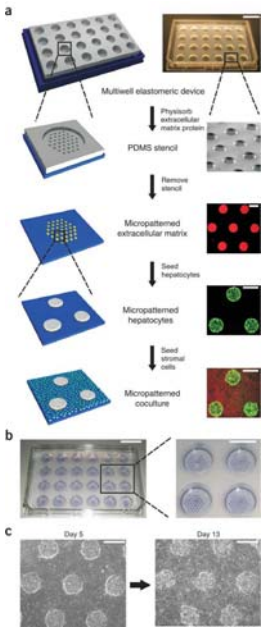

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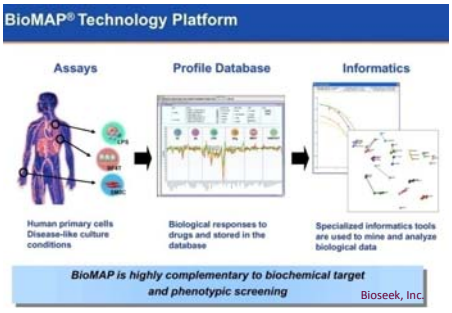
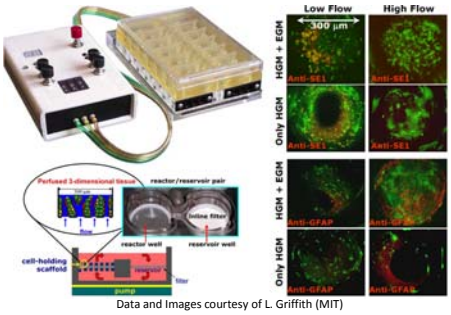


3D Liver Tissue Bioreactor



Data and Images courtesy of L. Griffith (MIT)

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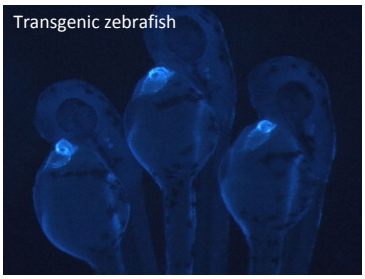
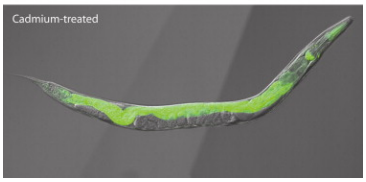
Invertebrates- and Lower Vertebrate Organisms-Based Screening





Peterson et al., NeuroToxicology (2008)

19

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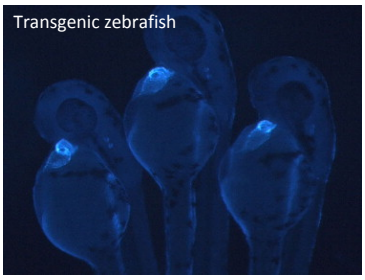

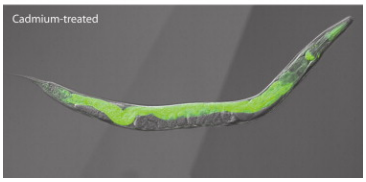

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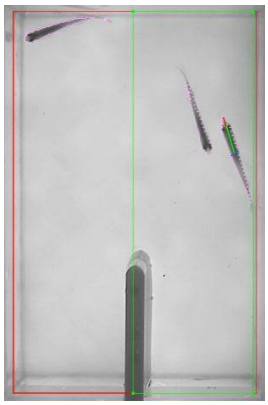

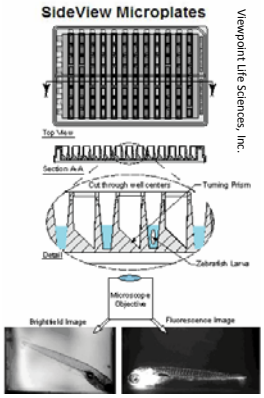

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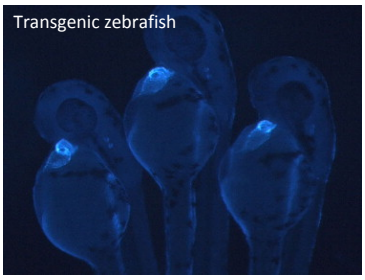

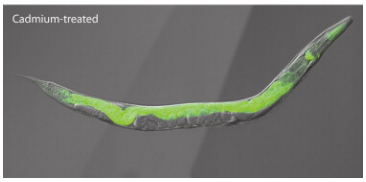

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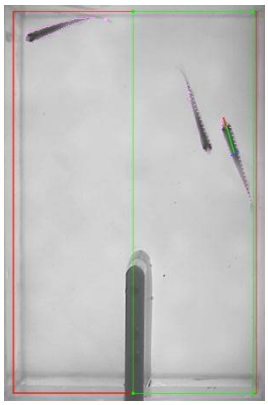
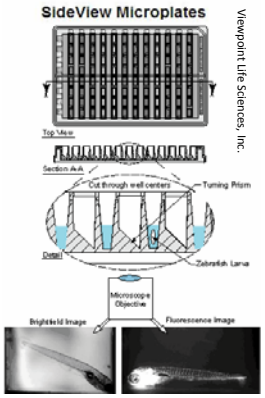
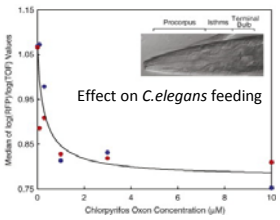
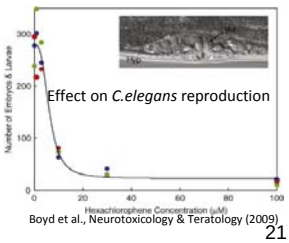




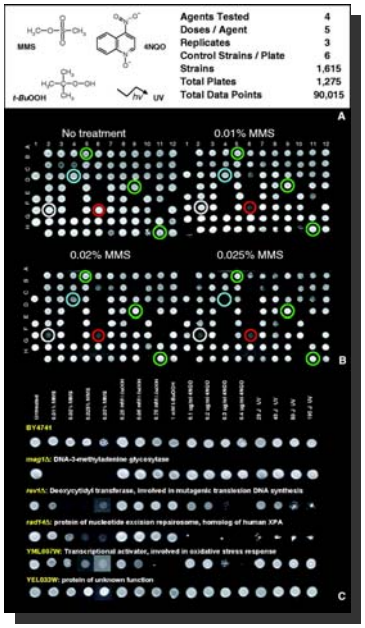




Boyd et al., Neurotoxicology & Teratology (2009)

21

Damage Recovery Pathways in *Saccharomyces cerevisiae* Revealed by Genomic Phenotyping and Interactome Mapping



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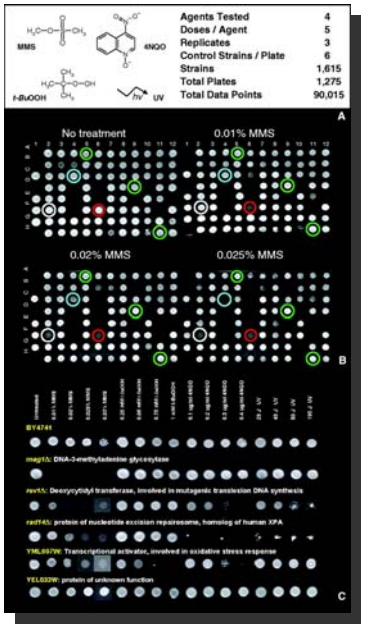

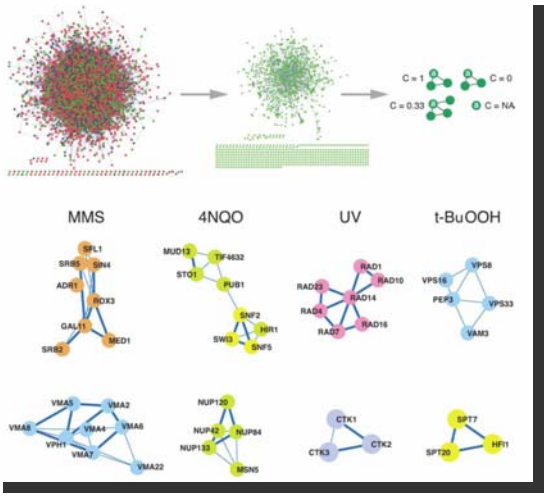

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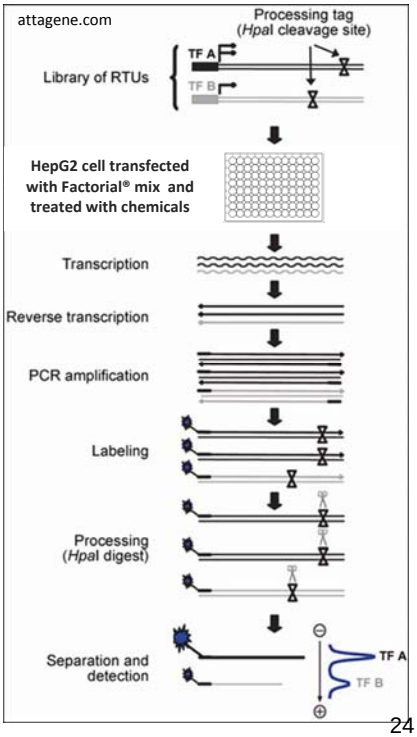
Begley et al., Molecular Cancer Research (2002)
Fry et al., Annual Review of Microbiology (2005)

NATURE METHODS | VOL.5 NO.3 | MARCH 2008 | 253

Homogeneous reporter system enables quantitative functional assessment of multiple transcription factors

Sergei Romanov[1], Alexander Medvedev[1], Maria Gambarian[1], Natalia Poltoratskaya[1], Matt Moeser[1], Liubov Medvedeva[1], Mikhail Gambarian[2], Luda Diatchenko[3] & Sergei Makarov[1]



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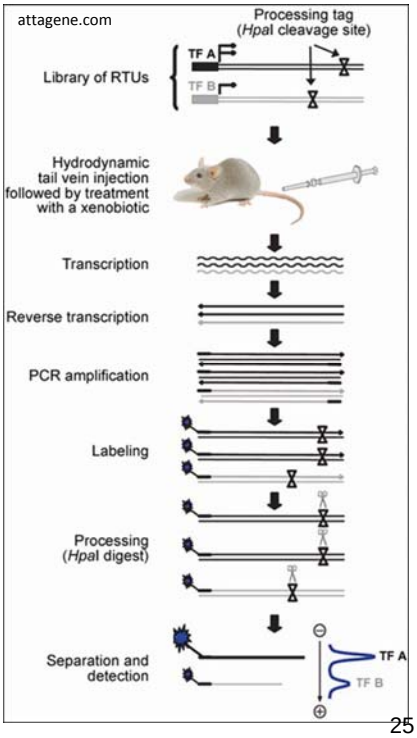

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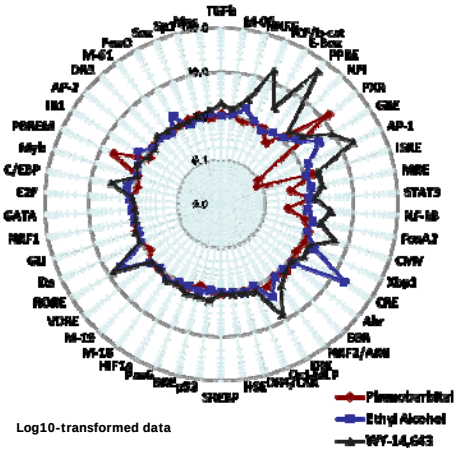
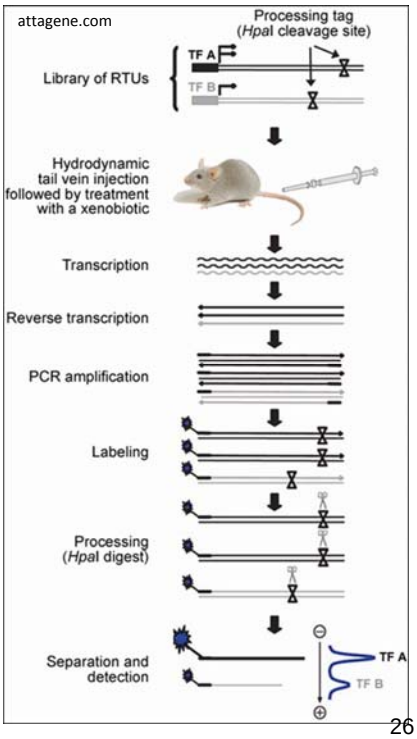
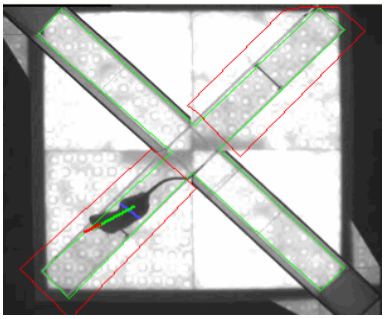
Comparative analysis of the *in vivo* liver effects of 3 toxicants



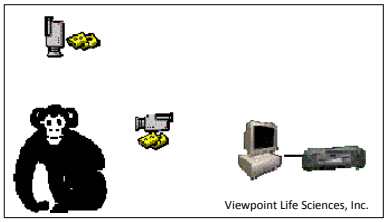


26

Mammalian Organisms-Based Screening



Viewpoint Life Sciences, Inc.



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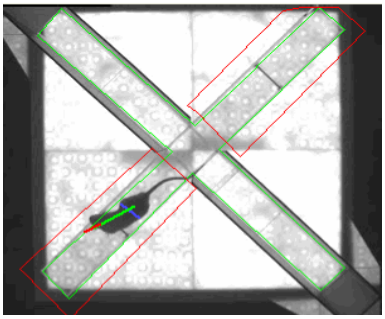
Mammalian Organisms-Based Screening



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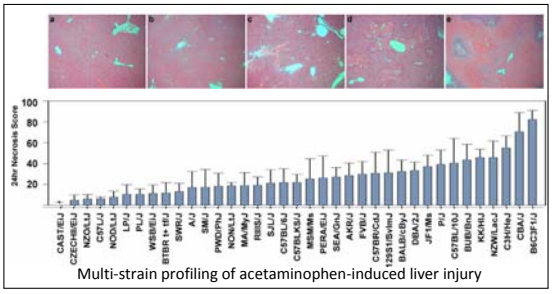
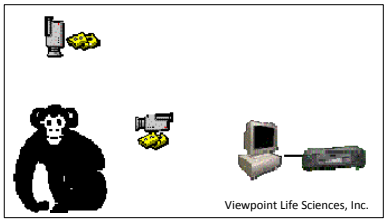


Multi-strain profiling of acetaminophen-induced liver injury

Harrill et al., Genome Research (2009)



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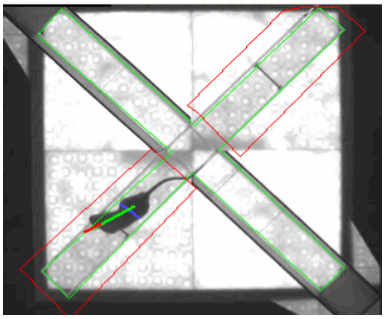
Mammalian Organisms-Based Screening



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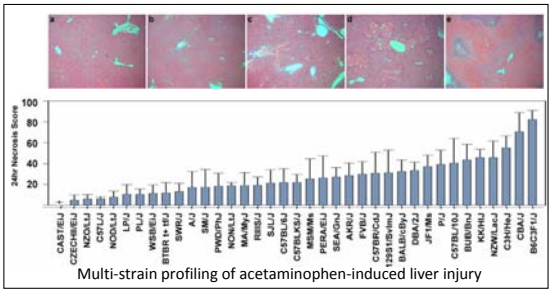

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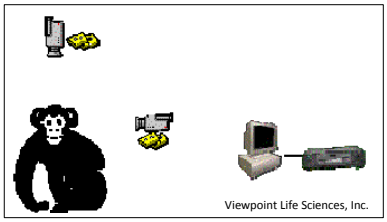

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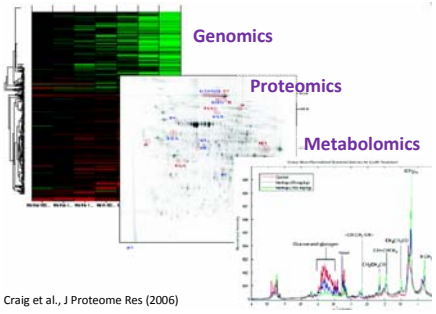
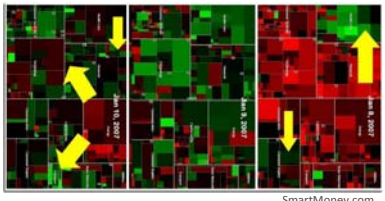


Craig et al., J Proteome Res (2006)

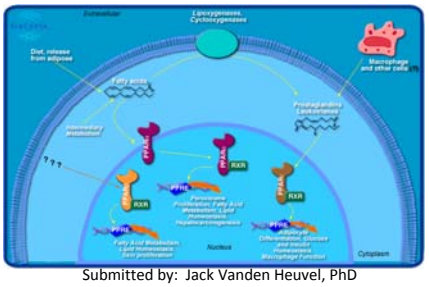
29

High-Dimension Low Sample Size Data



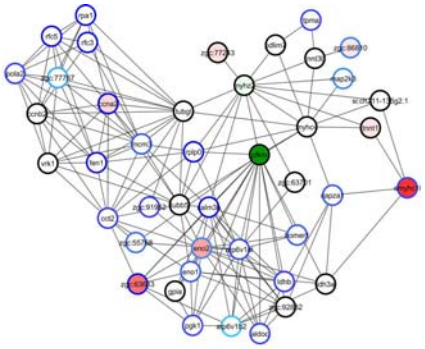
SmartMoney.com

BIOCARTA PATWAY: Basic mechanism of action of PPARα, PPARβ(δ) and PPARγ and effects on gene expression

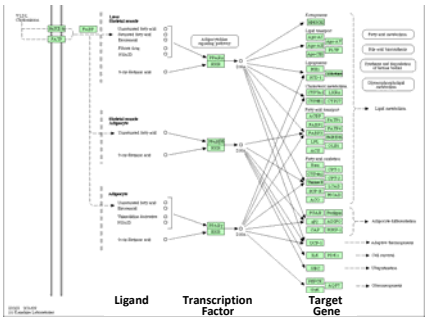


Submitted by: Jack Vanden Heuvel, PhD

Cytoscape-generated NETWORK (also referred to as INTERACTOME)



KEGG PATWAY: PPAR signaling



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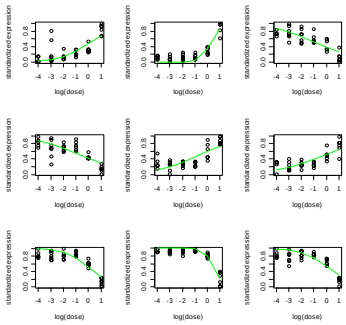
Dose-Response Pathway Analysis for Gene Expression Data



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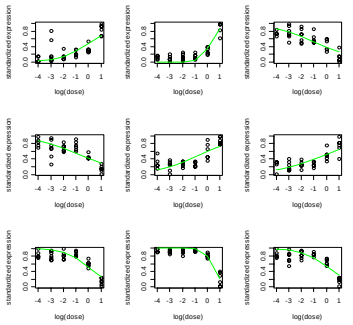
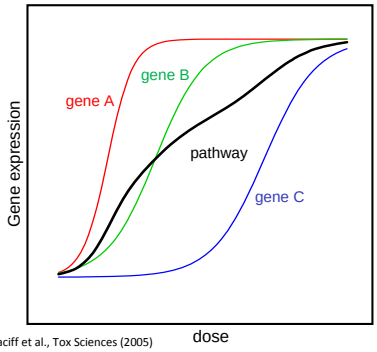
Dose-Response Pathway Analysis for Gene Expression Data

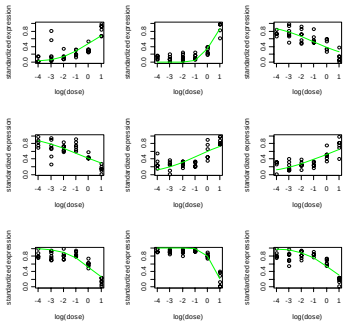


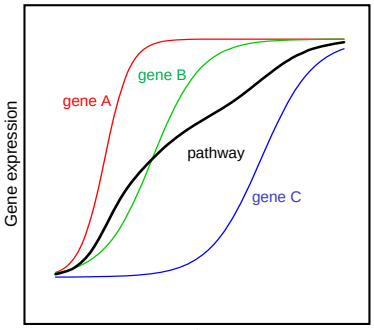


Data from Naciff et al., Tox Sciences (2005)

32

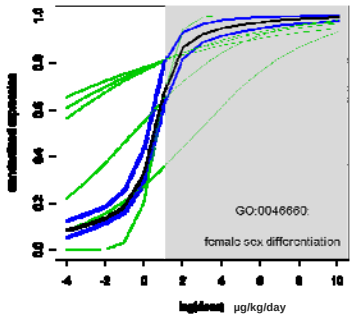
Dose-Response Pathway Analysis for Gene Expression Data

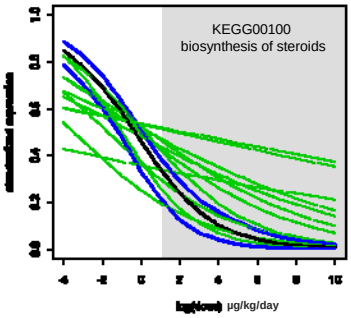




Data from Naciff et al., Tox Sciences (2005)

Pathway Dose Response Profiles





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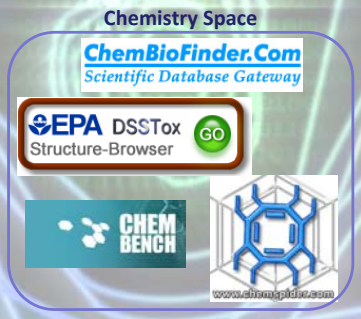
Sending The Data To The Cyberspace: Who Will Find It?
34

Sending The Data To The Cyberspace: Who Will Find It?



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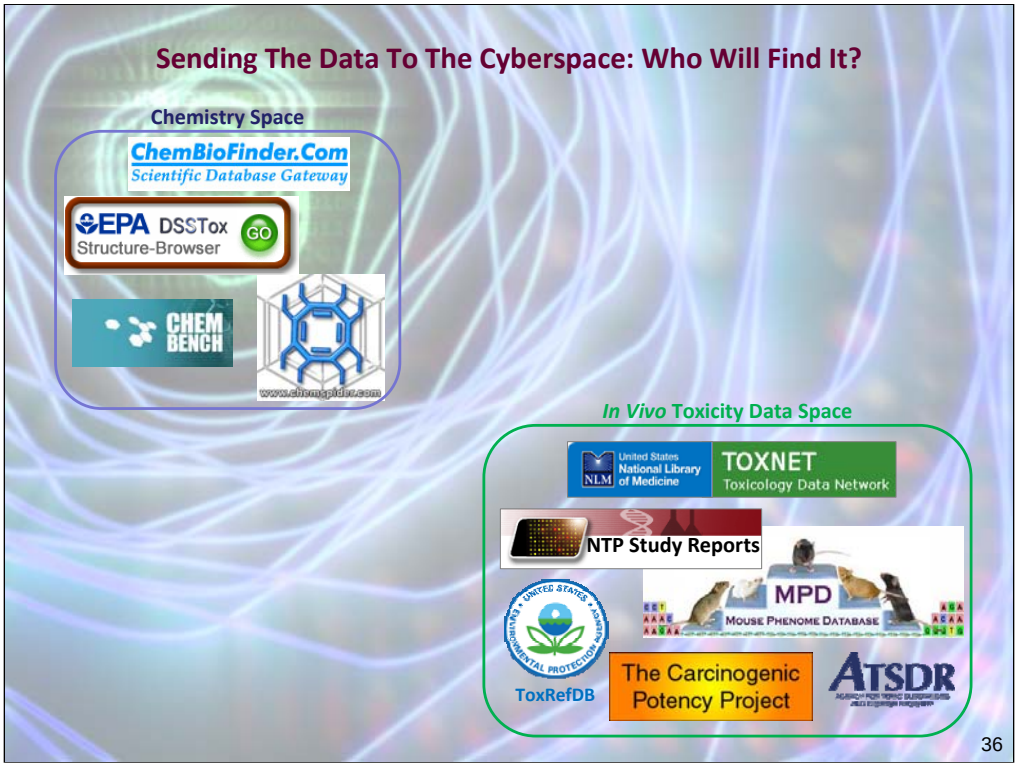
Sending The Data To The Cyberspace: Who Will Find It?



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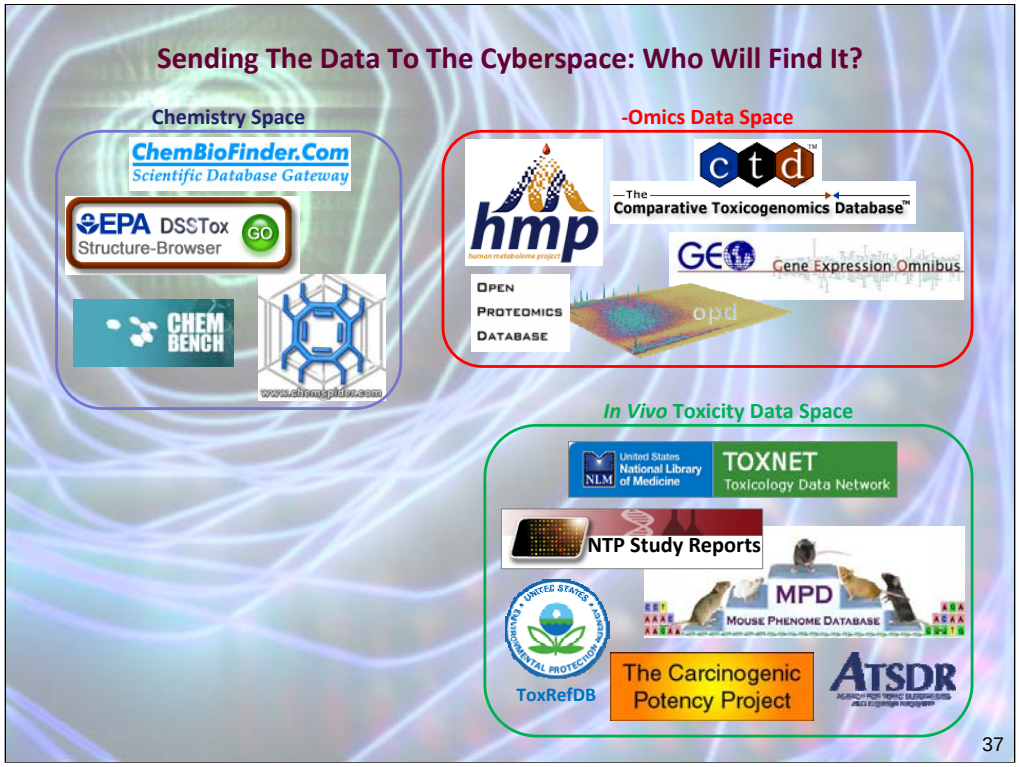
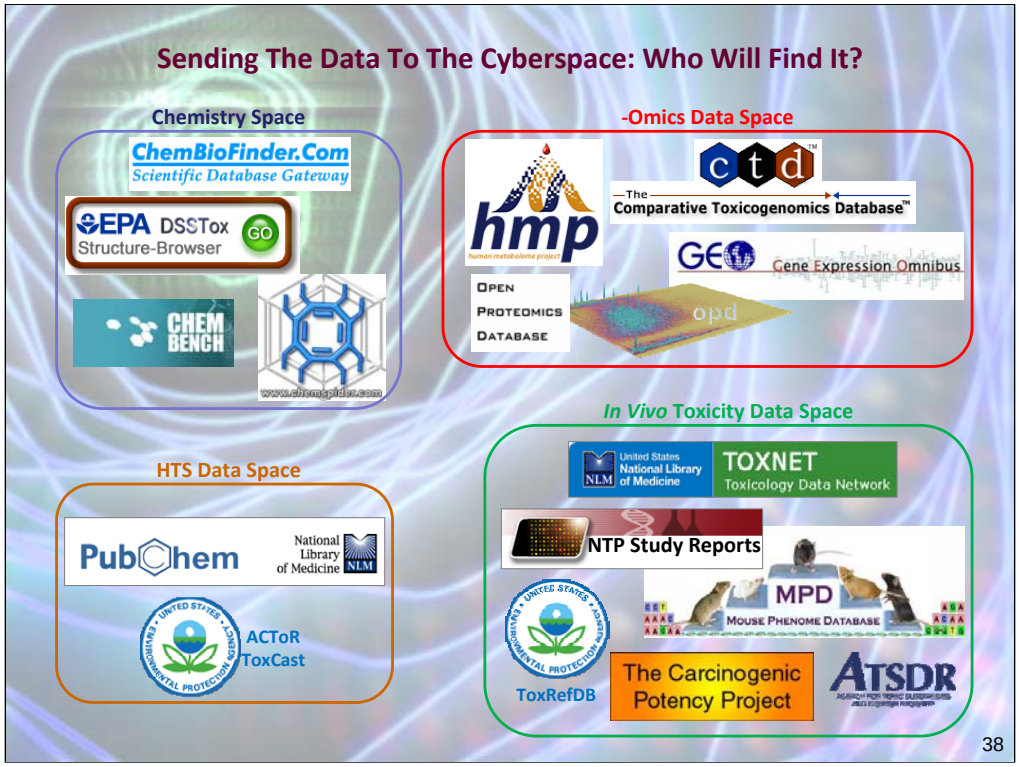

Sending The Data To The Cyberspace: Who Will Find It?
Chemistry Space
ChemBioFinder.Com
Scientific Database Gateway
EPA DSSTox
Structure-Browser
GO
CHEM BENCH
www.chemspider.com
-Omics Data Space
hmp
human metabolome project
ctd
The Comparative Toxicogenomics Database
GEO
Gene Expression Omnibus
OPEN PROTEOMICS DATABASE
opd
In Vivo Toxicity Data Space
United States National Library of Medicine
NLM
TOXNET
Toxicology Data Network
NTP Study Reports
MPD
Mouse Phenome Database
ToxRefDB
The Carcinogenic Potency Project
ATSDR
37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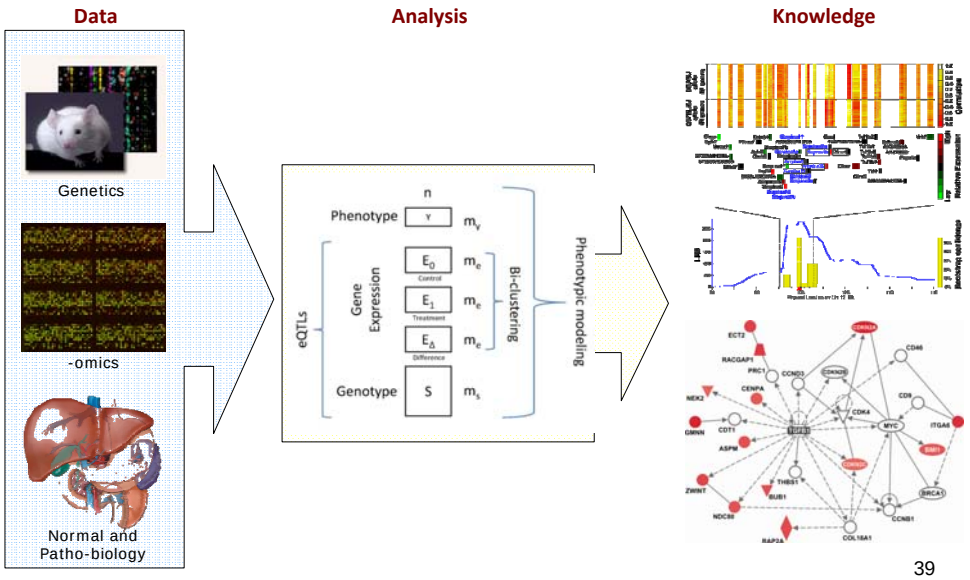
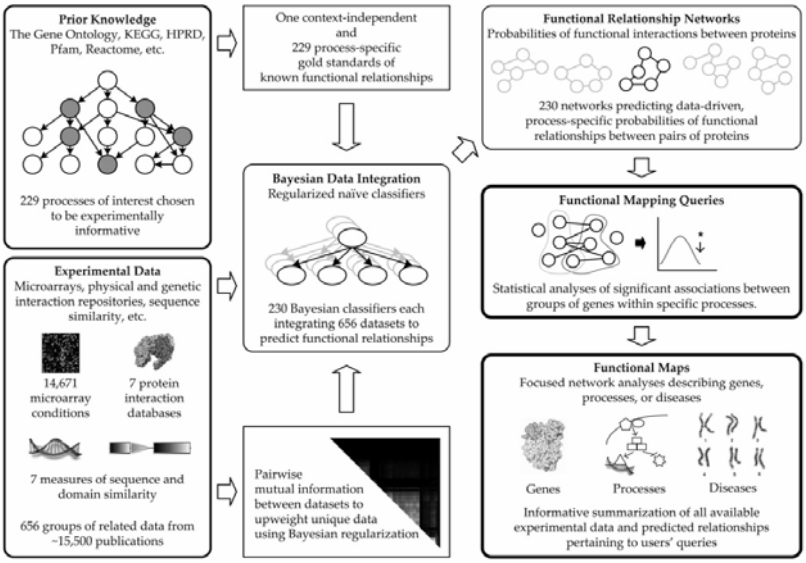
NTP Study Reports
MPD
Mouse Phenome Database
ToxRefDB
The Carcinogenic Potency Project
ATSDR
HTS Data Space
PubChem
National Library of Medicine
ACToR
ToxCast
38

Population-wide predictions from toxicity profiling: linking toxicology with –omics and genetics



39

Exploring the human genome with functional maps



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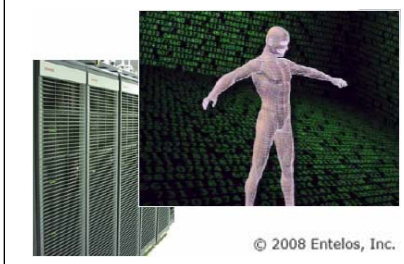
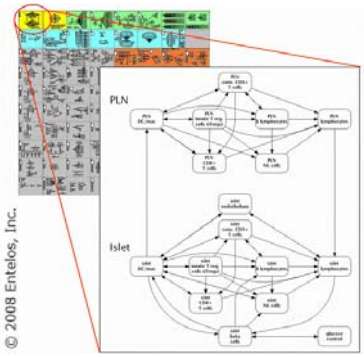
Huttenhower et al., Genome Research (2009)





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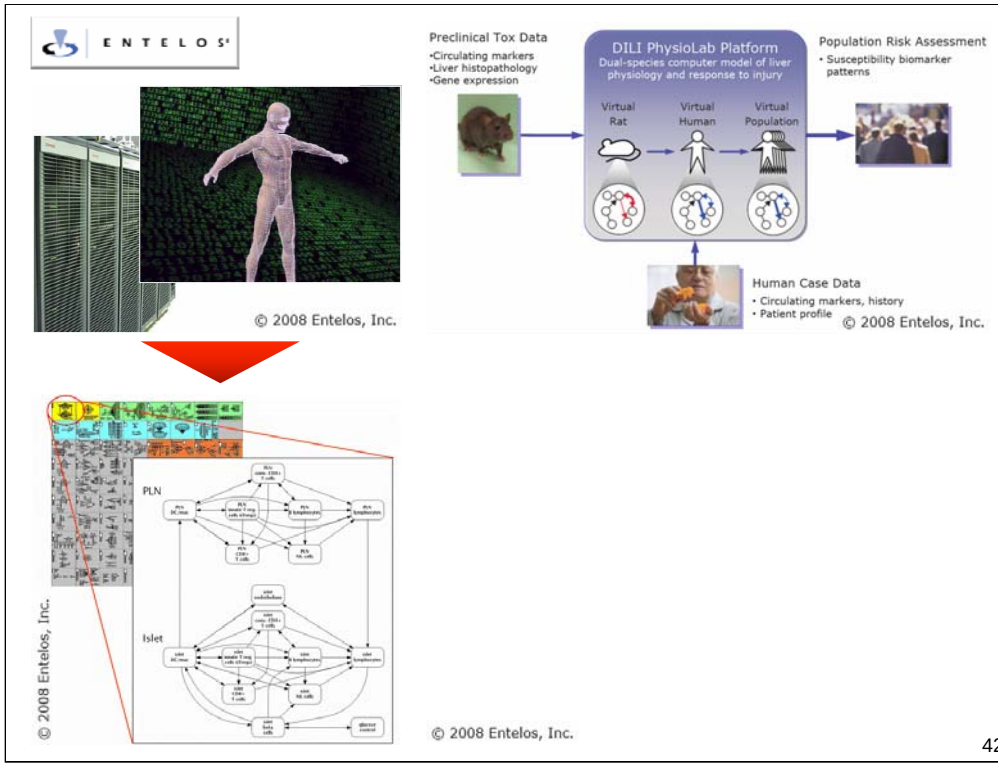
ENTELOS
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Preclinical Tox Data
•Circulating markers
•Liver histopathology
•Gene expression
DILI PhysioLab Platform
Dual-species computer model of liver physiology and response to injury
Virtual Rat
Virtual Human
Virtual Population
Population Risk Assessment
• Susceptibility biomarker patterns
Human Case Data
• Circulating markers, history
• Patient profile
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PLN
Islet
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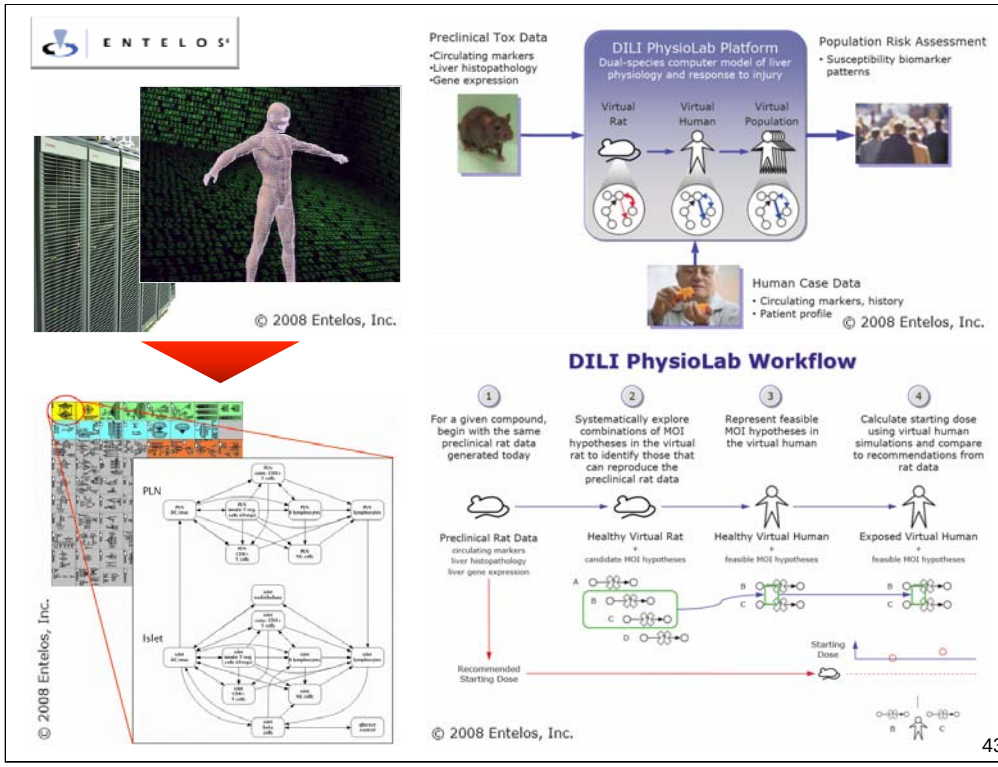
ENTELOS
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Preclinical Tox Data
•Circulating markers
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DILI PhysioLab Platform
Dual-species computer model of liver physiology and response to injury
Virtual Rat
Virtual Human
Virtual Population
Population Risk Assessment
• Susceptibility biomarker patterns
Human Case Data
• Circulating markers, history
• Patient profile
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PLN
Islet
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DILI PhysioLab Workflow
1
For a given compound, begin with the same preclinical rat data generated today
2
Systematically explore combinations of MOI hypotheses in the virtual rat to identify those that can reproduce the preclinical rat data
3
Represent feasible MOI hypotheses in the virtual human
4
Calculate starting dose using virtual human simulations and compare to recommendations from rat data
Preclinical Rat Data
circulating markers
liver histopathology
liver gene expression
Healthy Virtual Rat
candidate MOI hypotheses
Healthy Virtual Human
feasible MOI hypotheses
Exposed Virtual Human
feasible MOI hypotheses
Recommended Starting Dose
Starting Dose
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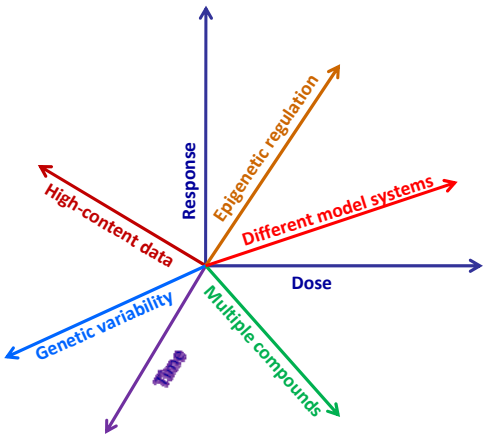
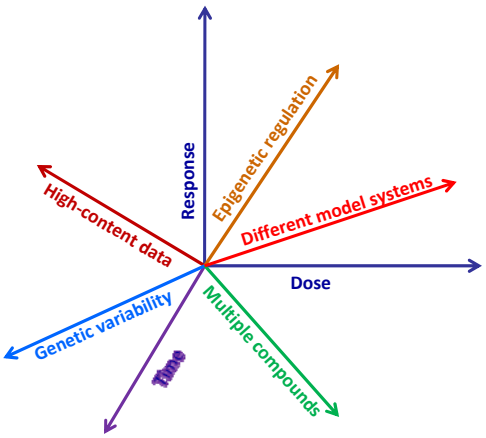

Response
Epigenetic regulation
Different model systems
Dose
Multiple compounds
Time
Genetic variability
High-content data

44


The More I Think
The More Confused I Get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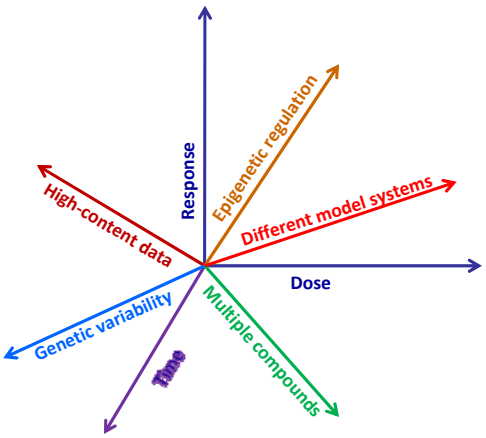
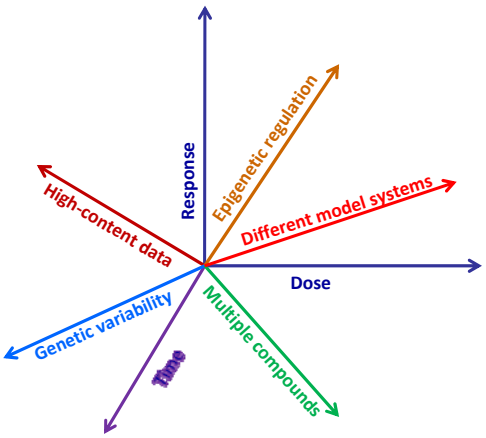
45



ROAD READY

Interdisciplinary graduate training program

46



ROAD READY

Interdisciplinary graduate training program

47

Use of Emerging Science for Environmental Health Decisions

A Standing Committee of the National Academies

Thomas A. Gasiewicz *(Chair)*, University of Rochester School of Medicine in New York
Tina Bahadori, American Chemistry Council
Caroline L. Baier-Anderson, Environmental Defense Fund
Kim Boekelheide, Brown University
George P. Daston, Procter & Gamble Company
William H. Farland, Colorado State University
Susan J. Fisher, University of California, San Francisco
Shuk-mei Ho, University of Cincinnati
Stephen M. Rappaport, University of California, Berkeley
Ivan Rusyn, University of North Carolina, Chapel Hill
Martin L. Stephens, The Humane Society of the United States
Helmut Zarbl, Robert Wood Johnson Medical School
Lauren A. Zeise, California Environmental Protection Agency

Workshops and information at **http://nas.edu/envirohealth**

July 30-31, 2009, Washington, DC
Use of Emerging Science and Technologies to Explore Epigenetic Mechanisms Underlying the Developmental Basis for Disease

September 21-22, 2009, Location TBD
Computational Toxicology: From Data to Analyses to Applications

December 8-9, 2009, Washington, DC
The Exposome: A Powerful Approach for Evaluating Environmental Effects on Chronic Diseases

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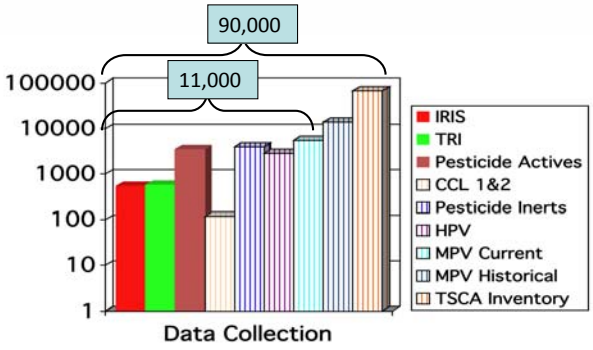
EPA United States Environmental Protection Agency

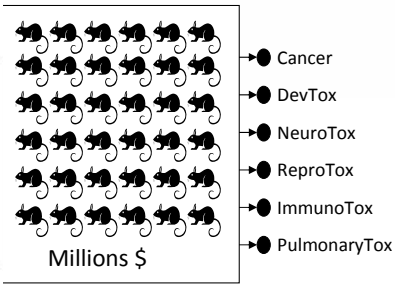
ACToR
Aggregated Computational Toxicology Resource

Change Needed Because …..

Too Many Chemicals



Too High a Cost



…and not enough data.

Judson, et al *EHP in press*

EPA Reacts to Challenge of the NRC on the Future of Toxicity Testing

Strategic Goals
- Toxicity Pathway ID and Screening
- Toxicity Based Risk Assessment
- Institutional Transition

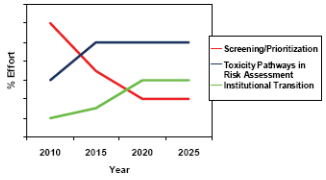


Figure 6. Relative (%) emphasis of the three main components of this strategic plan over its expected 20-year duration.

The Chemical Landscape Project

- What is the unique set of chemicals EPA is most concerned with?
- Targets for the overall ToxCast Program
- How much is know about these chemicals?
- Where are the data gaps?
- Collaboration across EPA
  - ORD, OPP, OPPT, OW, GLNPO, EDSP
- Running this study required building a database
  - Origin of the ACToR project

Summary of Chemical Landscape Analysis

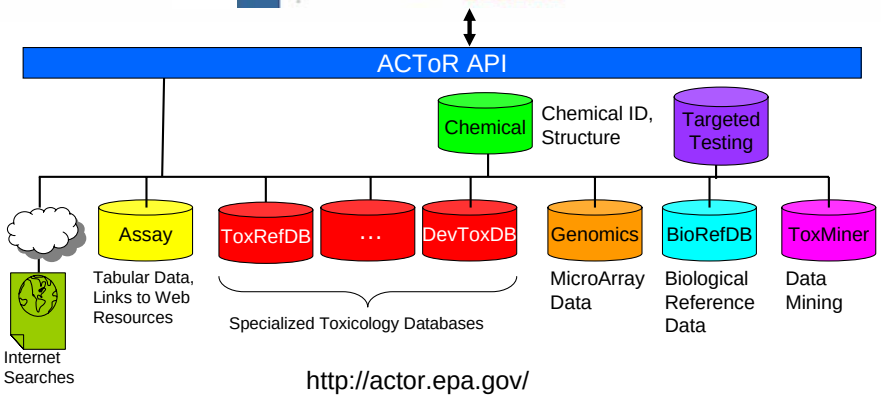
- Total Count: 9,912

- Fraction of chemicals evaluated for specific classes of toxicity:
  - General Hazard (usually acute data) 59%
  - Carcinogenicity 26%
  - Genotoxicity 28%
  - Developmental Toxicity 29%
  - Reproductive Toxicity 11%

EHP Electronic Publication, December 2008

ACToR
Aggregated Computational Toxicology Resource

ACToR Web Browser



http://actor.epa.gov/

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ACToR Definitions

- Substance
  - A chemical from one source
  - Name(s), CASRN
  - Source-specific unique ID
  - Assay Data
- Compound
  - Chemical structure from one source
  - Source-specific unique ID
- Generic Chemical
  - CASRN
  - Link to many substance (each with same CASRN)
  - Link to at most one compound
  - Links to all assay data from susbtances with same CASRN

ACToR Definitions

- Assay
  - A collection of data on one or more substances
  - Comes from one data source
  - Can have several types of data included
  - Looks like and Excel spreadsheet
- Assay Component
  - One column of an assay table
- Assay Result
  - A data value for one substance and one assay component

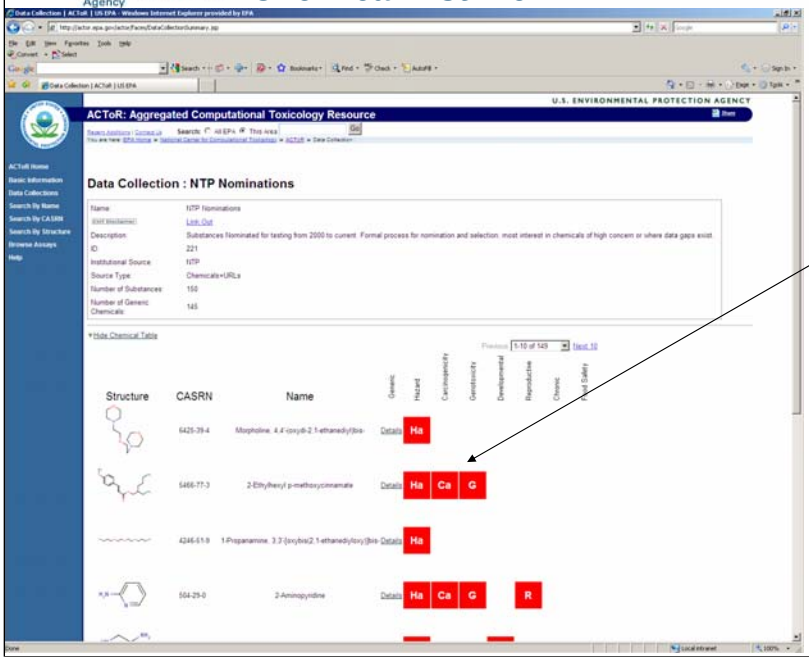
ACToR Definitions

- Assay Phenotype
  - Type of disease associated with the assay
    - Carcinogenicity, GeneTox, …
- Assay Category
  - Type of data: tabular, links to the web, human exposure
  - Allows assays to be grouped together
- Data Collection
  - A source of data
  - Substances
  - Compounds
  - Assays

Main Data Views

- Search by names, CASRN, Structure
- View lists of chemicals
- View lists of assays
- View list of assay collections
- View data associated with a generic chemical

Chemical List View



Red box indicates that data is available for that phenotype, not that chemical causes that phenotype

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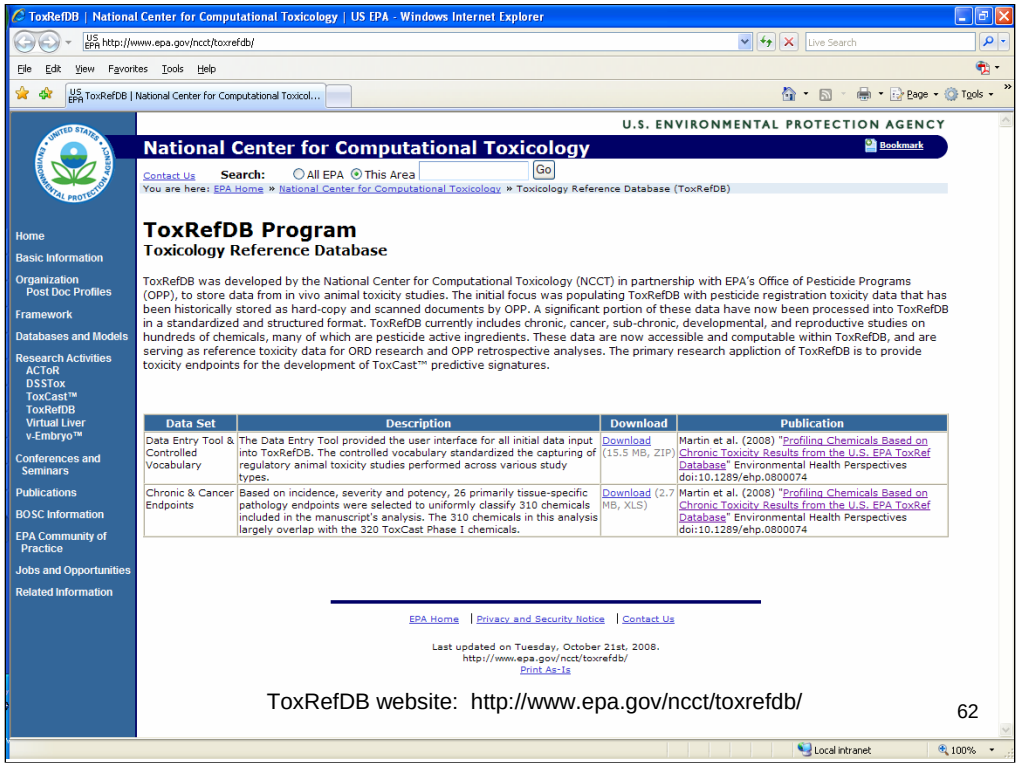
United States Environmental Protection Agency

Statistics

Category	Count
Data Collections	261
Substances	1,578,922
Compounds	955,016
Generic Chemicals	531,517
Generic Chemicals with Structure	418,191
Assays	1,357
Assay Components	3,910
Assay Results	3,553,507

ToxRefDB

- Relational phenotypic/toxicity database
- Provides in vivo anchor for ToxCast predictions
- Three study types
  - Chronic/Cancer rat and mouse (Martin, et al, EHP 2008)
  - Rat multigenerational Reproduction (Martin, et al, submitted)
  - Rat & Rabbit developmental (Knudsen, et al, internal review)
- Two types of synthesis
  - Supervised (common individual phenotypes)
  - Unsupervised (machine based clustering of phenotype patterns)



ToxRefDB website: http://www.epa.gov/ncct/toxrefdb/

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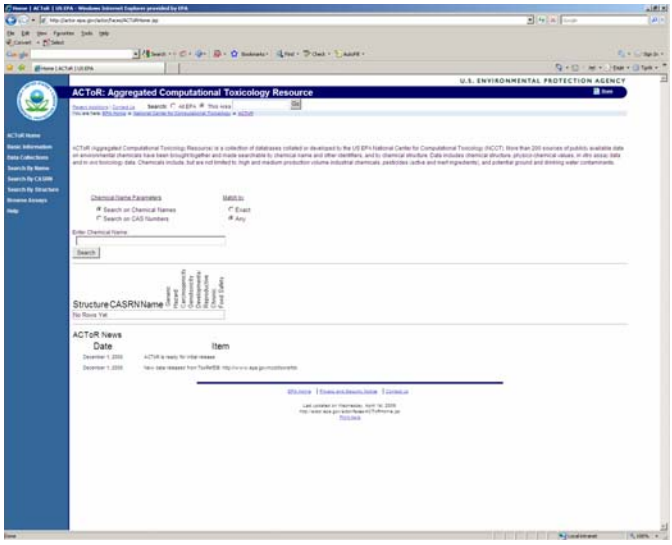
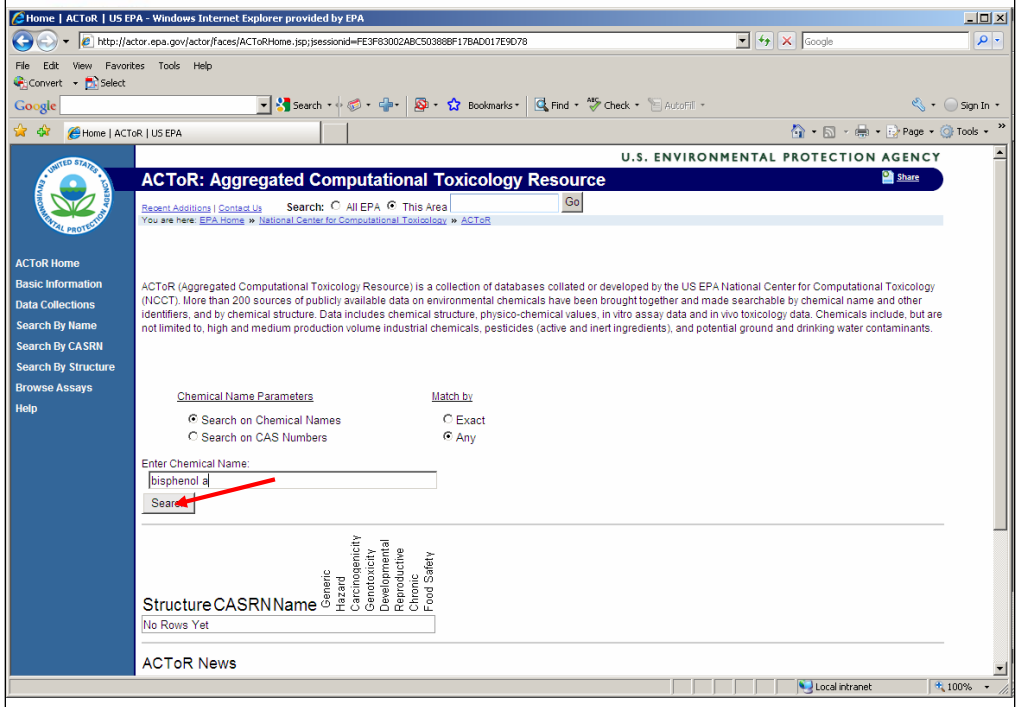
United States Environmental Protection Agency

Demo



http://actor.epa.gov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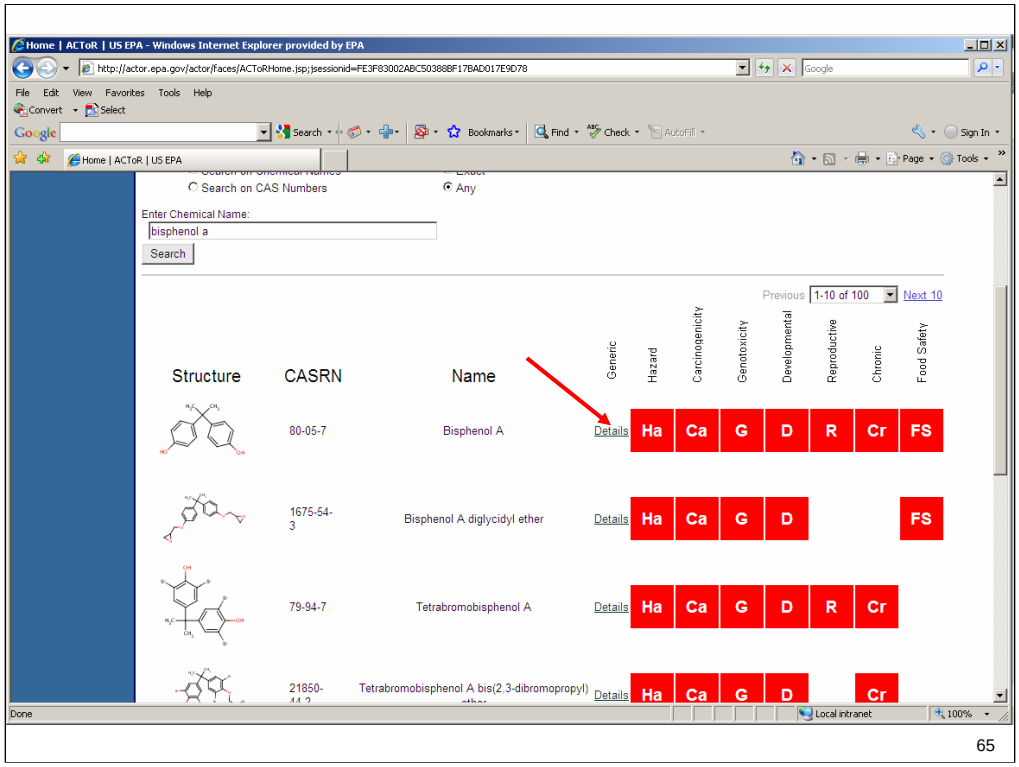
Chemical Name Parameters
Search on Chemical Names
Search on CAS Numbers
Match by
Exact
Any
Enter Chemical Name:
bisphenol a
Search
Structure
CASRN
Name
Generic Hazard
Carcinogenicity
Genotoxicity
Developmental
Reproductive
Chronic
Food Safety
No Rows Yet
ACToR News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http://actor.epa.gov/actor/faces/ACToRHome.jsp;jsessionid=FE3F83002ABC50388BF17BAD017E9D78
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Any
Enter Chemical Name:
bisphenol a
Search
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CASRN
Name
Generic
Hazard
Carcinogenicity
Genotoxicity
Developmental
Reproductive
Chronic
Food Safety
80-05-7
Bisphenol A
Details
Ha Ca G D R Cr FS
1675-54-3
Bisphenol A diglycidyl ether
Details
Ha Ca G D FS
79-94-7
Tetrabromobisphenol A
Details
Ha Ca G D R Cr
21850-
Tetrabromobisphenol A bis(2,3-dibromopropyl)
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Ha Ca G D Cr
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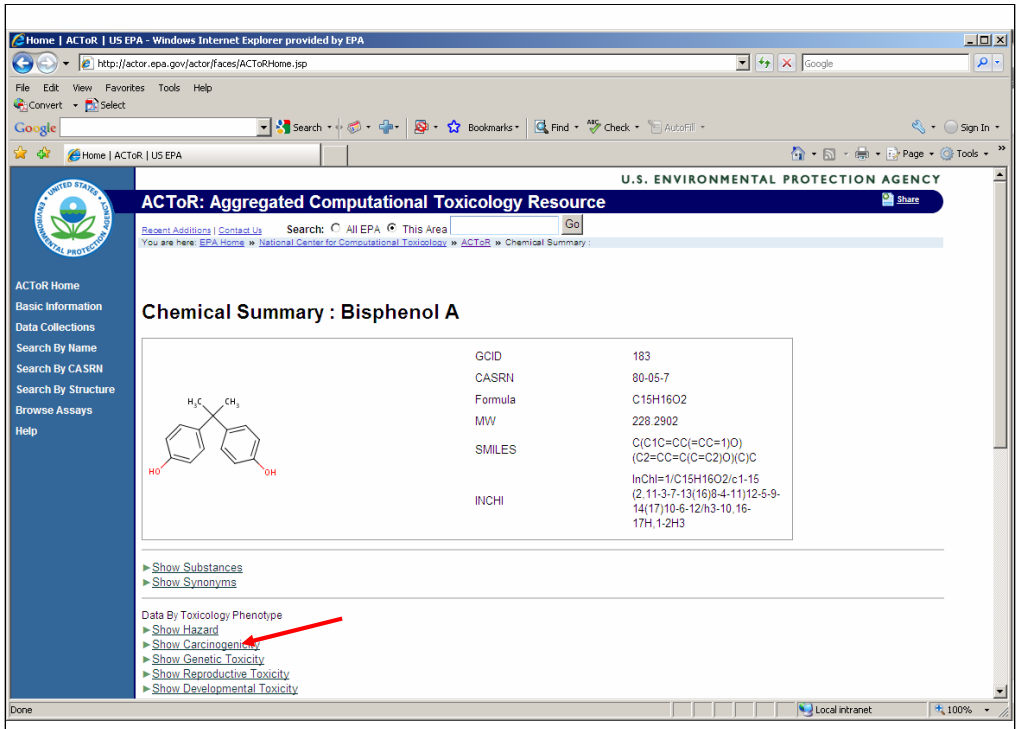
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Browse Assays
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Chemical Summary : Bisphenol A
GCID 183
CASRN 80-05-7
Formula C15H16O2
MW 228.2902
SMILES C(C1C=CC(=CC=1)O)(C2=CC=C(C=C2)O)(C)C
INCHI InChI=1/C15H16O2/c1-15(2,11-3-7-13(16)8-4-11)12-5-9-14(17)10-6-12/h3-10,16-17H,1-2H3
Show Substances
Show Synonyms
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Show Hazard
Show Carcinogenicity
Show Genetic Toxicity
Show Reproductive Toxicity
Show Developmental Toxicity
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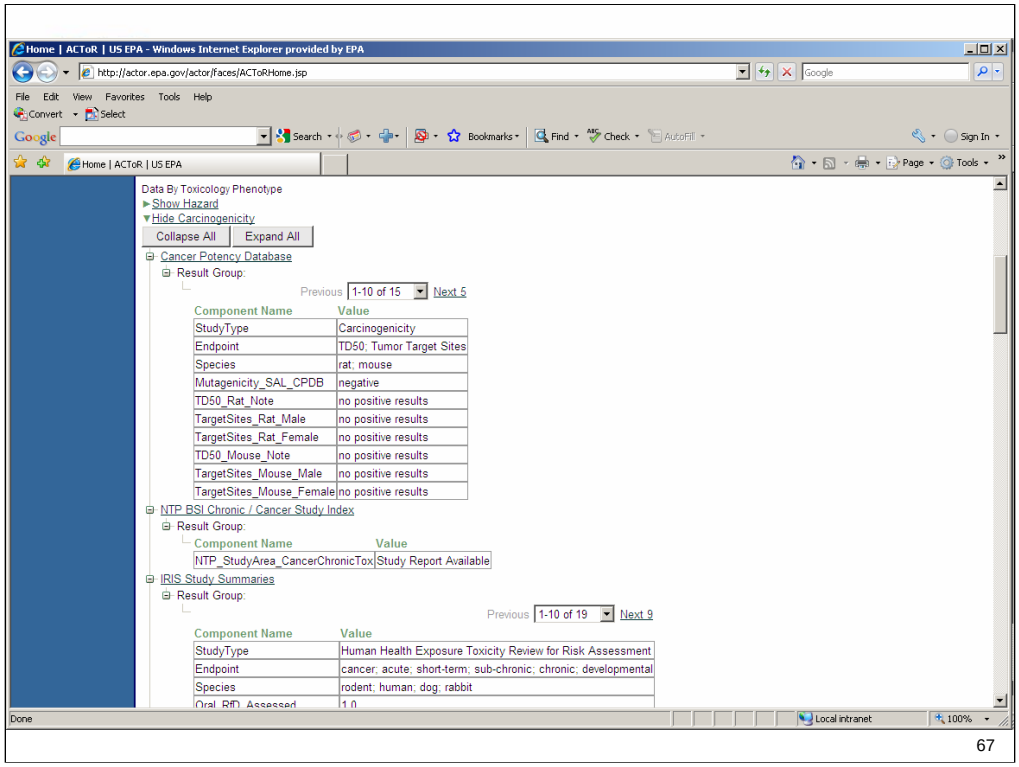
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http://actor.epa.gov/actor/faces/ACToRHome.jsp
Data By Toxicology Phenotype
Show Hazard
Hide Carcinogenicity
Collapse All
Expand All
Cancer Potency Database
Result Group:
Previous 1-10 of 15 Next 5
Component Name Value
StudyType Carcinogenicity
Endpoint TD50; Tumor Target Sites
Species rat; mouse
Mutagenicity_SAL_CPDB negative
TD50_Rat_Note no positive results
TargetSites_Rat_Male no positive results
TargetSites_Rat_Female no positive results
TD50_Mouse_Note no positive results
TargetSites_Mouse_Male no positive results
TargetSites_Mouse_Female no positive results
NTP BSI Chronic / Cancer Study Index
Result Group:
Component Name Value
NTP_StudyArea_CancerChronicTox Study Report Available
IRIS Study Summaries
Result Group:
Previous 1-10 of 19 Next 9
Component Name Value
StudyType Human Health Exposure Toxicity Review for Risk Assessment
Endpoint cancer; acute; short-term; sub-chronic; chronic; developmental
Species rodent; human; dog; rabbit
Oral RfD Assessed 1.0
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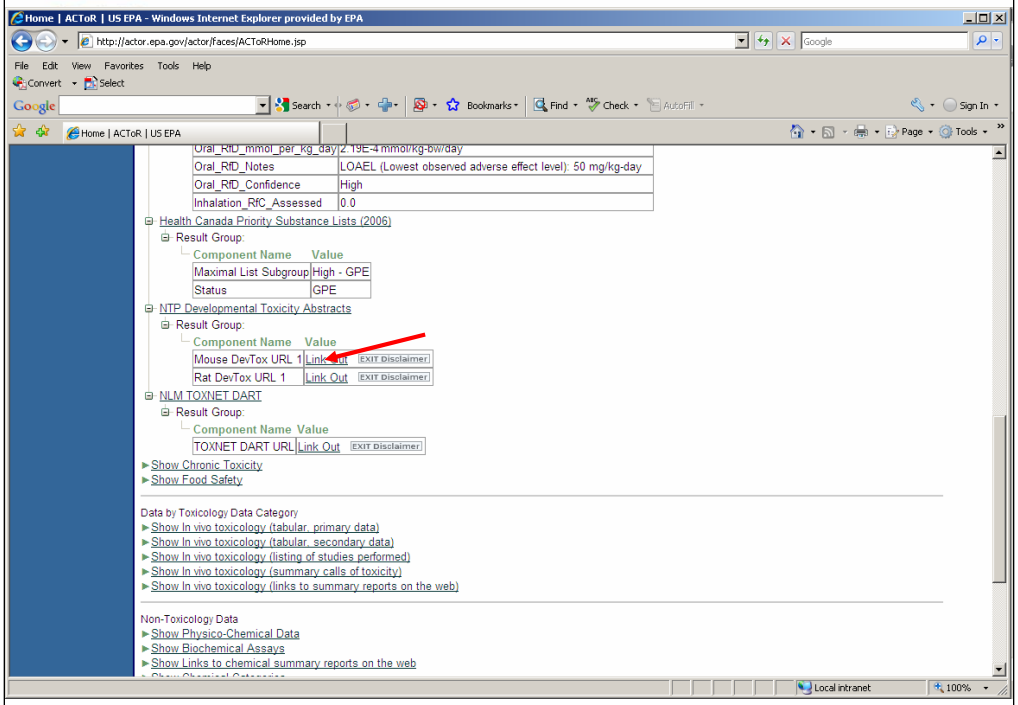
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Oral_RfD_Notes
LOAEL (Lowest observed adverse effect level): 50 mg/kg-day
Oral_RfD_Confidence
High
Inhalation_RfC_Assessed
0.0
Health Canada Priority Substance Lists (2006)
Result Group:
Component Name
Value
Maximal List Subgroup
High - GPE
Status
GPE
NTP Developmental Toxicity Abstracts
Result Group:
Component Name
Value
Mouse DevTox URL 1
Link Out
EXIT Disclaimer
Rat DevTox URL 1
Link Out
EXIT Disclaimer
NLM TOXNET DART
Result Group:
Component Name
Value
TOXNET DART URL
Link Out
EXIT Disclaimer
Show Chronic Toxicity
Show Food Safety
Data by Toxicology Data Category
Show In vivo toxicology (tabular, primary data)
Show In vivo toxicology (tabular, secondary data)
Show In vivo toxicology (listing of studies performed)
Show In vivo toxicology (summary calls of toxicity)
Show In vivo toxicology (links to summary reports on the web)
Non-Toxicology Data
Show Physico-Chemical Data
Show Biochemical Assays
Show Links to chemical summary reports on the web
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Abstract for Teratology: Bisphenol A - National Toxicology Program - Windows Internet Explorer provided by EPA
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Abstract for Teratology: Bisphenol A
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Teratologic Evaluation of Bisphenol A: (CAS No. 80-05-7) Administered to CD® Rats on Gestational Days 6 Through 15
NTP Study TER85051
ABSTRACT
Bisphenol A (BPA), a widely distributed industrial chemical used in making epoxy resins and polycarbonates, was evaluated for toxic and teratogenic effects in timed-pregnant Sprague Dawley CD rats (n=27-29). BPA (0, 160, 320, 640 and 1280 mg/kg/day) suspended in corn oil was given by gavage (5.0 mL/kg body weight) daily on gestational days (gd) 6 through 15. Females were weighed and observed daily. At sacrifice a total of 18-29 confirmed-pregnant females per treatment group were evaluated. The graivd uterus of each dam was weighed, and the number of implantation sites and live, dead, or resorbed fetuses were recorded. All live fetuses were weighed and examined for external, visceral, and skeletal malformations. Dams exhibited clinical signs of toxicity including piloerection, weight loss, lethargy, pica, rough coat, wet urogenital area, and alopecia. These were seen in all dose groups, and with greater frequency at higher doses.
Maternal mortality was 0% for all but the 1280 mg/kg/day dose group, which was 26%. Due to this high mortality, data from the 1280 mg/kg/day group will not be further considered in this summary.
Maternal body weight on gd 0 and gd 6 did not differ among the remaining dose groups. But at gd 11 and 15, maternal body weight was lowered for all BPA treatment groups. Gravid uterine weight, absolute maternal liver weight, and relative maternal liver weight were unaffected by treatment. BPA produced NO significant fetal effects at doses ¾ 640 mg/kg.
In conclusion, BPA in rats was not a developmental toxicant at doses that were maternally toxic. The developmental NOAEL was 640 mg/kg. A maternal NOAEL was not established, based on effects on maternal body weight; the LOAEL for maternal body weight effect in this study was 160 mg/kg.
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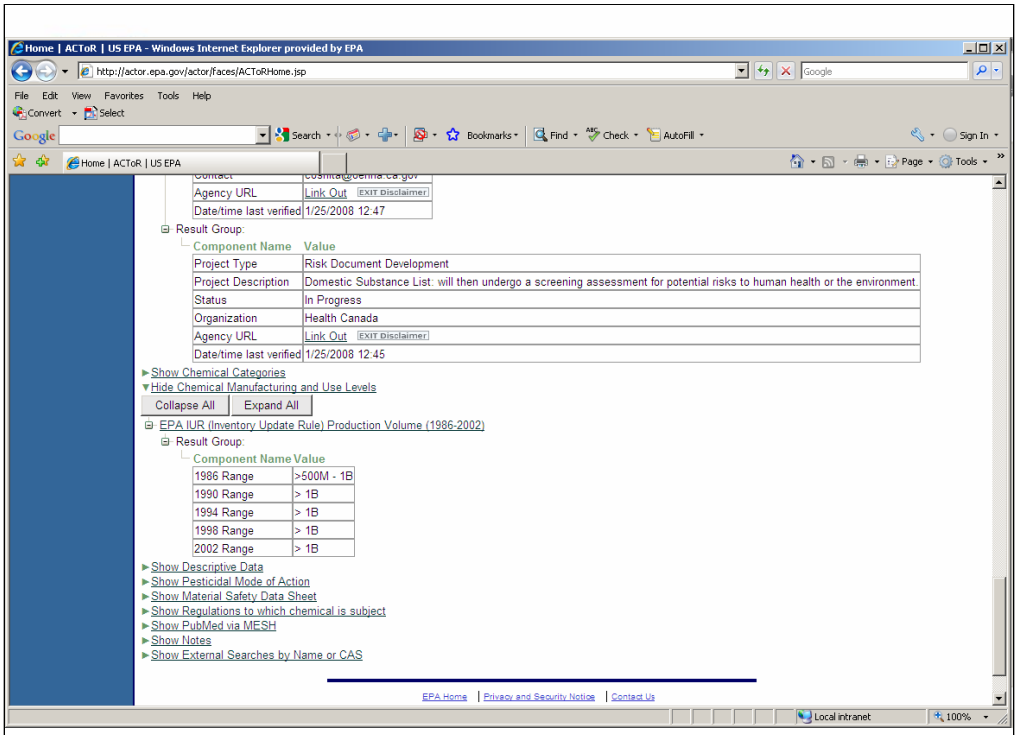
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Agency URL Link Out EXIT Disclaimer
Date/time last verified 1/25/2008 12:47
Result Group:
Component Name Value
Project Type Risk Document Development
Project Description Domestic Substance List: will then undergo a screening assessment for potential risks to human health or the environment.
Status In Progress
Organization Health Canada
Agency URL Link Out EXIT Disclaimer
Date/time last verified 1/25/2008 12:45
Show Chemical Categories
Hide Chemical Manufacturing and Use Levels
Collapse All
Expand All
EPA IUR (Inventory Update Rule) Production Volume (1986-2002)
Result Group:
Component Name Value
1986 Range >500M - 1B
1990 Range > 1B
1994 Range > 1B
1998 Range > 1B
2002 Range > 1B
Show Descriptive Data
Show Pesticidal Mode of Action
Show Material Safety Data Sheet
Show Regulations to which chemical is subject
Show PubMed via MESH
Show Notes
Show External Searches by Name or CAS
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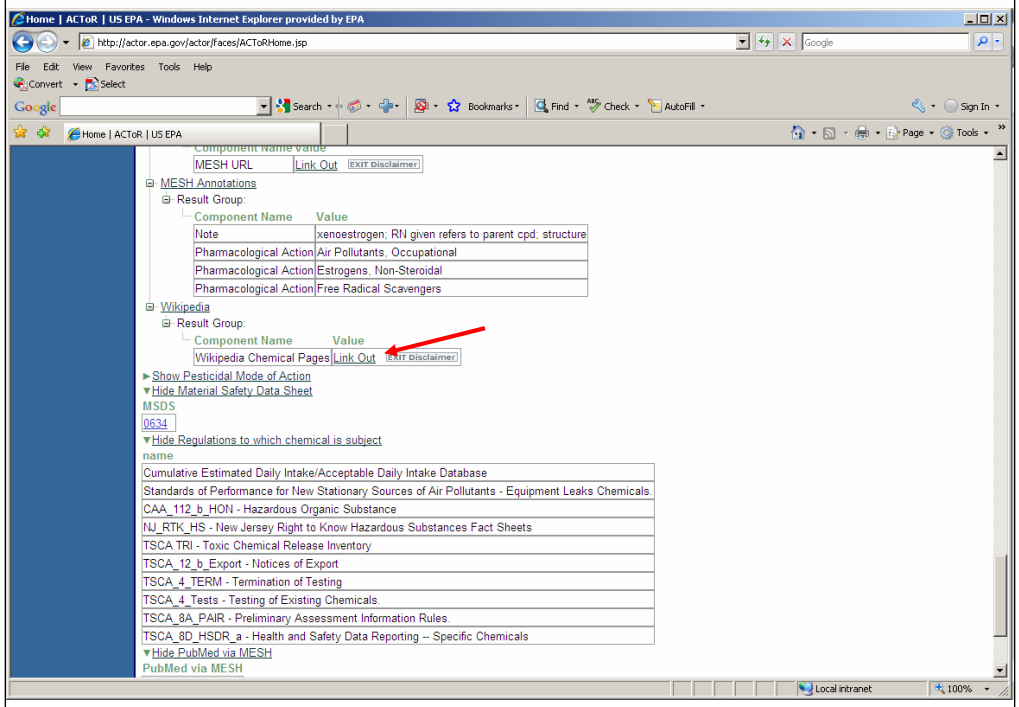
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http://actor.epa.gov/actor/faces/ACToRHome.jsp
MESH URL
Link Out
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MESH Annotations
Result Group:
Component Name
Value
Note
xenoestrogen; RN given refers to parent cpd; structure
Pharmacological Action
Air Pollutants, Occupational
Pharmacological Action
Estrogens, Non-Steroidal
Pharmacological Action
Free Radical Scavengers
Wikipedia
Result Group:
Component Name
Value
Wikipedia Chemical Pages
Link Out
EXIT Disclaimer
Show Pesticidal Mode of Action
Hide Material Safety Data Sheet
MSDS
0634
Hide Regulations to which chemical is subject
name
Cumulative Estimated Daily Intake/Acceptable Daily Intake Database
Standards of Performance for New Stationary Sources of Air Pollutants - Equipment Leaks Chemicals.
CAA_112_b_HON - Hazardous Organic Substance
NJ_RTK_HS - New Jersey Right to Know Hazardous Substances Fact Sheets
TSCA TRI - Toxic Chemical Release Inventory
TSCA_12_b_Export - Notices of Export
TSCA_4_TERM - Termination of Testing
TSCA_4_Tests - Testing of Existing Chemicals.
TSCA_8A_PAIR - Preliminary Assessment Information Rules.
TSCA_8D_HSDR_a - Health and Safety Data Reporting -- Specific Chemicals
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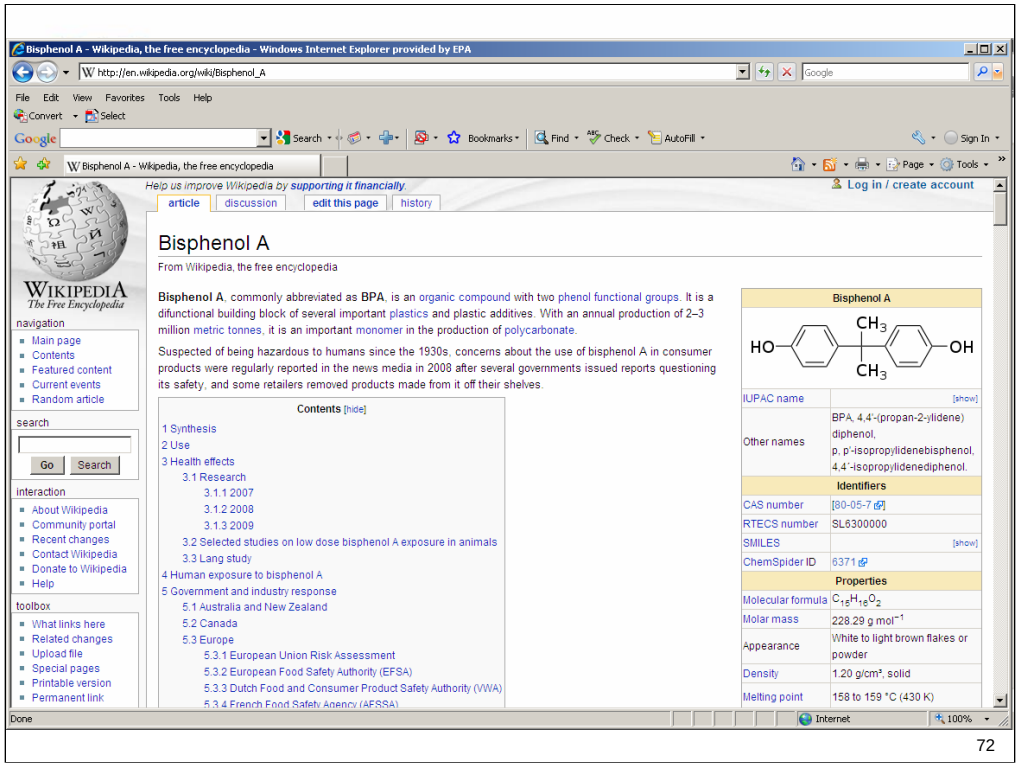
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Bisphenol A
From Wikipedia, the free encyclopedia
Bisphenol A, commonly abbreviated as BPA, is an organic compound with two phenol functional groups. It is a difunctional building block of several important plastics and plastic additives. With an annual production of 2–3 million metric tonnes, it is an important monomer in the production of polycarbonate.
Suspected of being hazardous to humans since the 1930s, concerns about the use of bisphenol A in consumer products were regularly reported in the news media in 2008 after several governments issued reports questioning its safety, and some retailers removed products made from it off their shelves.
Contents [hide]
1 Synthesis
2 Use
3 Health effects
3.1 Research
3.1.1 2007
3.1.2 2008
3.1.3 2009
3.2 Selected studies on low dose bisphenol A exposure in animals
3.3 Lang study
4 Human exposure to bisphenol A
5 Government and industry response
5.1 Australia and New Zealand
5.2 Canada
5.3 Europe
5.3.1 European Union Risk Assessment
5.3.2 European Food Safety Authority (EFSA)
5.3.3 Dutch Food and Consumer Product Safety Authority (VWA)
5.3.4 French Food Safety Agency (AFSSA)
Bisphenol A
HO
OH
CH3
CH3
IUPAC name
Other names
BPA, 4,4'-(propan-2-ylidene) diphenol, p, p'-isopropylidenebisphenol, 4,4'-isopropylidenediphenol.
Identifiers
CAS number
RTECS number
SL6300000
SMILES
ChemSpider ID
6371
Properties
Molecular formula
Molar mass
228.29 g mol−1
Appearance
White to light brown flakes or powder
Density
1.20 g/cm³, solid
Melting point
158 to 159 °C (430 K)
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Random article
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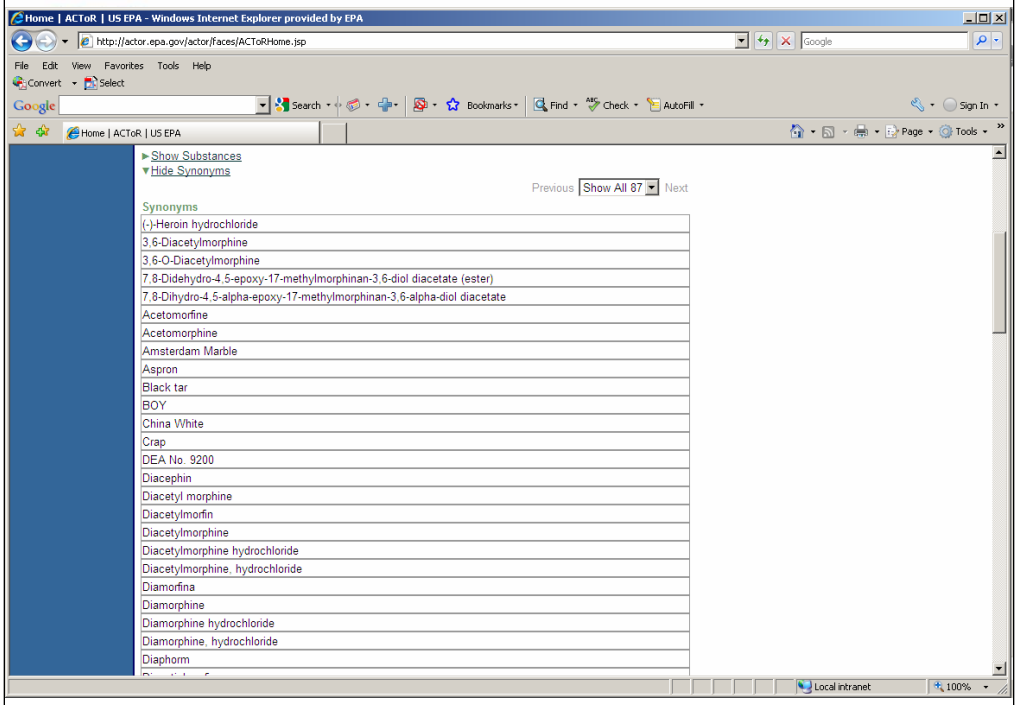
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Show Substances
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Synonyms
(-)-Heroin hydrochloride
3,6-Diacetylmorphine
3,6-O-Diacetylmorphine
7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol diacetate (ester)
7,8-Dihydro-4,5-alpha-epoxy-17-methylmorphinan-3,6-alpha-diol diacetate
Acetomorfine
Acetomorphine
Amsterdam Marble
Aspron
Black tar
BOY
China White
Crap
DEA No. 9200
Diacephin
Diacetyl morphine
Diacetylmorfin
Diacetylmorphine
Diacetylmorphine hydrochloride
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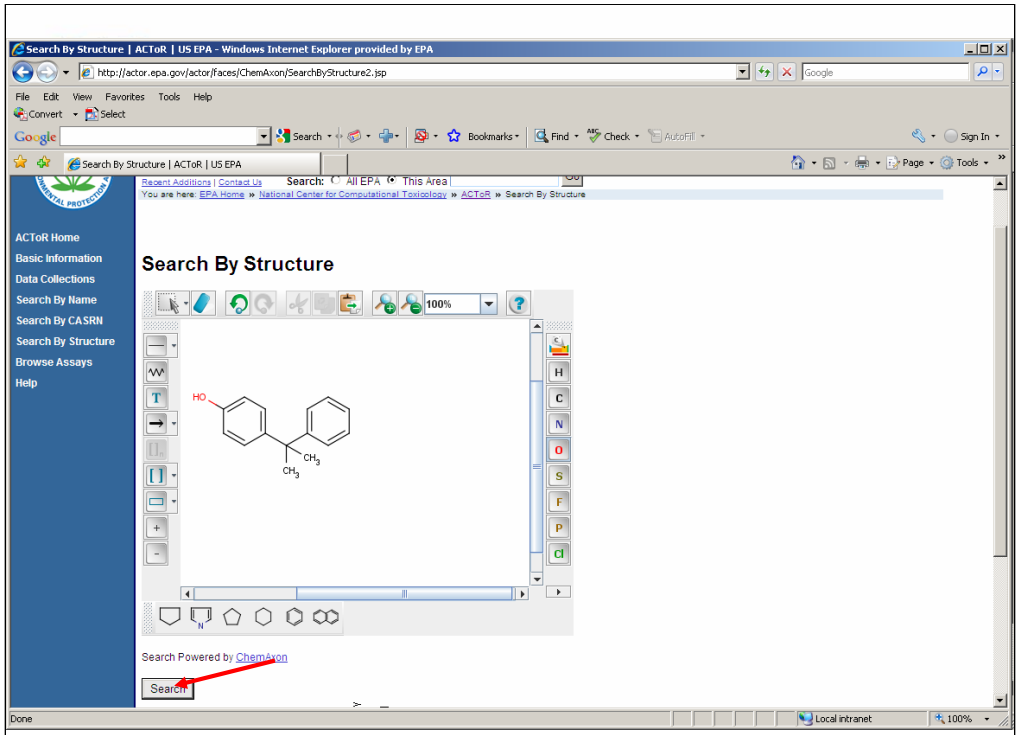
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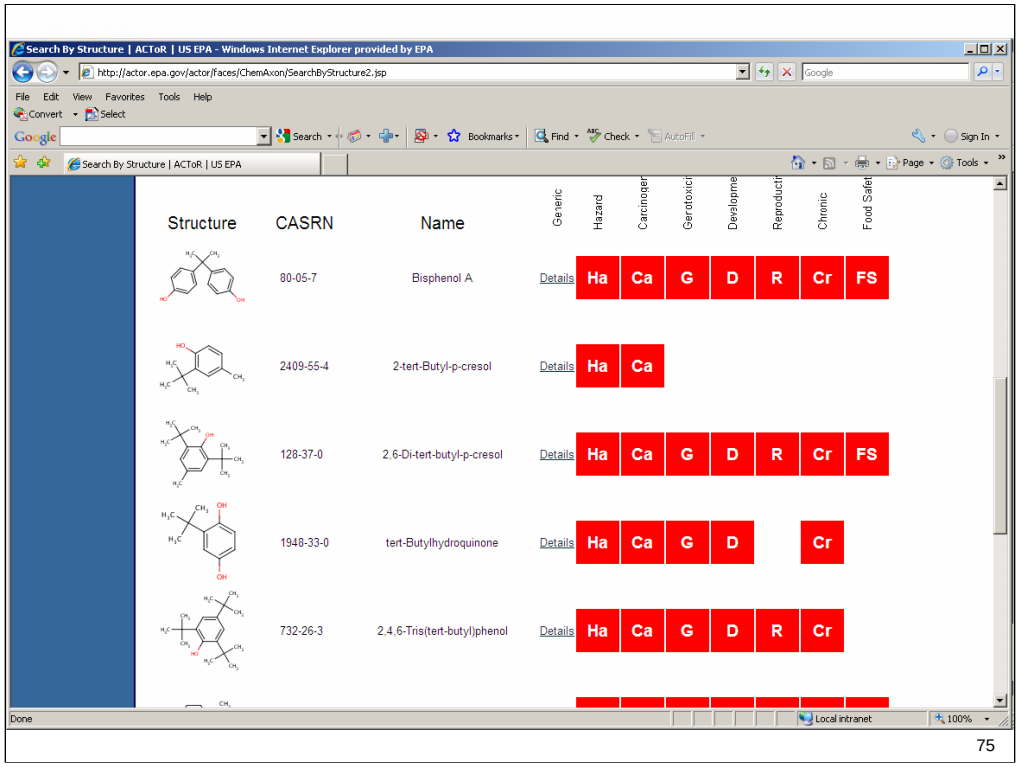
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Structure
CASRN
Name
Generic
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Carcinogen
Genotoxici
Developme
Reproducti
Chronic
Food Safet
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Bisphenol A
Details
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Ca
G
D
R
Cr
FS
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Ca
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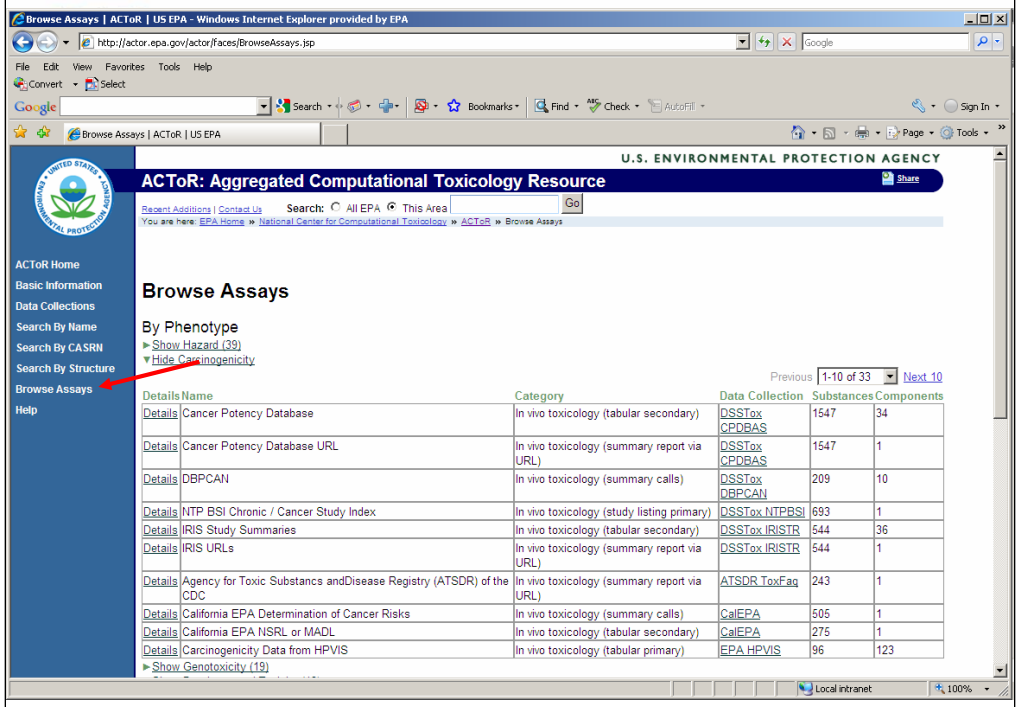
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Search By Structure
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By Phenotype
Show Hazard (39)
Hide Carcinogenicity
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Details Name Category Data Collection Substances Components
Details Cancer Potency Database In vivo toxicology (tabular secondary) DSSTox CPDBAS 1547 34
Details Cancer Potency Database URL In vivo toxicology (summary report via URL) DSSTox CPDBAS 1547 1
Details DBPCAN In vivo toxicology (summary calls) DSSTox DBPCAN 209 10
Details NTP BSI Chronic / Cancer Study Index In vivo toxicology (study listing primary) DSSTox NTPBSI 693 1
Details IRIS Study Summaries In vivo toxicology (tabular secondary) DSSTox IRISTR 544 36
Details IRIS URLs In vivo toxicology (summary report via URL) DSSTox IRISTR 544 1
Details Agency for Toxic Substancs andDisease Registry (ATSDR) of the CDC In vivo toxicology (summary report via URL) ATSDR ToxFaq 243 1
Details California EPA Determination of Cancer Risks In vivo toxicology (summary calls) CalEPA 505 1
Details California EPA NSRL or MADL In vivo toxicology (tabular secondary) CalEPA 275 1
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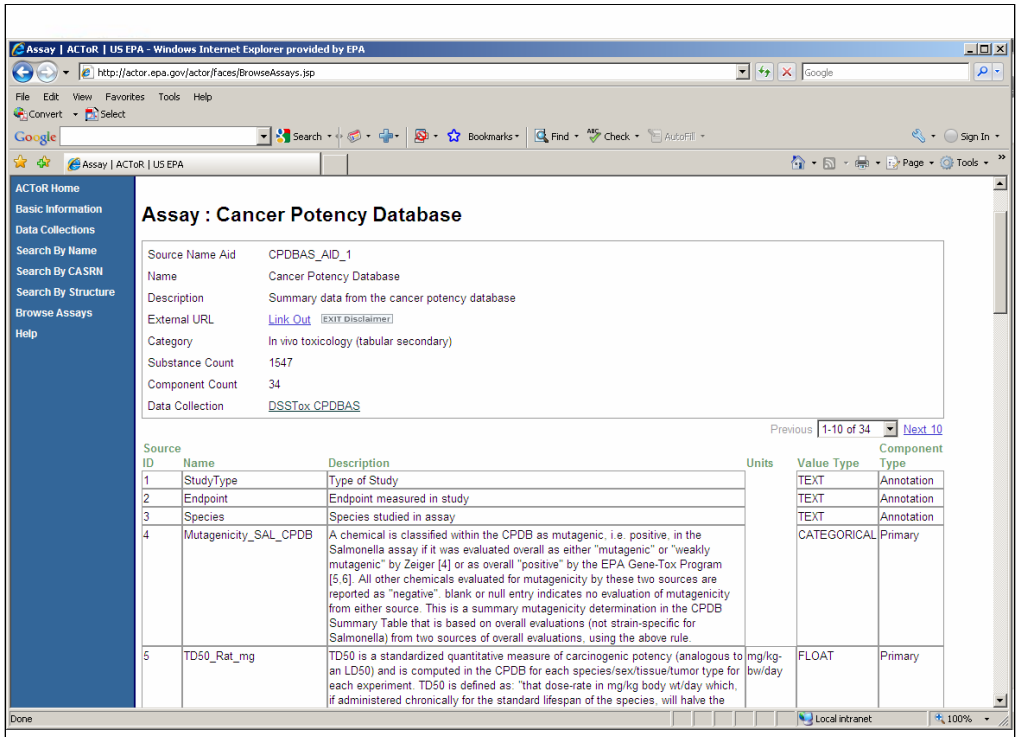
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Assay : Cancer Potency Database
Source Name Aid CPDBAS_AID_1
Name Cancer Potency Database
Description Summary data from the cancer potency database
External URL Link Out EXIT Disclaimer
Category In vivo toxicology (tabular secondary)
Substance Count 1547
Component Count 34
Data Collection DSSTox CPDBAS
Previous 1-10 of 34 Next 10
Source ID | Name | Description | Units | Value Type | Component Type
1 | StudyType | Type of Study | | TEXT | Annotation
2 | Endpoint | Endpoint measured in study | | TEXT | Annotation
3 | Species | Species studied in assay | | TEXT | Annotation
4 | Mutagenicity_SAL_CPDB | A chemical is classified within the CPDB as mutagenic, i.e. positive, in the Salmonella assay if it was evaluated overall as either "mutagenic" or "weakly mutagenic" by Zeiger [4] or as overall "positive" by the EPA Gene-Tox Program [5,6]. All other chemicals evaluated for mutagenicity by these two sources are reported as "negative". blank or null entry indicates no evaluation of mutagenicity from either source. This is a summary mutagenicity determination in the CPDB Summary Table that is based on overall evaluations (not strain-specific for Salmonella) from two sources of overall evaluations, using the above rule. | | CATEGORICAL | Primary
5 | TD50_Rat_mg | TD50 is a standardized quantitative measure of carcinogenic potency (analogous to an LD50) and is computed in the CPDB for each species/sex/tissue/tumor type for each experiment. TD50 is defined as: "that dose-rate in mg/kg body wt/day which, if administered chronically for the standard lifespan of the species, will halve the | mg/kg-bw/day | FLOAT | Primary
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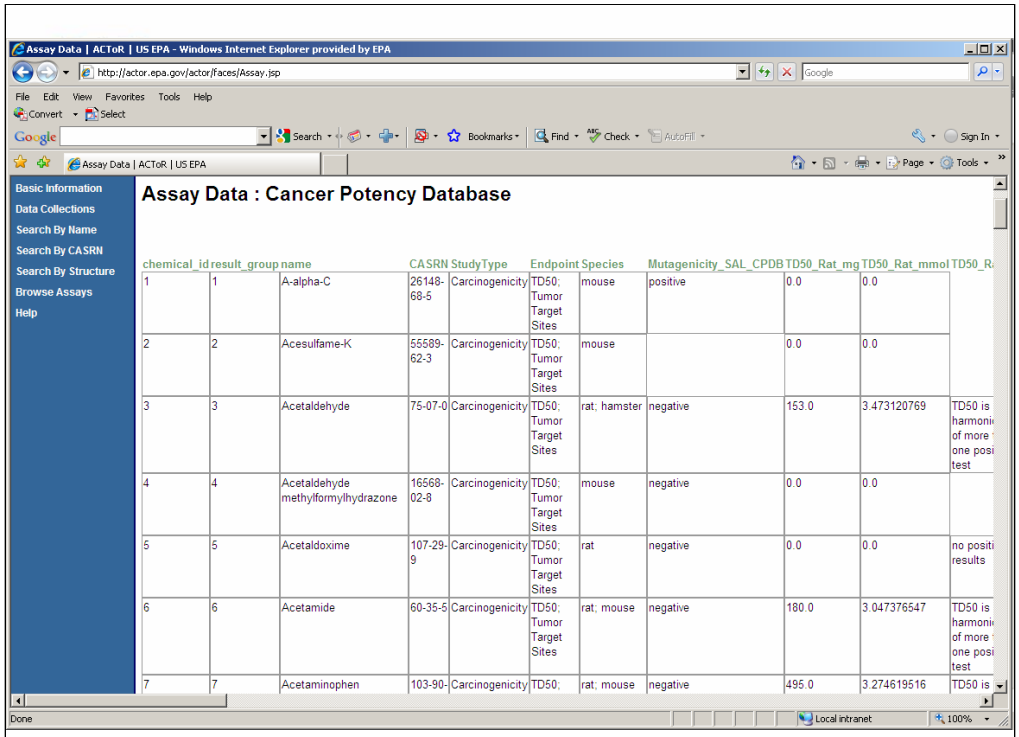
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Search By Structure
Browse Assays
Help
Assay Data : Cancer Potency Database
chemical_id result_group name CASRN StudyType Endpoint Species Mutagenicity_SAL_CPDB TD50_Rat_mg TD50_Rat_mmol TD50_R
1 1 A-alpha-C 26148-68-5 Carcinogenicity TD50; Tumor Target Sites mouse positive 0.0 0.0
2 2 Acesulfame-K 55589-62-3 Carcinogenicity TD50; Tumor Target Sites mouse 0.0 0.0
3 3 Acetaldehyde 75-07-0 Carcinogenicity TD50; Tumor Target Sites rat; hamster negative 153.0 3.473120769 TD50 is harmoni of more one posi test
4 4 Acetaldehyde methylformylhydrazone 16568-02-8 Carcinogenicity TD50; Tumor Target Sites mouse negative 0.0 0.0
5 5 Acetaldoxime 107-29-9 Carcinogenicity TD50; Tumor Target Sites rat negative 0.0 0.0 no positi results
6 6 Acetamide 60-35-5 Carcinogenicity TD50; Tumor Target Sites rat; mouse negative 180.0 3.047376547 TD50 is harmoni of more one posi test
7 7 Acetaminophen 103-90- Carcinogenicity TD50; rat; mouse negative 495.0 3.274619516 TD50 is
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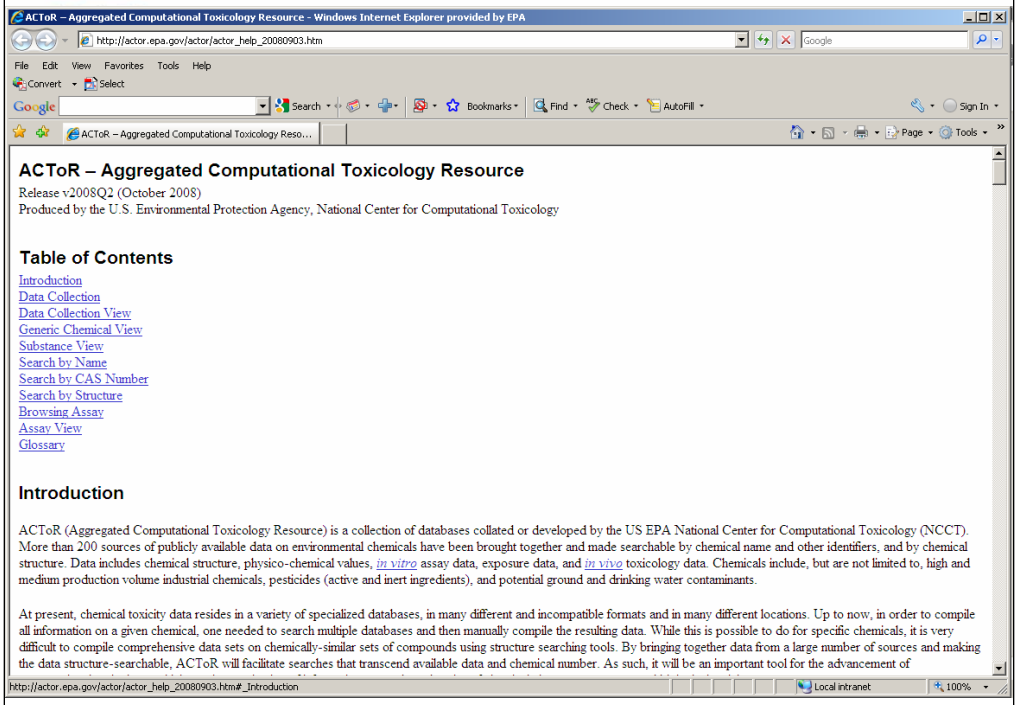
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Release v2008Q2 (October 2008)
Produced by the U.S. Environmental Protection Agency, National Center for Computational Toxicology
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Introduction
ACToR (Aggregated Computational Toxicology Resource) is a collection of databases collated or developed by the US EPA National Center for Computational Toxicology (NCCT). More than 200 sources of publicly available data on environmental chemicals have been brought together and made searchable by chemical name and other identifiers, and by chemical structure. Data includes chemical structure, physico-chemical values, in vitro assay data, exposure data, and in vivo toxicology data. Chemicals include, but are not limited to, high and medium production volume industrial chemicals, pesticides (active and inert ingredients), and potential ground and drinking water contaminants.
At present, chemical toxicity data resides in a variety of specialized databases, in many different and incompatible formats and in many different locations. Up to now, in order to compile all information on a given chemical, one needed to search multiple databases and then manually compile the resulting data. While this is possible to do for specific chemicals, it is very difficult to compile comprehensive data sets on chemically-similar sets of compounds using structure searching tools. By bringing together data from a large number of sources and making the data structure-searchable, ACToR will facilitate searches that transcend available data and chemical number. As such, it will be an important tool for the advancement of
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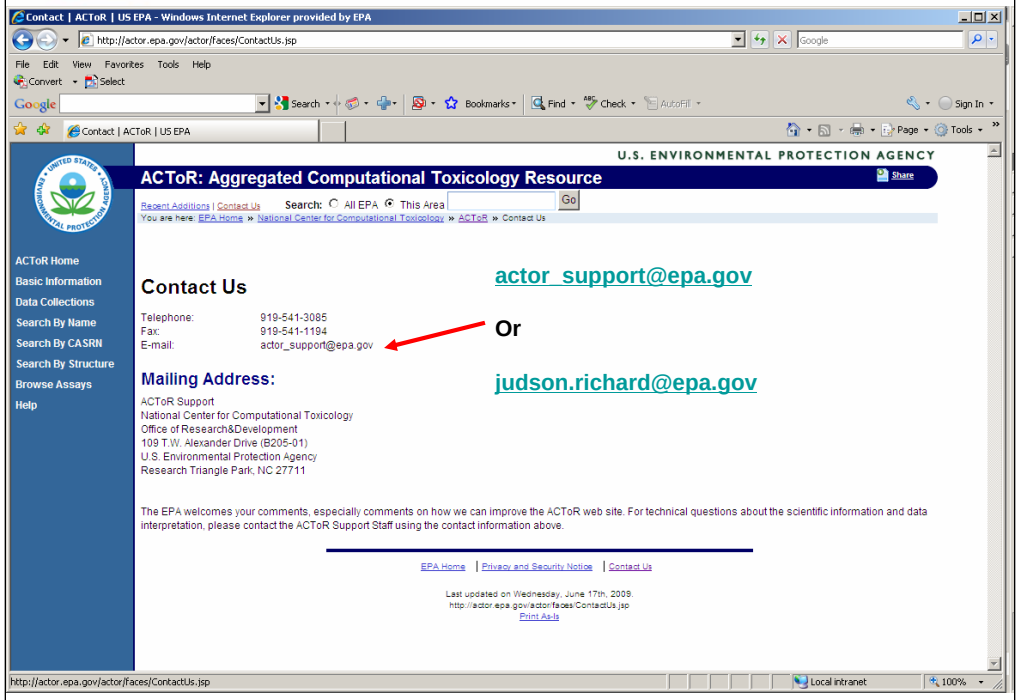
What's Next?

- More Data Collections
  - Development version >400
  - Current Focus on exposure / biomonitoring / food residues
- ToxRefDB
  - Compiling tabular information from guideline studies
    - EPA
    - NTP
    - Literature
- Cleanup of chemical structures
- Enhance generic chemical page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Fax: 919-541-1194
E-mail: actor_support@epa.gov
Mailing Address:
ACToR Support
National Center for Computational Toxicology
Office of Research&Development
109 T.W. Alexander Drive (B205-01)
U.S. Environmental Protection Agency
Research Triangle Park, NC 27711
actor_support@epa.gov
Or
judson.richard@epa.gov
The EPA welcomes your comments, especially comments on how we can improve the ACToR web site. For technical questions about the scientific information and data interpretation, please contact the ACToR Support Staff using the contact information above.
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