



Computational Toxicology: New Approaches to Improve Environmental Health Protection

Presentation to the 4th International Academic Conference on
Environmental and Occupational Medicine
Kunming, China
October 17, 2006



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Are you ready for the revolution?

D Butler, *Nature* Feb 15 2001; 409, 758 - 760

- "small experiments driven by individual investigators will give way to a world in which multi-disciplinary teams....emerge as the key players.....in the era of systems biology in which the ability to create mathematical models describing the function of networks of genes and proteins is just as important as traditional lab skills."
- "the research teams that will be most successful....are those that switch effortlessly between the lab bench and the suite of sophisticated computational tools."

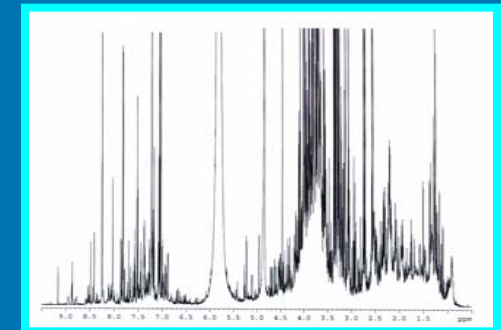
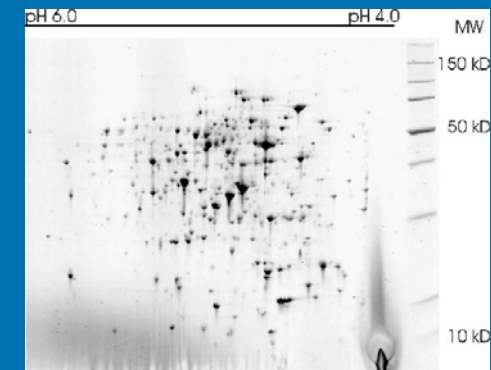
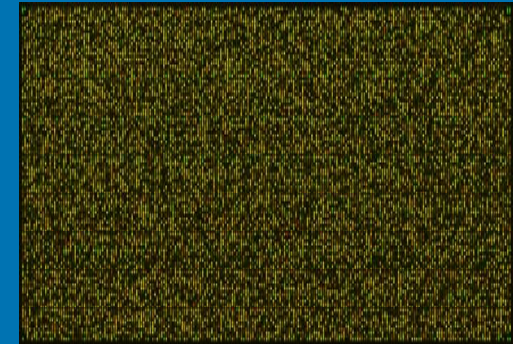
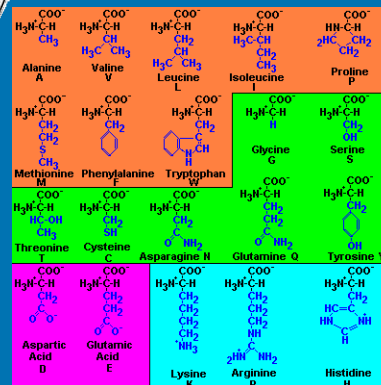
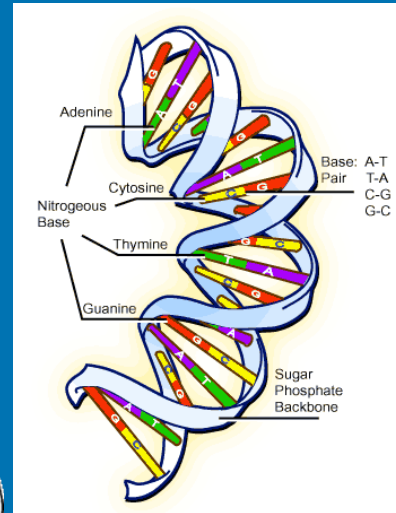
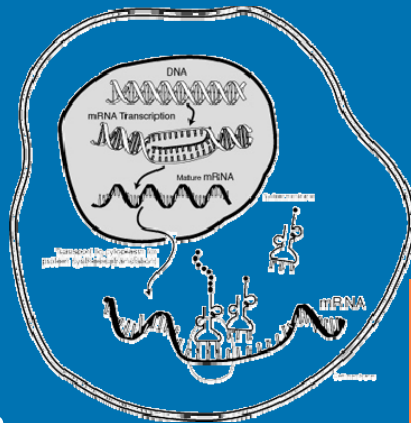
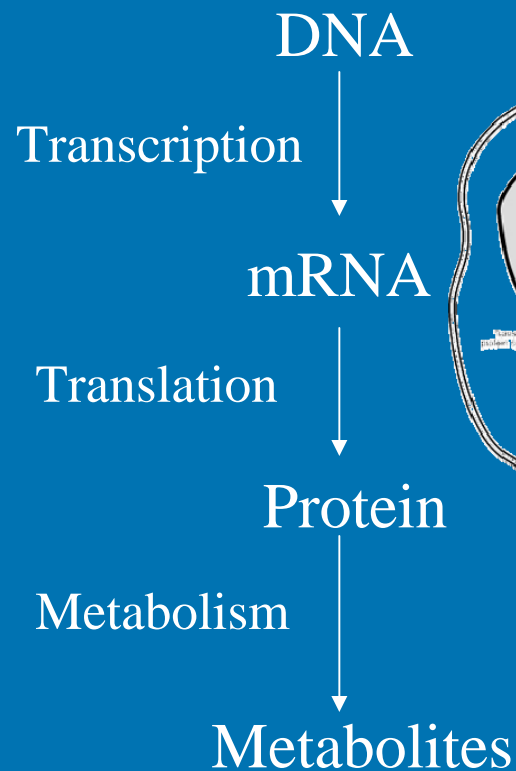


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Enabling Technologies

Molecular Biology



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"...to integrate modern computing and information technology with molecular biology to improve Agency prioritization of data requirements and risk assessment of chemicals"

www.epa.gov/comptox



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What's It All About

- Digitization
 - Legacy data
 - Dispersed data
- Scale
 - Chemicals
 - Biological space
 - Levels of biological organization
- Quantifying
 - Physiology, biochemical pathways and networks, biology
- Data mining and management



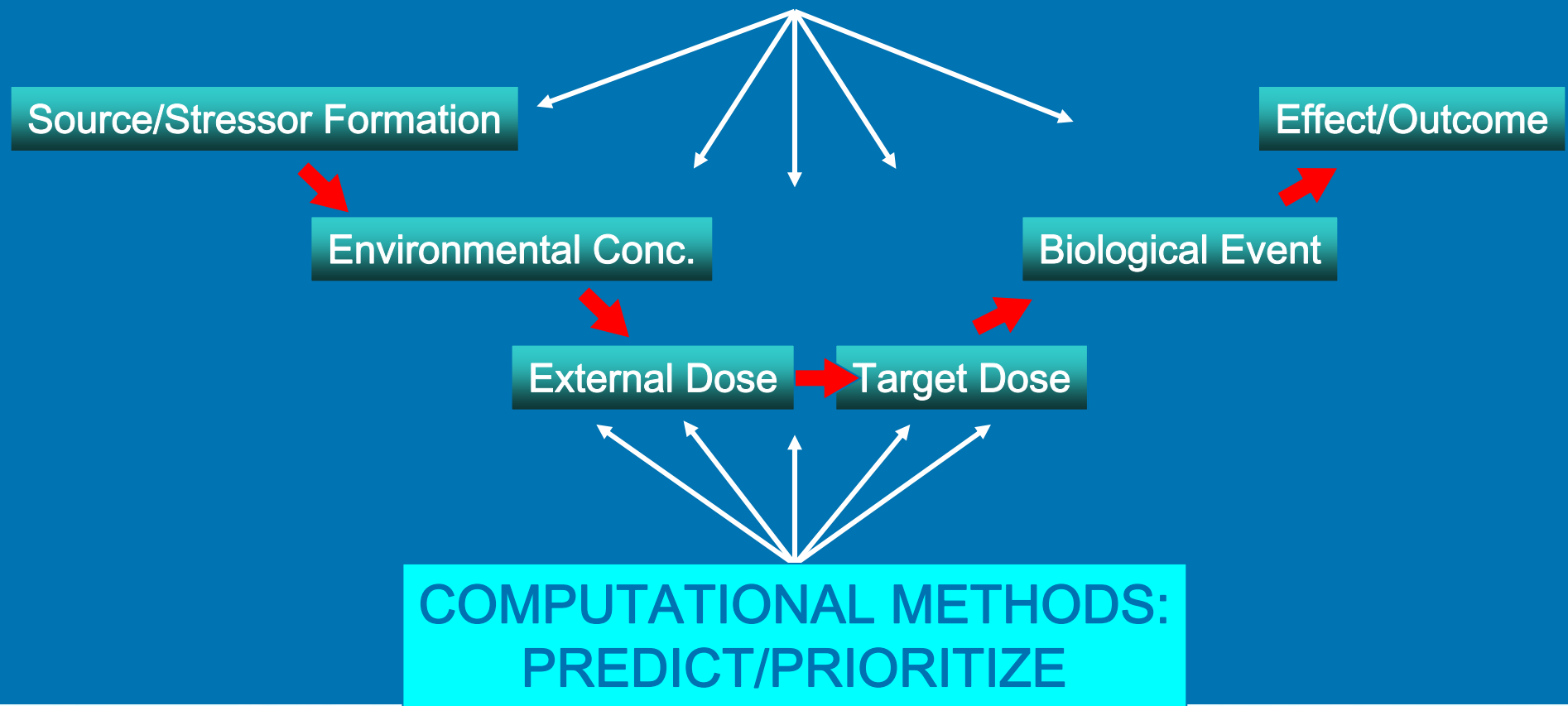
The Source to Outcome Continuum

Historically the problem has been approached one chemical at a time, one stage at a time, with little progress in predicting across the stages and across chemicals. Current demands on the EPA are making this an untenable approach. Computational Toxicology was initiated to provide new thinking to overcoming the bottlenecks.



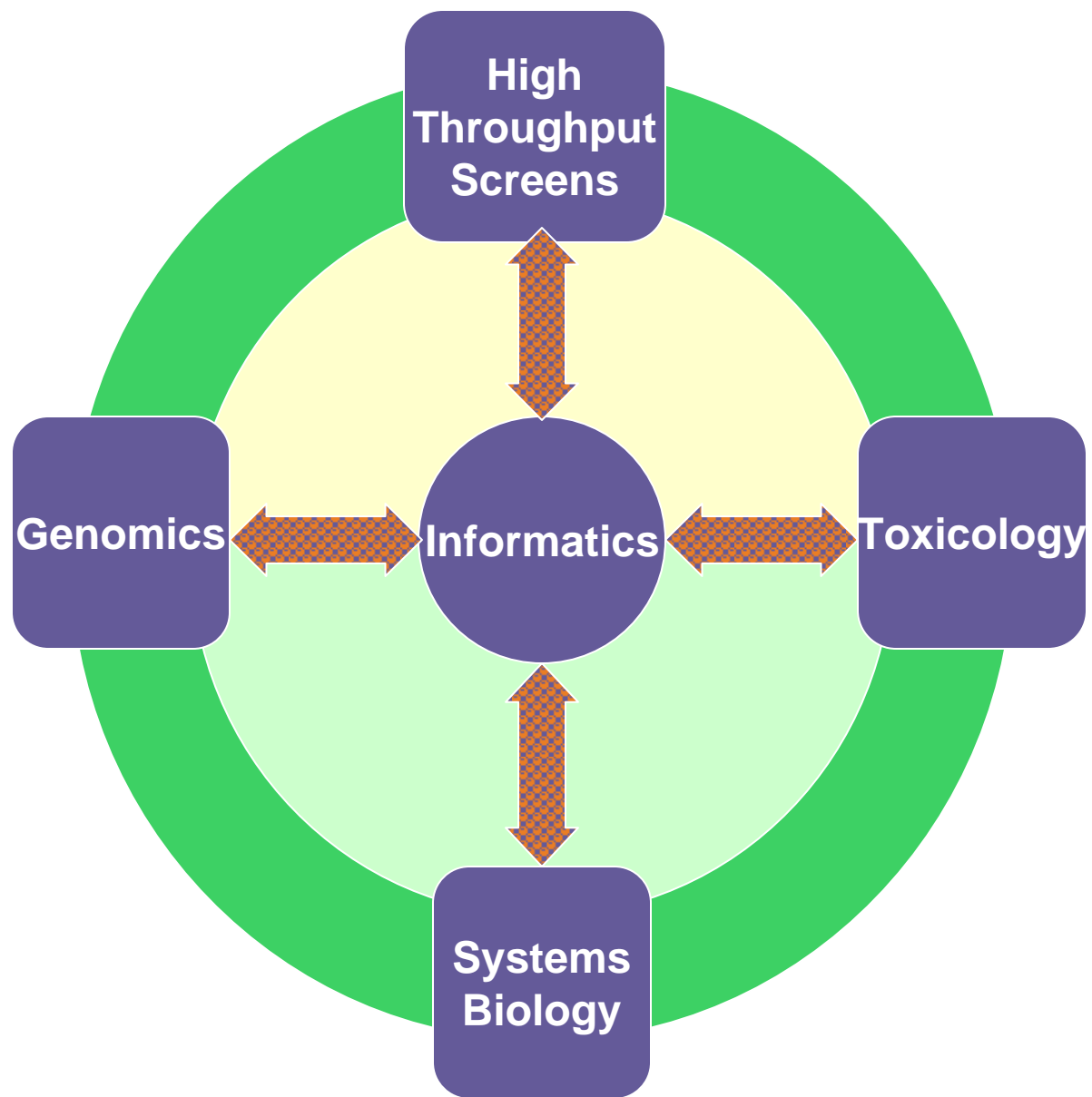
The Source to Outcome Continuum

GENOMICS, PROTEOMICS, and METABONOMICS:
IDENTIFY/CHARACTERIZE



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Toxicity of conazoles in Integrated Toxicogenomics Study

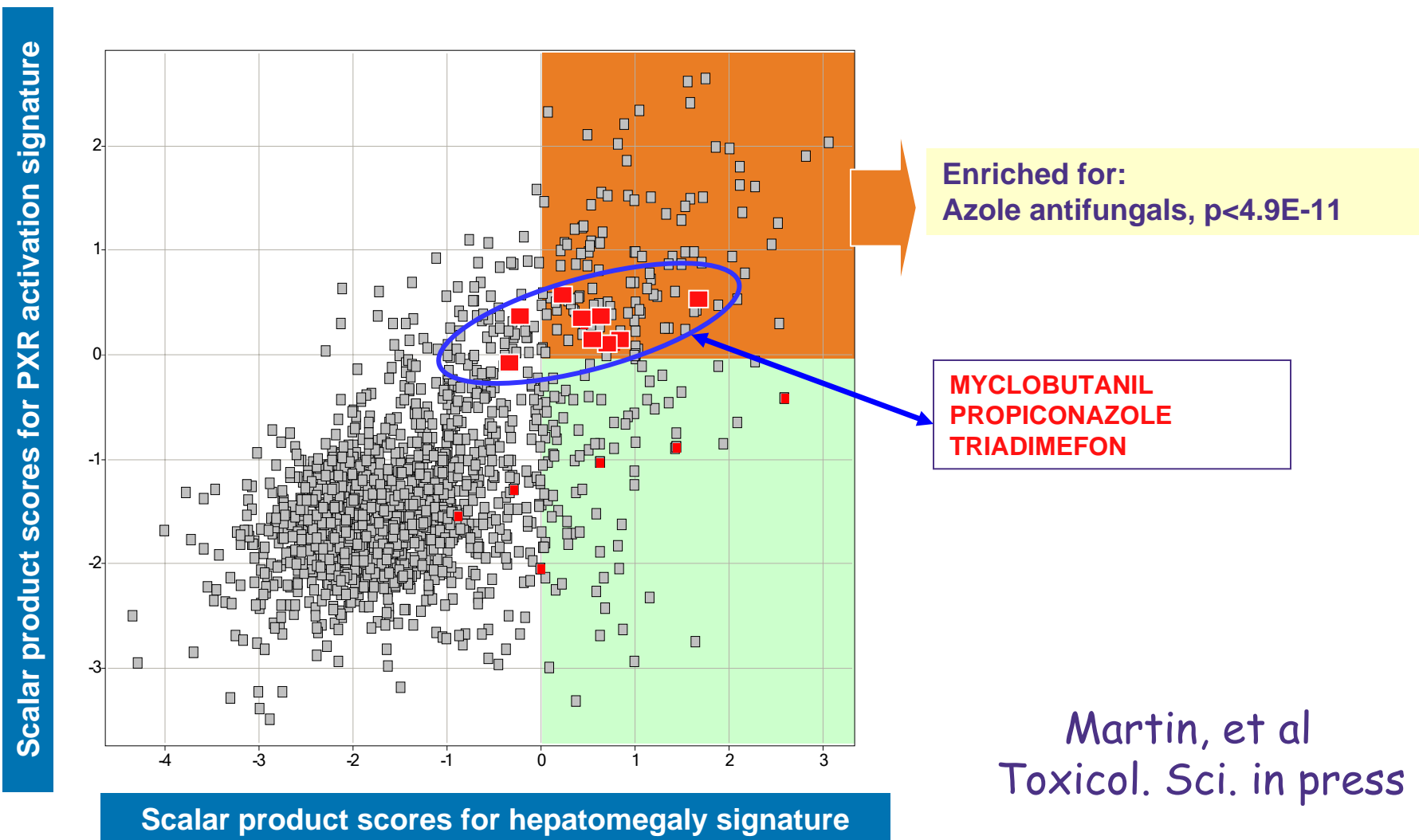
Chemical	Liver Toxicity	Liver Tumors	Thyroid Disruption	Testicular Toxicity
Myclobutanil	NO	NO	NO	YES
Propiconazole	YES	YES	NO	NO
Triadimefon	YES	YES	YES	YES

Common MOA across conazoles, tissues, cancer/non-cancer?

Use combination of toxicology and genomics to answer these questions.



Iconix genomics signatures combine with their reference database to correctly group EPA compounds with other conazole antifungals



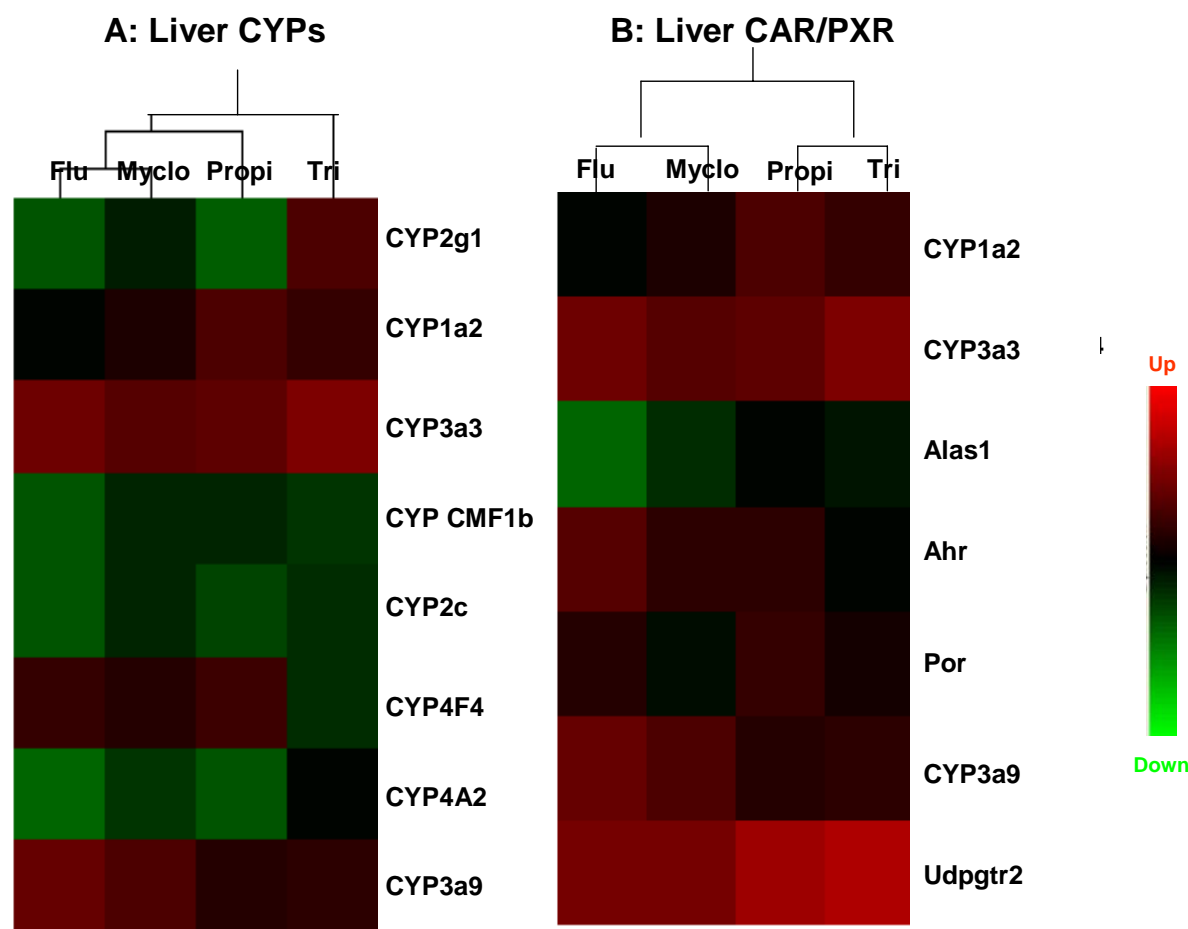
Martin, et al
Toxicol. Sci. in press



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CYP and CAR/PXR are differentially expressed in conazole treated rat livers



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Toxicological Information Gaps

The image displays a collage of overlapping web browser windows from 2005, illustrating various toxicological information sources and regulatory frameworks. The windows include:

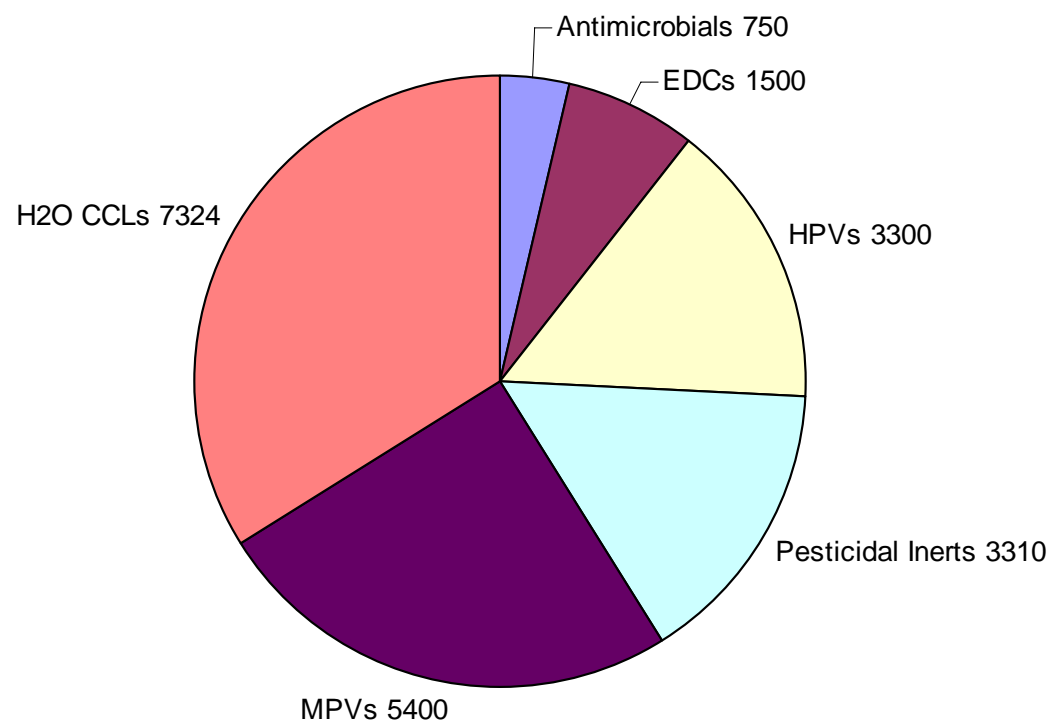
- EPA/OPP High Production Volume (HPV) Challenge Program:** The HPV Voluntary Challenge Chemical List.
- EPA/OSCP Endocrine Disruptor Screening Program:** The Endocrine Disruptor Screening Program.
- EPA Drinking Water Contaminant Candidate List (CCL):** The Drinking Water Contaminant Candidate List.
- EPA Pesticides - Inert (other) Pesticide Ingredients:** The Pesticides - Inert (other) Pesticide Ingredients.
- European Commission - Enterprise and Industry:** The REACH (Registration, Evaluation and Authorisation of Chemicals) website, which prominently displays "THE NEW EU CHEMICALS LEGISLATION - REACH".

The REACH website content includes:

- THE NEW EU CHEMICALS LEGISLATION - REACH**
- On 29 October 2003,** the European Commission adopted a proposal for a new EU regulatory framework for chemicals, [COM \(2003\) 644](#). Under the proposed new system called REACH (Registration, Evaluation and Authorisation of Chemicals), enterprises that manufacture or import more than one tonne of a chemical substance per year would be required to register it in a central database.
- The aims of the proposed new Regulation** are to improve the protection of human health and the environment while maintaining the competitiveness and enhancing the innovative capability of the EU chemicals industry. REACH would furthermore give greater responsibility to industry to manage the risks from chemicals and to provide safety information on the substances. This information would be passed down the chain of production.
- The proposal has been drafted in close consultation** with all interested parties, including an [internet consultation](#). This has allowed the Commission to propose a streamlined and cost-effective system. The proposal is now being considered by the European Parliament and the Council of the EU for adoption under the so-called co-decision procedure.

The collage also features a sidebar with "How to Participate" and "Who's Participating" information, and a taskbar at the bottom with various application icons and a system clock showing 4:47 PM.

>10,000 Chemicals in Need of Evaluation

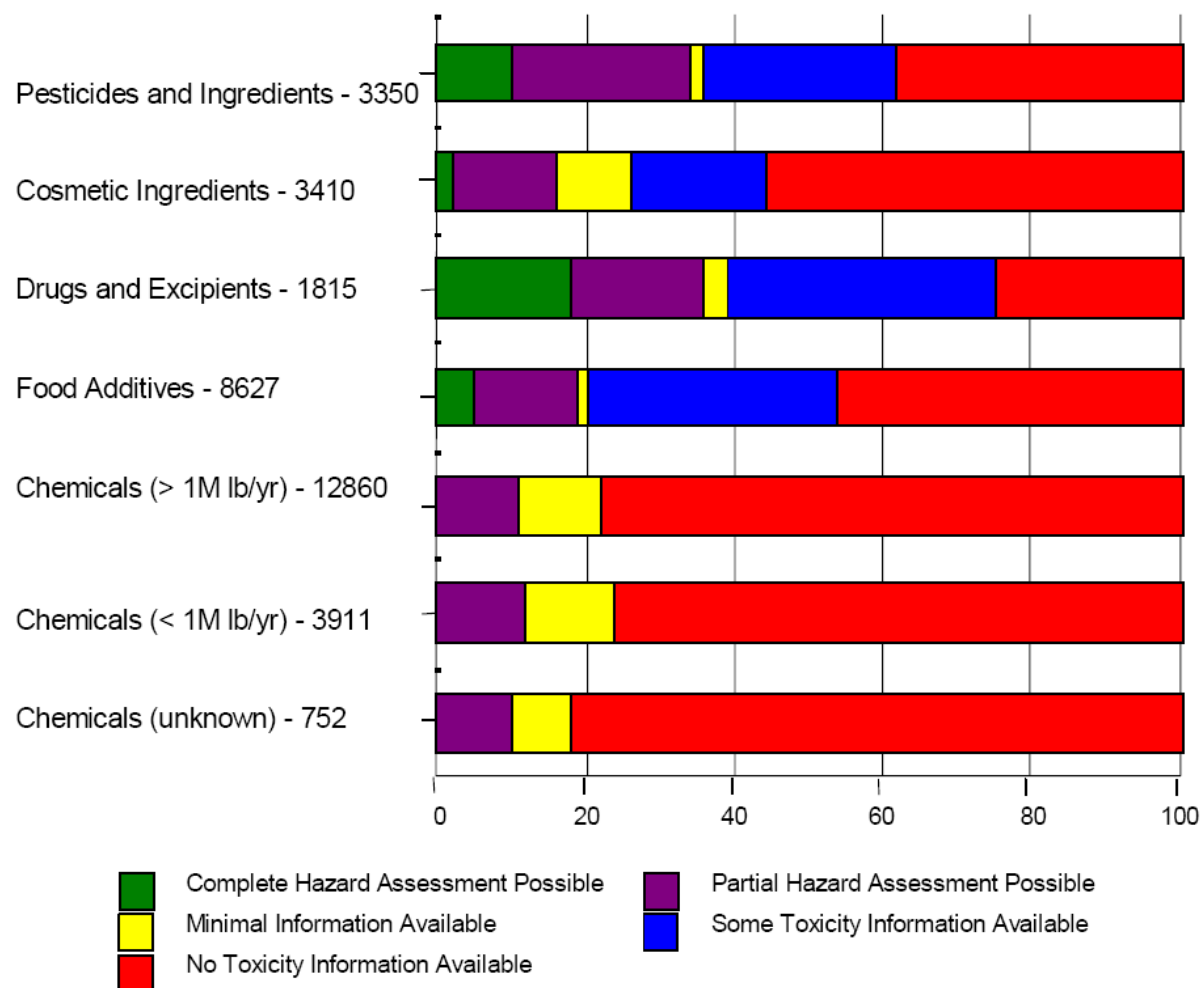


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Large Data Gaps Exist for Many Chemical Types

Estimated Mean Percent in Selected Universe



Strategies for Closing the Chemical Data Gap

by John S. Applegate and Katherine Baer



Building a science

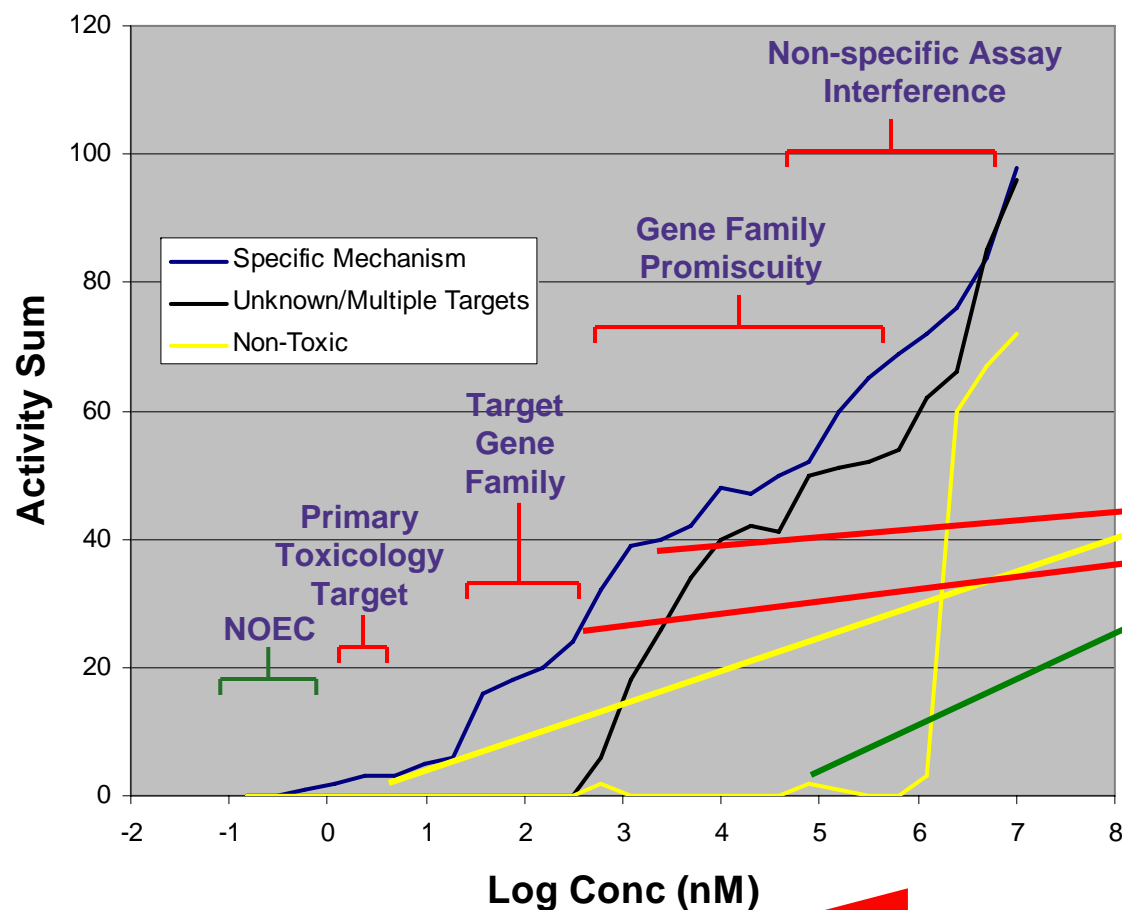
A Center for Progressive Reform Publication

April 2006

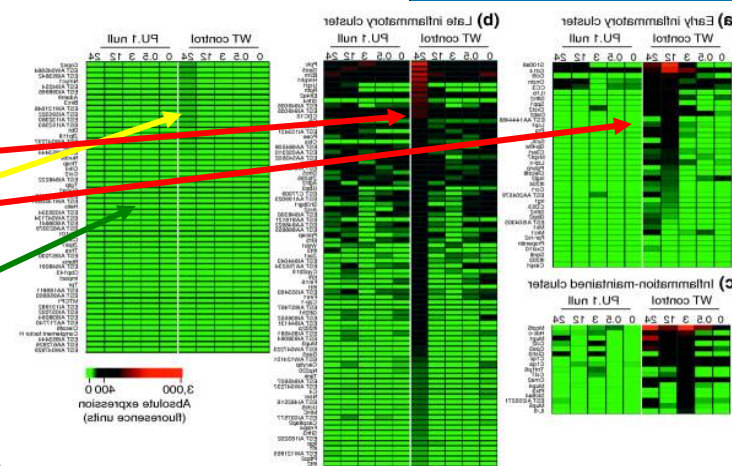
tal decisions

Bioactivity Profile of Environmental Chemicals

Goal: assesses broad biological effect patterns and correlate with the patterns of known toxicants for forecasting potential for hazard



HTS Target Assay Panels



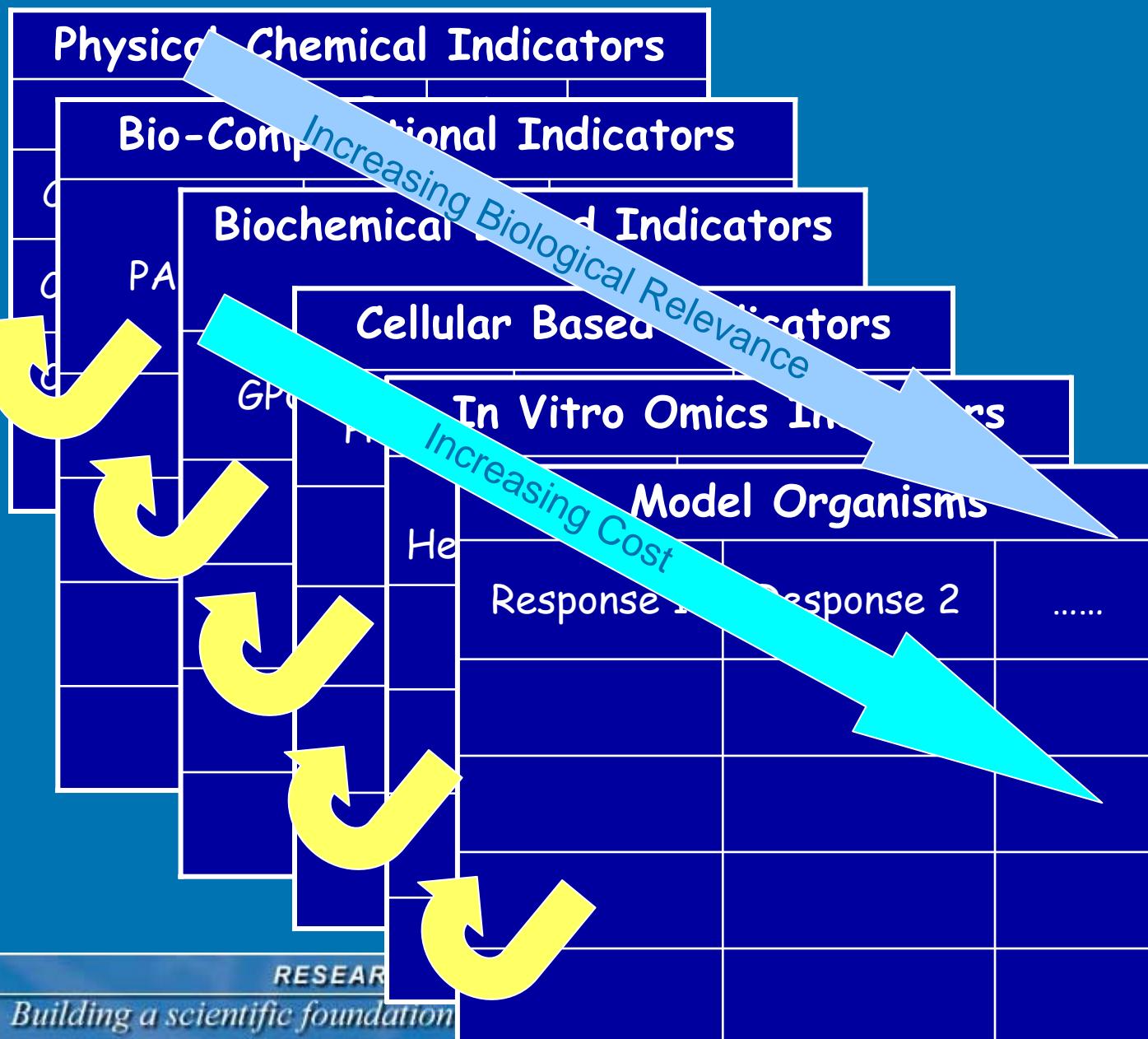
DEVELOPMENT

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ToxCast - A New EPA Research Program

(Dix et al, Toxicol Sci, 2006 in press)

Chemical Grouping
Bin 1
Bin 2
Bin 3
....
....
Bin



RESEARCH

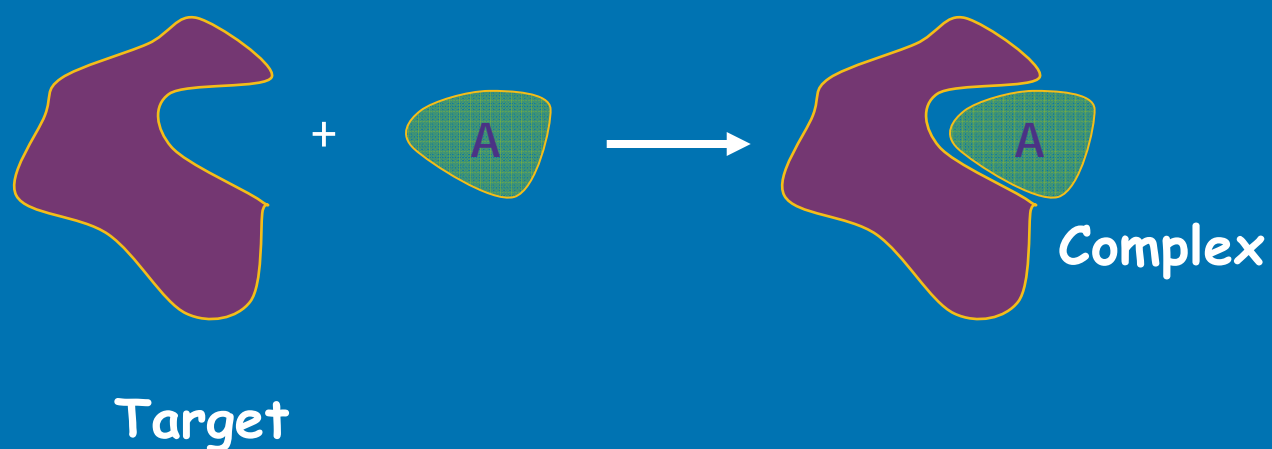
Building a scientific foundation

Pesticides as Proof of Concept

- ~800 Registered in the United States
- Wealth of Toxicological Information
 - Developmental, reproductive, chronic, etc
- Represent broad range of chemistries
 - Azoles, carbamates, pyrethroids, triazines, etc.
- Designed with biological activity in mind
 - Receptor binding, enzyme inhibition, cytoskeletal, etc.
- Have created a library of 400 for study



Molecular Docking Experiments & *virtual*-HTS



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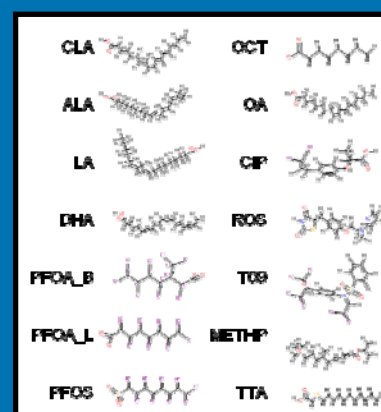
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PPAR Receptor and Molecular Docking

Affinity grid
for hPPAR- α

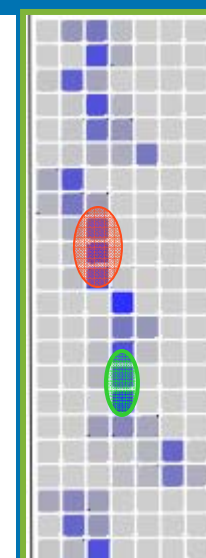
PDB ID: 1I7G

DOCKING A TOXICANT



Ligands in multiple charge states

CLA_ANION
CLA
ALA
ALA_ANION
LA
LA_ANION
DHA
DHA_ANION
PFOA_B
PFOA_L
PFOS
OCT
OA
OA_ANION
CIP
CIP
ROS
TO9
TO9_ANION
METHP
TTA
TTA_ANION



← Affinity increase

nM μ M mM

- PPAR- α agonist
- Fluorocarbons

Docking Animation: PFOAs & PPAR

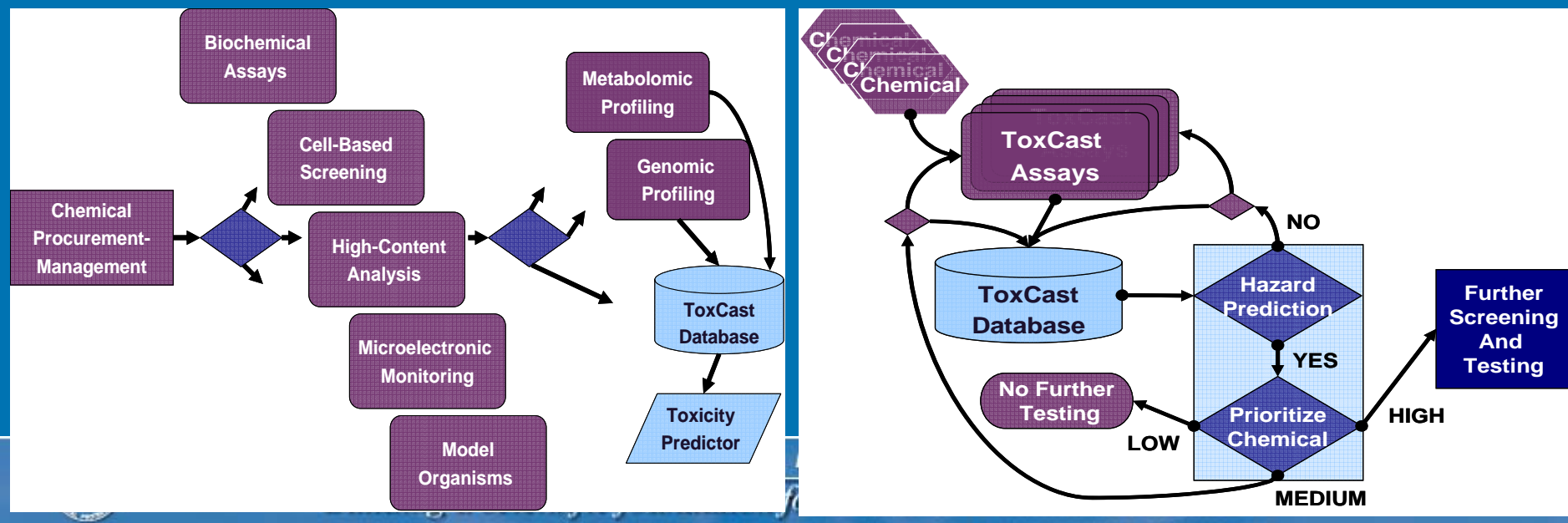


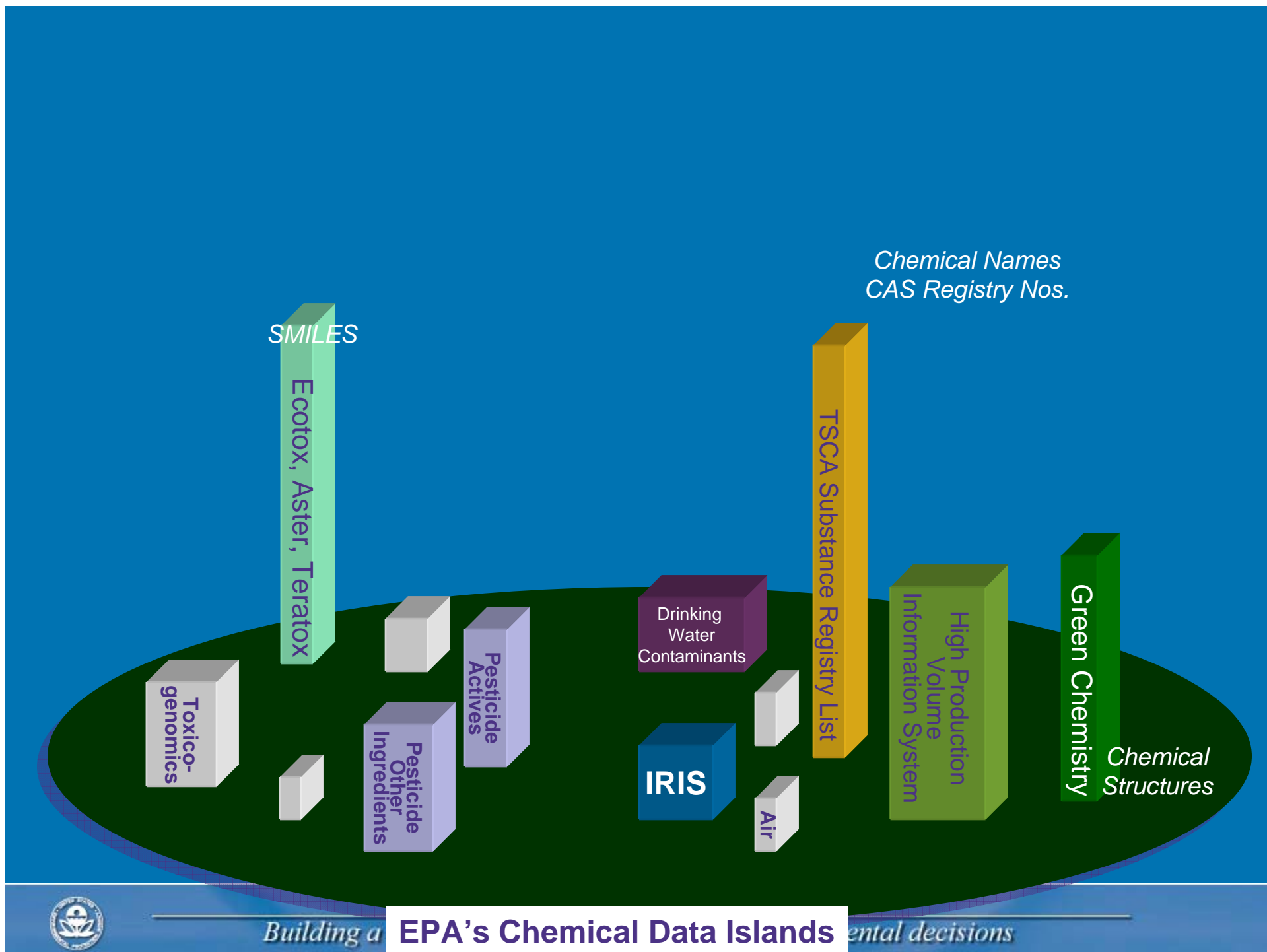
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ToxCast - Beyond Proof of Concept

- Availability of a science-based system to categorize chemicals of like properties and activities
 - Increasing confidence as database grows
 - Once operational, Mode of Action leads for new chemicals
 - Provide EPA Program Offices with a relatively inexpensive predictive tool box that heretofore has been seriously lacking
- Improve the efficiency and effectiveness of the use of animals in hazard identification and risk assessment





World Wide Web

National
Toxicology
Program

National Library
of Medicine

PubChem

Chemical
structures



European Chemicals
Bureau (SIDS)

Chemical Names
CAS Registry Nos.

SMILES

Ecotox, Aster, Teratox

Toxico-
genomics

Pesticide
Other
Ingredients

Pesticide
Actives

Drinking
Water
Contaminants

IRIS

Air

TSCA Substance Registry List

High Production
Volume
Information System

Green Chemistry

Chemical
Structures



Building a

EPA's Chemical Data Islands

mental decisions

World Wide Web

National
Toxicology
Program

National Library
of Medicine

PubChem

Chemical
structures



European Chemicals
Bureau (SIDS)

Chemical
structures

Chemical Names
CAS Registry Nos.

SMILES

Ecotox, Aster, Teratox

DSSTox

TSCA Substance Registry List

High Production
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About DSSTox

Work in Progress

Frequent Questions

Databases

Central Field Definition
Table

Apps, Tools & More

DSSTox Community

Site Map

Glossary of Terms

Help

U.S. Environmental Protection Agency

Distributed Structure-Searchable Toxicity (DSSTox) Public Database Network

<http://www.epa.gov/ncct/dsstox>

[Recent Additions](#) | [Contact Us](#) | [Print Version](#) Search:

[EPA Home](#) > [Research & Development](#) > [Health and Environmental Effects Research](#) > Distributed Structure-Searchable Toxicity (DSSTox) Public Database Network

DSSTox

The Distributed Structure-Searchable Toxicity (DSSTox) Database Network is a project of [EPA's Computational Toxicology Program](#), helping to build a public data foundation for improved structure-activity and predictive toxicology capabilities. The DSSTox website provides a public forum for publishing downloadable, standardized toxicity data files that include chemical structures. [More](#)

Recent Additions: 1Mar05

***New Database Additions:

- FDA Maximum (Recommended) Daily Dose Database ([FDAMDD](#)) of 1217 pharmaceuticals - 1Mar05

***Expanded and modified versions:

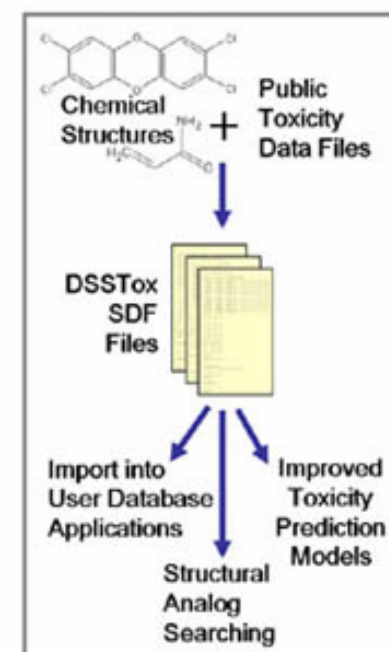
- Consolidated, updated Carcinogenic Potency Database - All Species ([CPDBAS](#)), 1451 compounds: 91 new records added to v2a
- CAS registry numbers added to [EPAFHM](#) and [DBPCAN](#)

***New Standard Fields added to all DSSTox files:

- [INChI](#) (IUPAC/NIST Chemical Identifier) unique structure-text codes
- [IUPAC](#) systematic chemical names (generated by ACD/Name)
- [Standard Toxicity Fields](#): StudyType, Species, Endpoint fields

***New Features of Site:

- [FTP Download Instructions](#) for easy access to archived and new DSSTox data files
- New information pages: [INChI](#), [DSSTox Standard Toxicity Fields](#)
- Links to [External Public Databases](#) adopting DSSTox standards: [ISSCAN](#) *new*



- [DSSTox Graphic Flowchart](#)
- [DSSTox Project Goals](#)
- [DSSTox Publications](#)

DSSTox Databases:

[CPDBAS v2a 1451 1Mar05](#)
[DBPCAN v2a 209 1Mar05](#)
[EPAFHM v2a 617 1Mar05](#)
[FDAMDD v1a 1217 1Mar05**](#)
[NCTRER v2a 232 1Mar05](#)

*** new addition*

Capturing the Legacy Data

Reference Toxicological Database - [frm_Study_General_Info_Input : Form]

File Edit View Insert Format Records Tools Window Help Adobe PDF

Tahoma 8 B I U

Reference Toxicological Database

Pesticides and other environmental chemicals

General Study and Review Input Form

Study and Review Identifiers

RTD# 0002 File Name 102104_12341234_3800_1.wpd

MRID# 12341234 TXR# 0004357

Supplemental MRID Nos Old Review IDs

56785678 TXR No. 0004358

Old Study IDs

Accession No. 102668 Review Year (most recent) 1996

Study Type and Data Quality

Study Type Prenatal developmental toxicity study

Data Usability 1

Deficiencies and Reviewer Comments Study followed GLP guidelines and after updated review was deemed acceptable.

Endpoints refer to study level results and do not require the addition of treatment groups

View or Add Endpoints

Test Material Information

PC Code 004006 Inprothrin

Lot# 745-1 Batch# 5A63 Source ABC Inc.

Purity (%) 96 Comments No Comments

EPAPTC ID 474

Animal and Dose Information

Species rat

Strain Sprague Dawley (CD)

Total # of Animals 50

Additional Comments Female (maternal) dosed rats

Route of Administration

Feed

Dose Range (do not include control) Min 5 -- Max 25 mg/kg/day

Duration (abs unit) 9 day

Additional Comments Dosed from GD 6-15

Treatment Group Input Form

Treatment Group Category Adult Sex Category F

Dose Units 5 mg/kg/day Duration Units 9 day #group 25

Save Delete New

Treatment Group List

Group ID	RTD #	Treatment Group Category	Sex Category	Dose (Units)	Duration (Units)	# Animals/Group	View or Add Results by Type
1	0002	Adult	F	5 mg/kg/day	9 day	25	
2	0002	Adult	F	25 mg/kg/day	9 day	25	
3	0002	Fetus	NA	5 mg/kg/day			
4	0002	Fetus	NA	25 mg/kg/day			

Record: 14 of 4

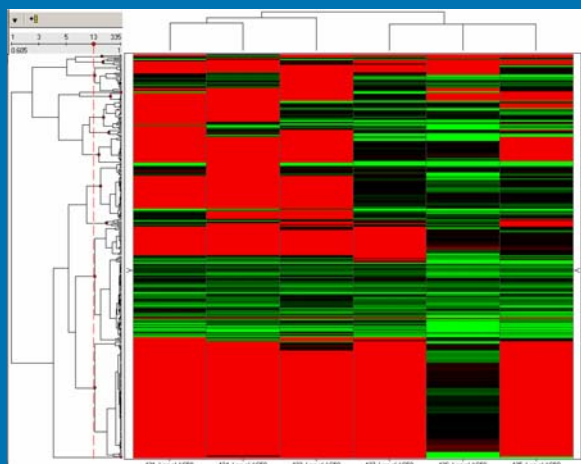
Record: 14 of 1

Form View

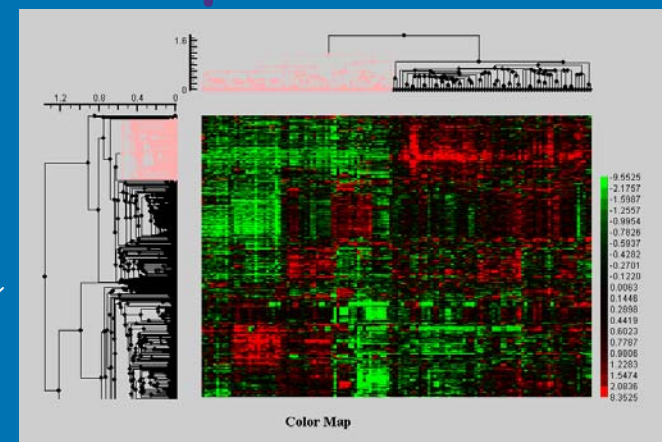
NUM



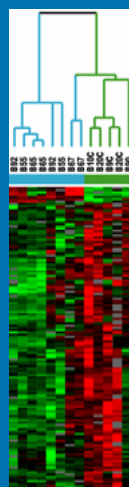
Correlating Domain Outputs



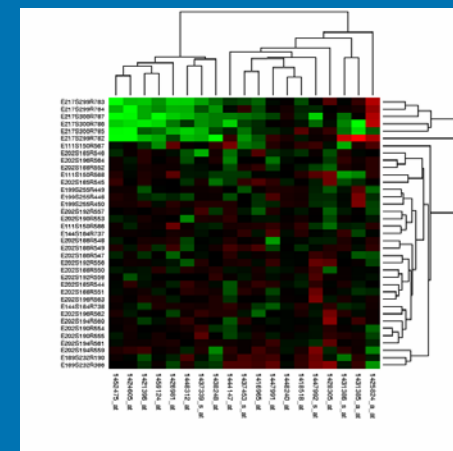
Cell based Assays



Physical chemical properties



Nuclear Receptors



Toxicology Endpoints

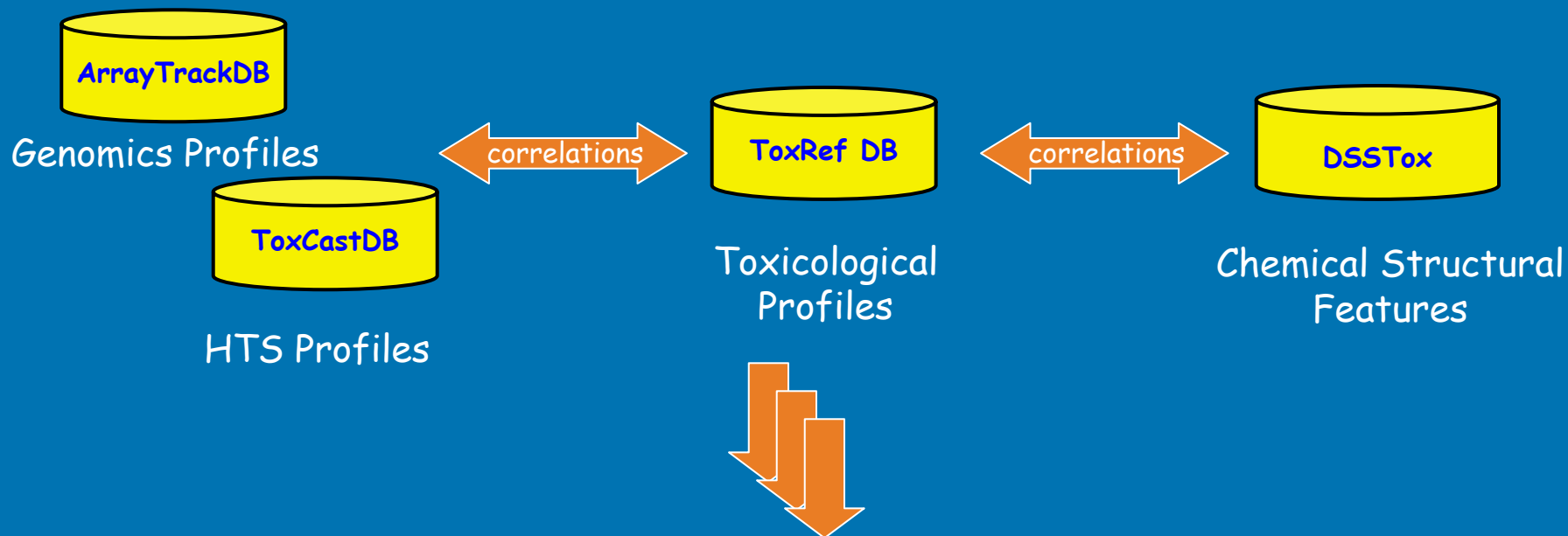
Profile Matching



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ToxCast Training Set - Pesticide Actives



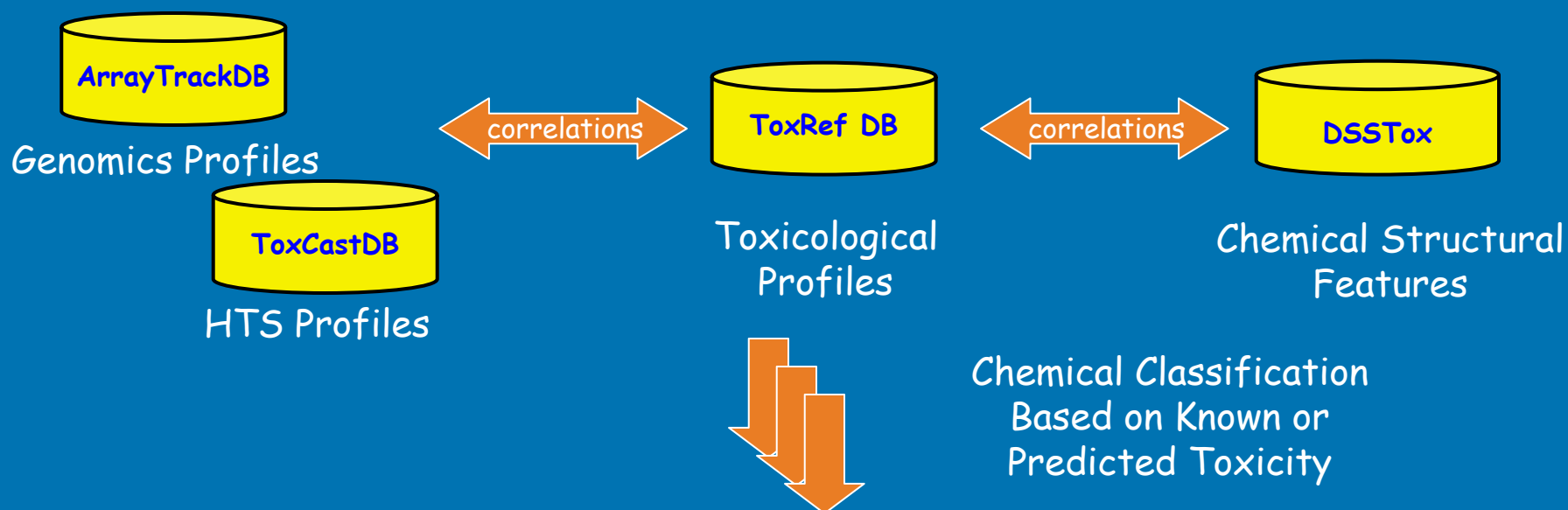
Chemical	HTS Profile Correlation	Genomic Profile Correlation	Male Fertility	Testicular Atrophy	Mouse Liver Tumors	Rat Thyroid Tumor
Myclobutanil	?	?	+	+	-	-
Propiconazole	?	?	-	-	+	-
Triadimefon	?	?	+	-	+	+



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ToxCast Chemical Classification of Environmental Chemicals



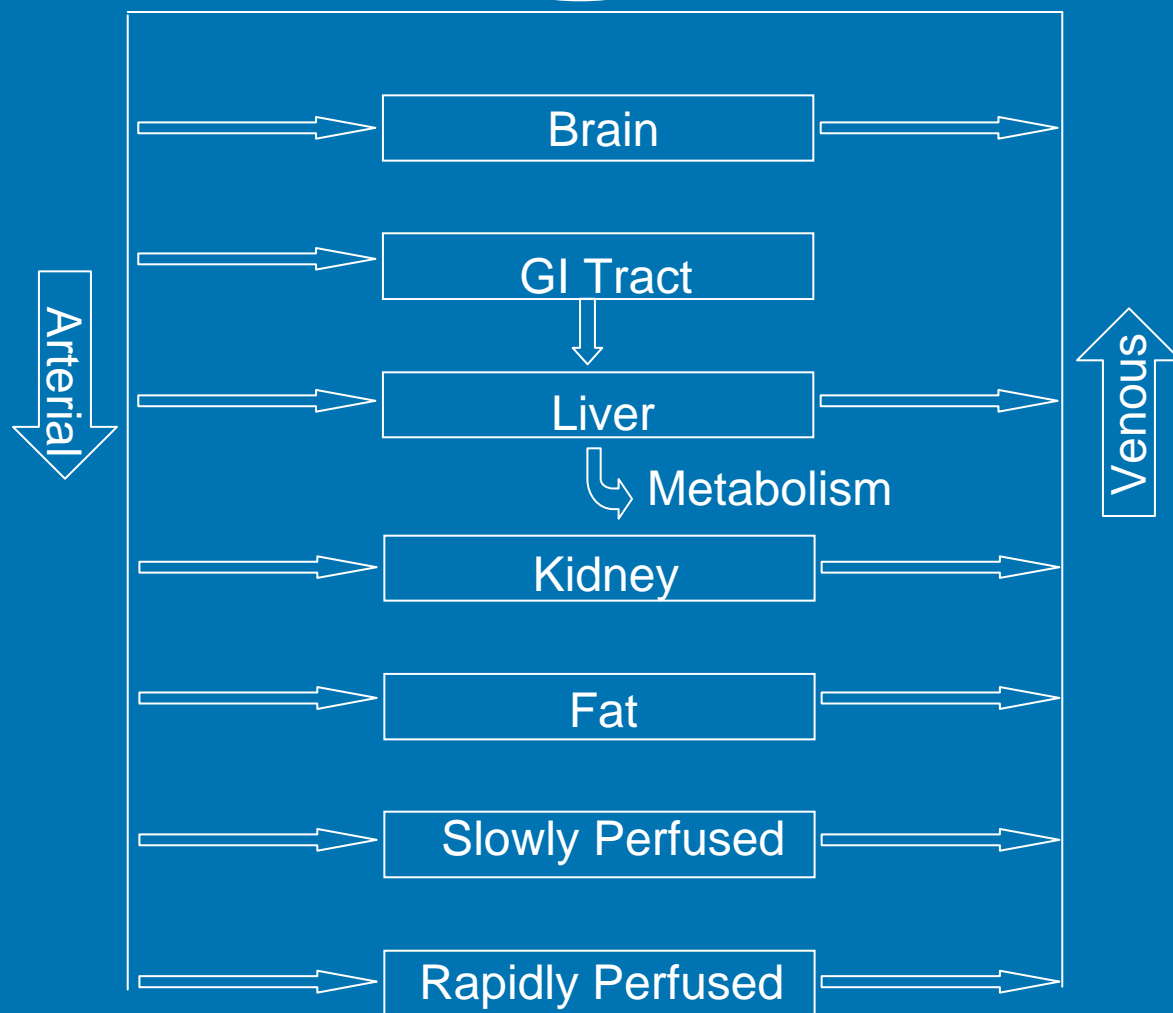
Profiles	Tox						
	Correlation Present	Liver Carcinogen	Kidney Carcinogen	DNT	NT	Liver Enzymes	Etc....
Chemical A	+	-	-	-	+	-	-
Chemical B	+	-	-	+	-	-	-
Chemical C	+	+	-	-	-	+	-
Chemical D	+	+	-	-	-	+	-
Chemical E	+	-	-	+	+	-	-
Chemical F	-	-	-	-	-	-	-



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Gas Exchange



Rats:

pnd10: 20 g

Adult: 200 g (60 day)

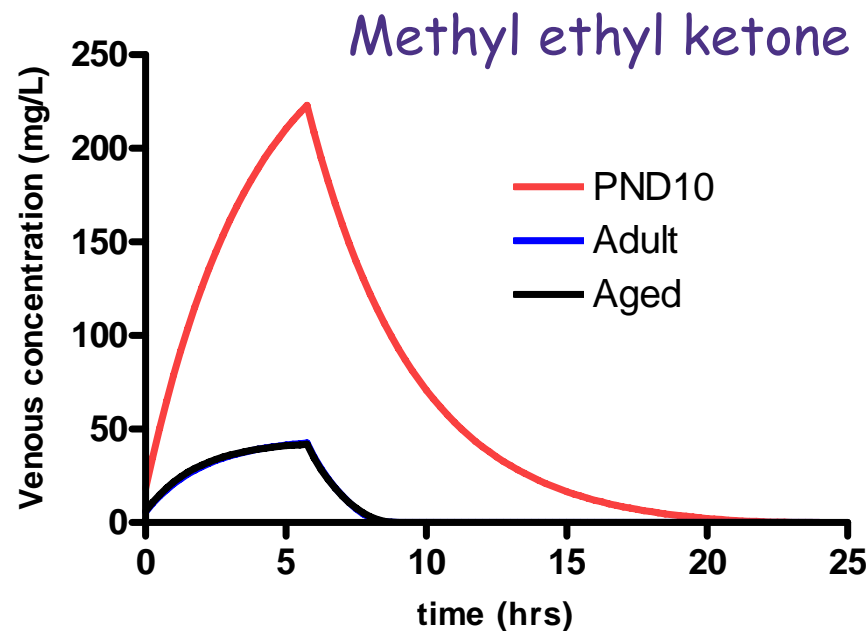
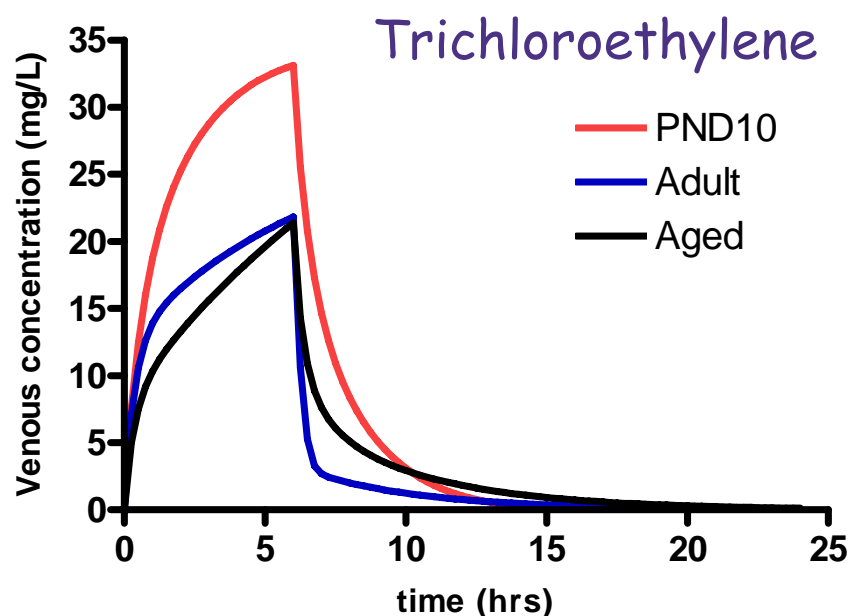
Aged: 450 g (2 yr)



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Predicted Venous Concentrations in rats - 6 hr 500 ppm



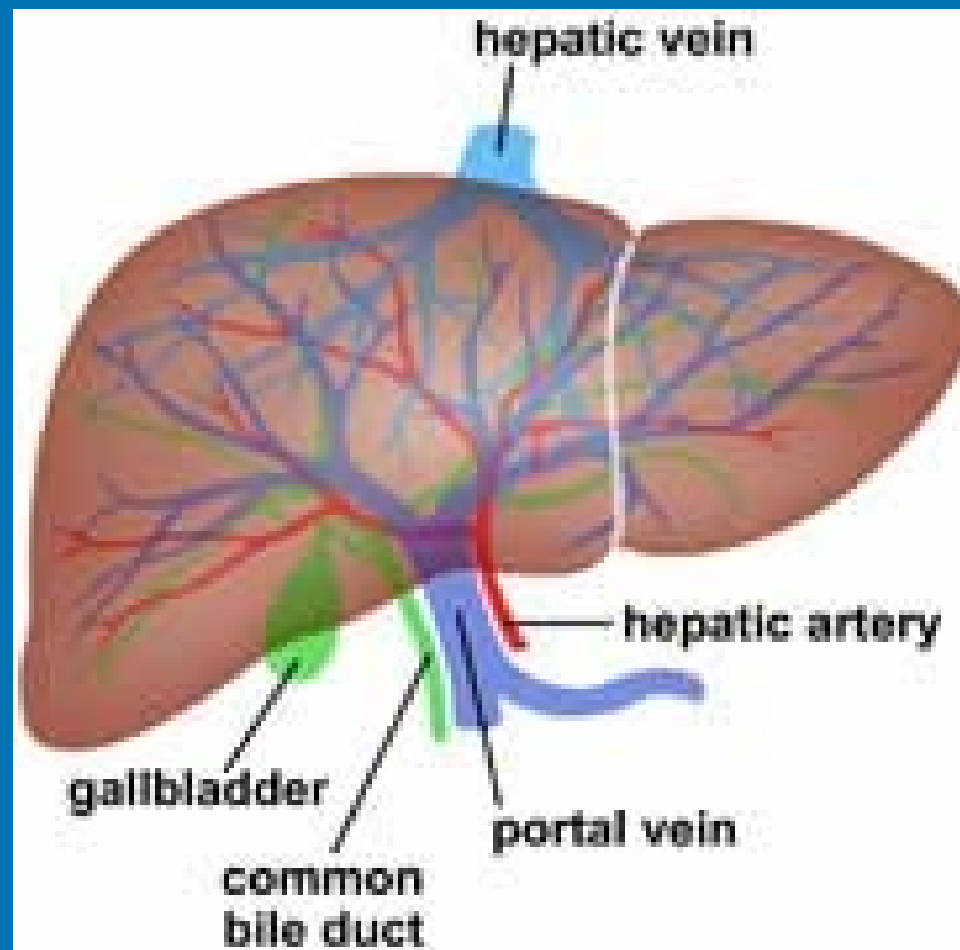
Modeling uses age-appropriate physiological and chemical specific (e.g., partition coefficients, metabolism rates) parameters



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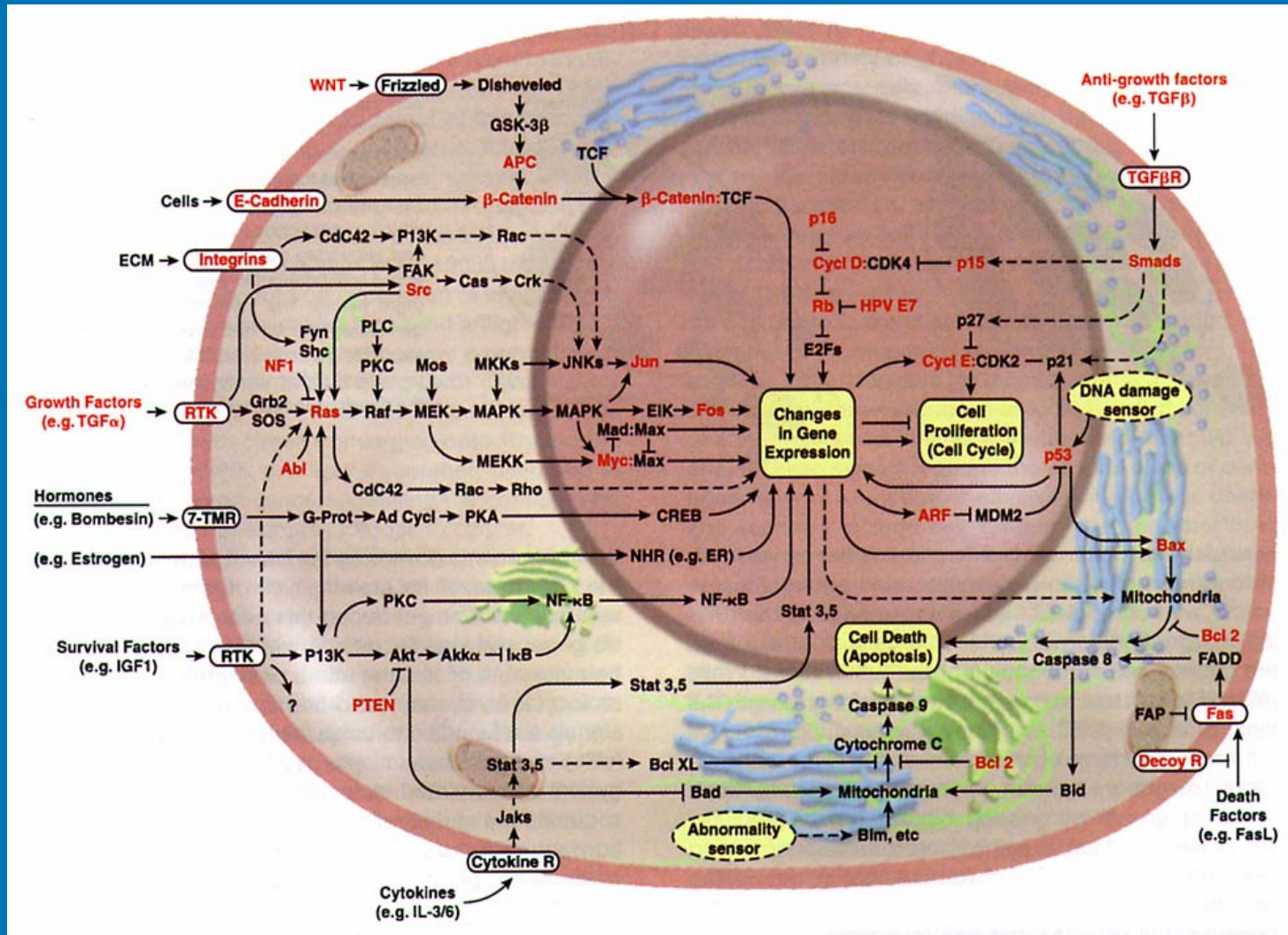
The Virtual Liver: A multiscale , computational model



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Molecular Circuitry



Hanahan and Weinberg, *Hallmarks of Cancer*, Cell, 100, 57-70, 2000.

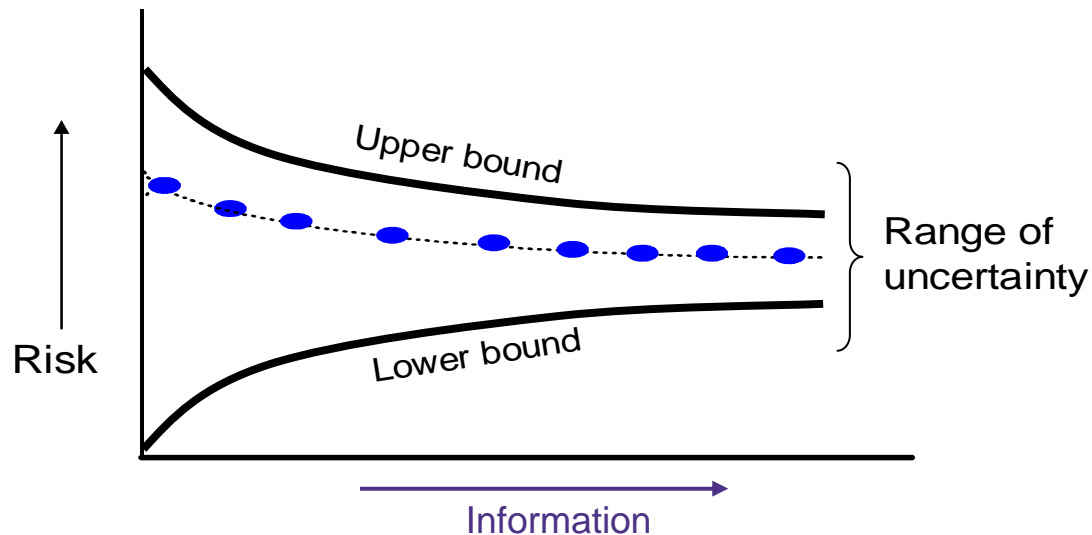


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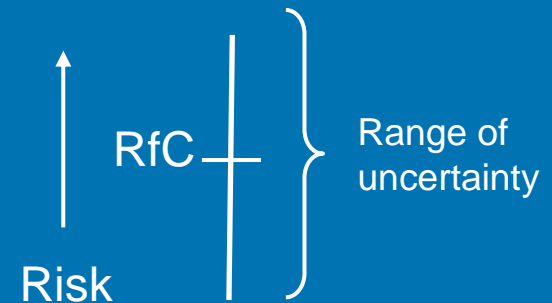
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Reduction of uncertainty in risk assessment

(Mechanism-based approach)

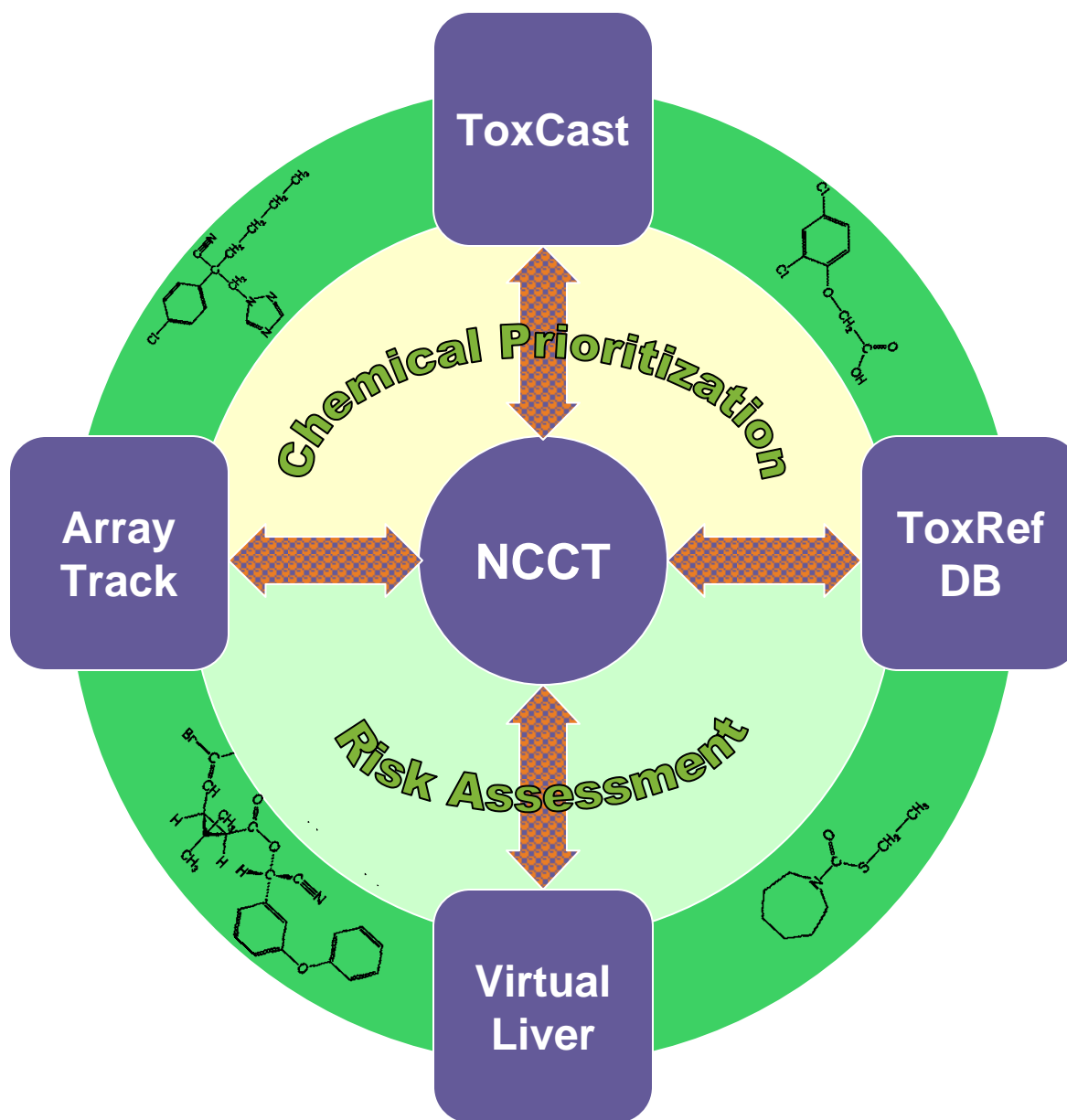


(Policy-based approach)



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Acknowledgements

- DSSTox
 - Ann Richard
- ToxCast and RefToxDB
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 - Tom Transue
- Life Stages
 - Hugh Barton
 - Chester Rodriguez
- Virtual Liver
 - Jerry Blancato
 - Rory Conolly
 - Imran Shah





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