

The art and practice of structure-activity modeling at the chemistry-toxicology interface



Ann Richard

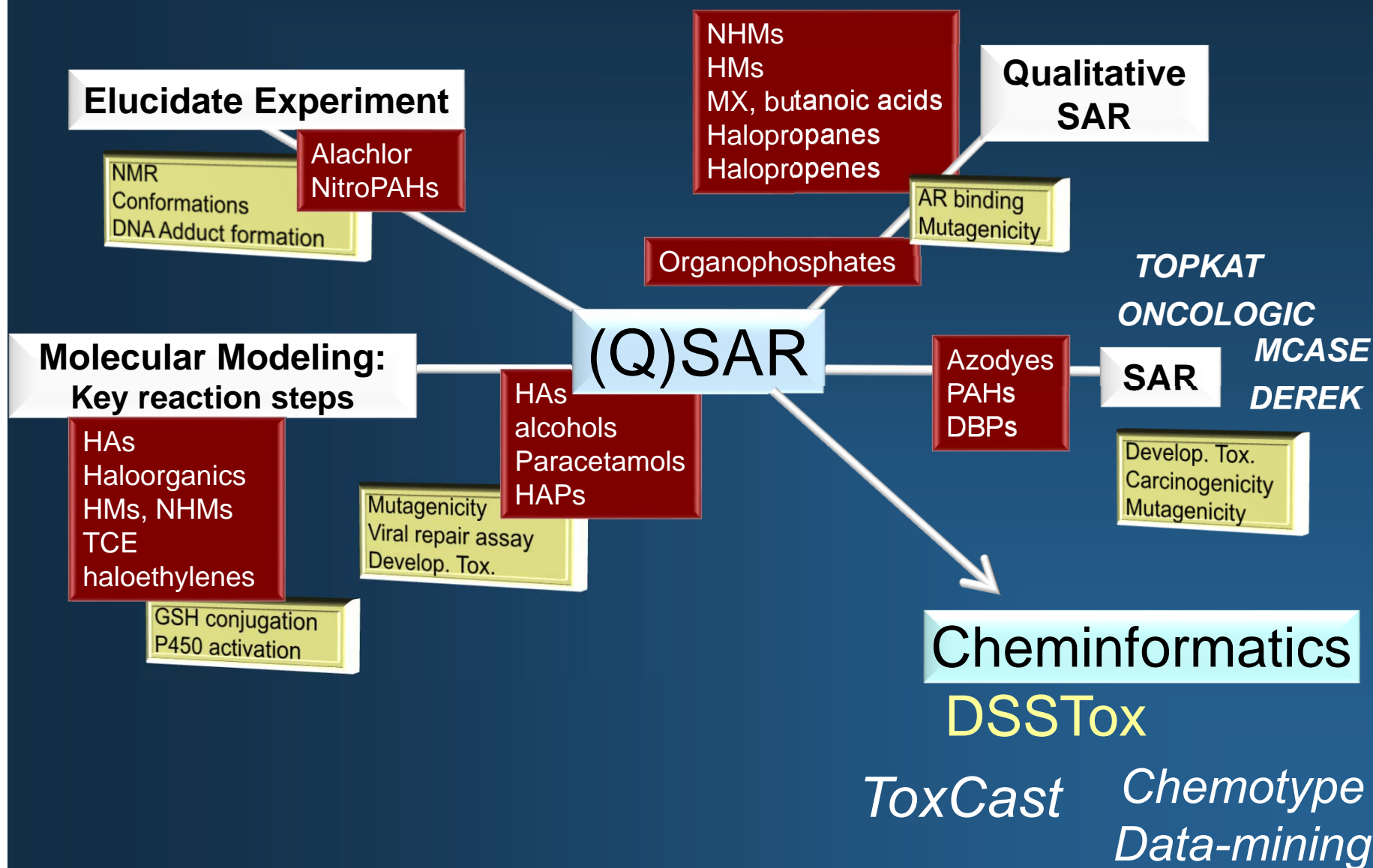
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Office of Research & Development

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Office of Research and Development
National Center for Computational Toxicology

This work was reviewed by EPA and approved for publication but does not necessarily reflect official Agency policy.

Past & present research at EPA:



Part I:

Computational chemistry & mechanism-based structure modeling

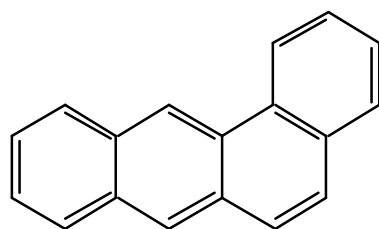
Focused application
Narrowly defined questions

Structure-Activity Relationship (SAR) postulate:

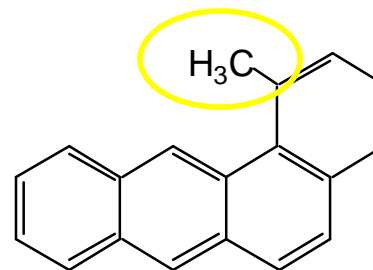
*similar molecules have similar activities
(except when they don't!)*

Structure-Activity Relationships (SAR)

$$\text{Activity} = f(\text{Structure})$$



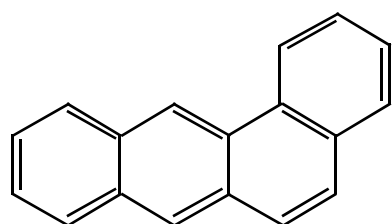
active



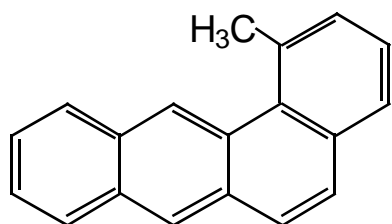
inactive

Methyl group leads to loss of carcinogenic activity

SAR Generalization



active



inactive

Statistical association
Mechanistic hypothesis



Class



PAHs

activating feature



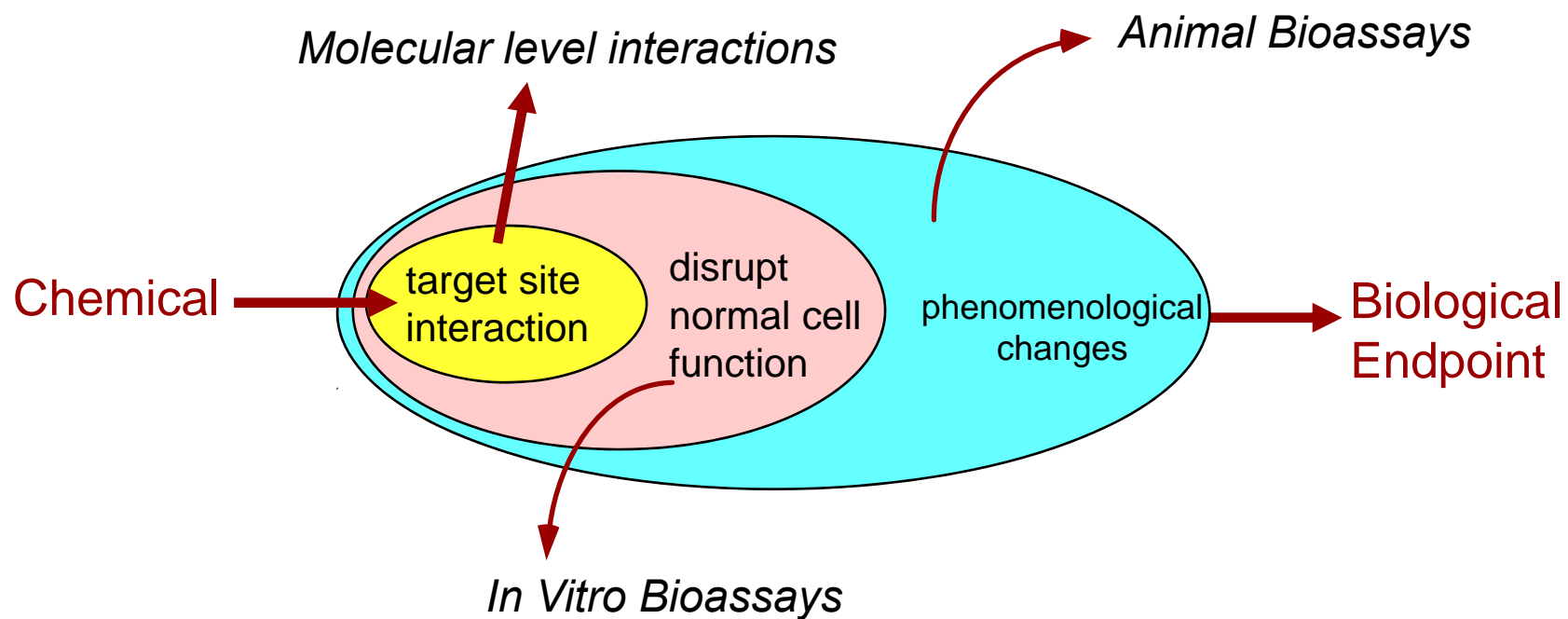
bay region

modulating feature

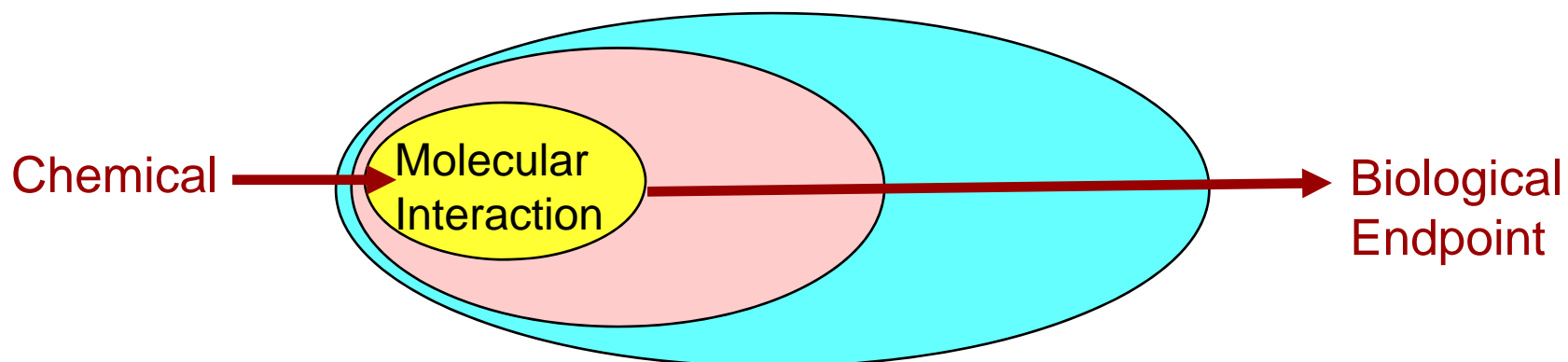


steric hindrance

Mechanisms of Toxicity



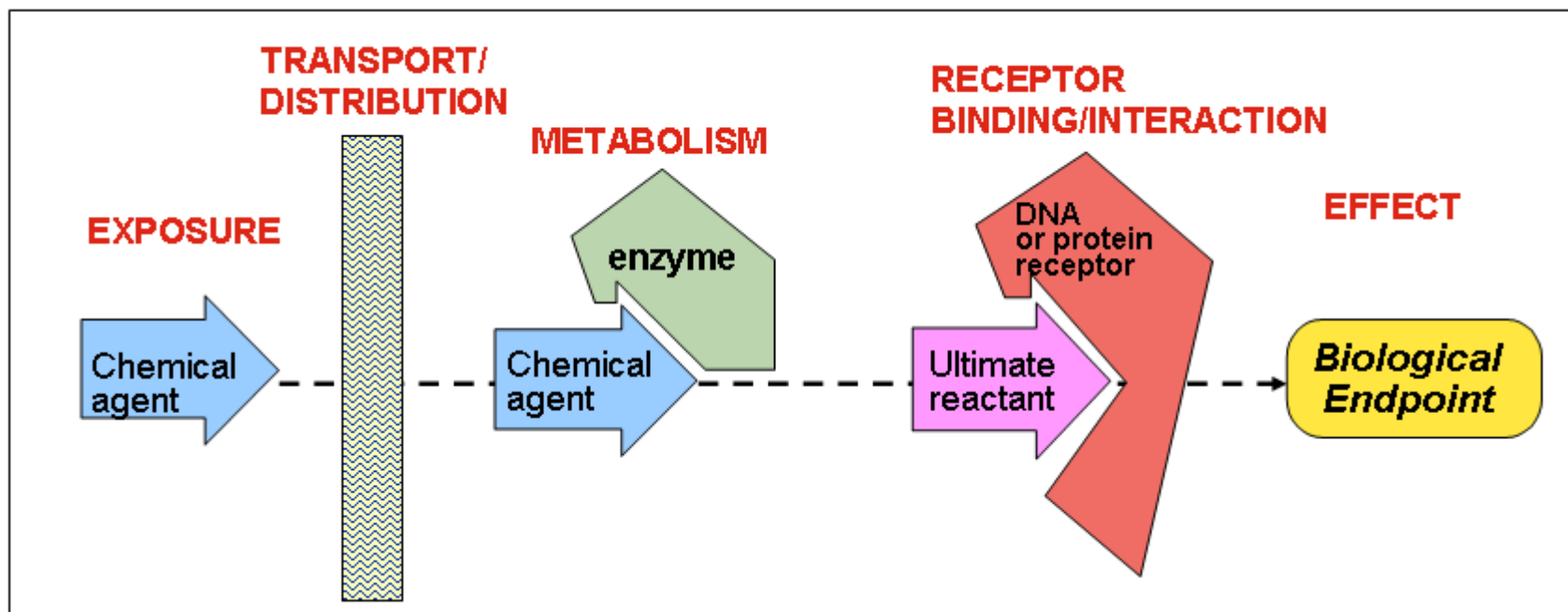
Structure-Activity Relationships



Similar chemicals
Relative properties
Common mechanism of action

Typical (Q)SAR Paradigm

$$\text{Activity} = \text{Constant} * \text{Prob}_{\text{site}} * \text{Prob}_{\text{rxn}}$$

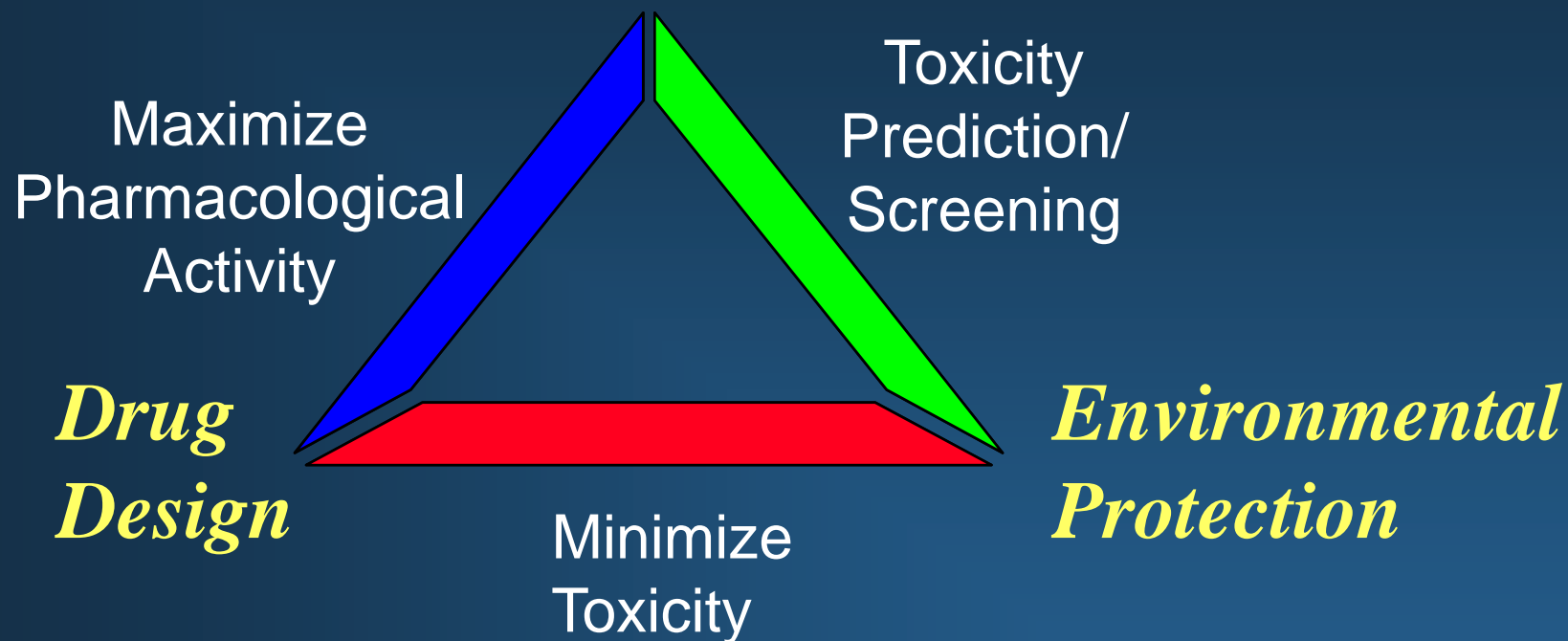


*vapor pressure
Solubility
Henry's const*

*log P(octanol/water)
acidity*

*electronic/ steric
3D properties
reactivity indicators
interaction energies*

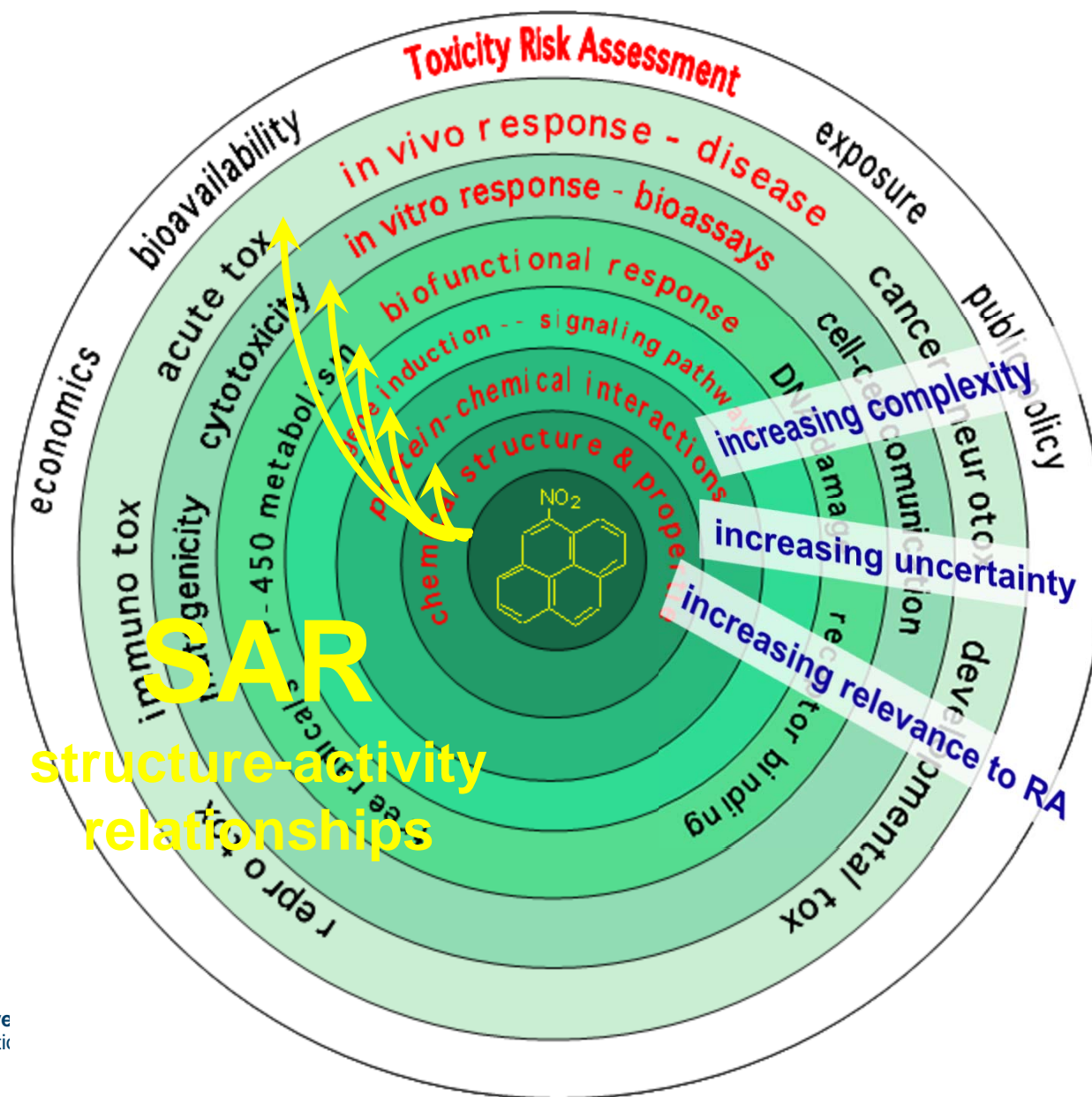
SAR Application



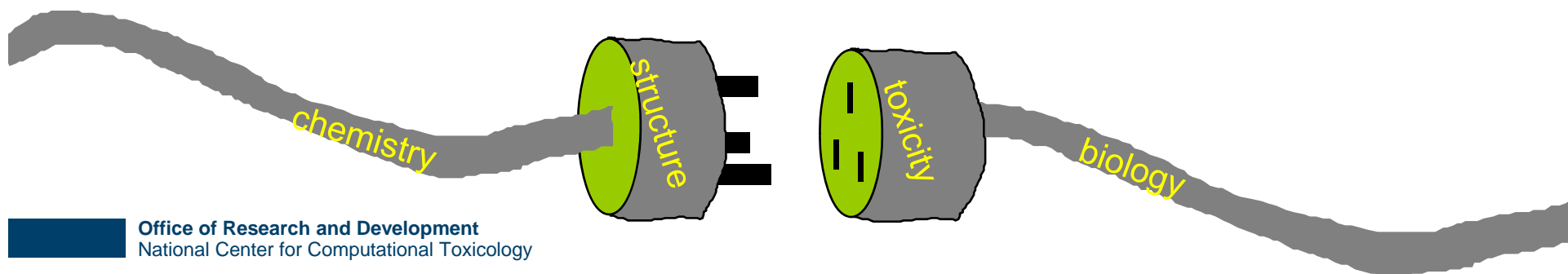
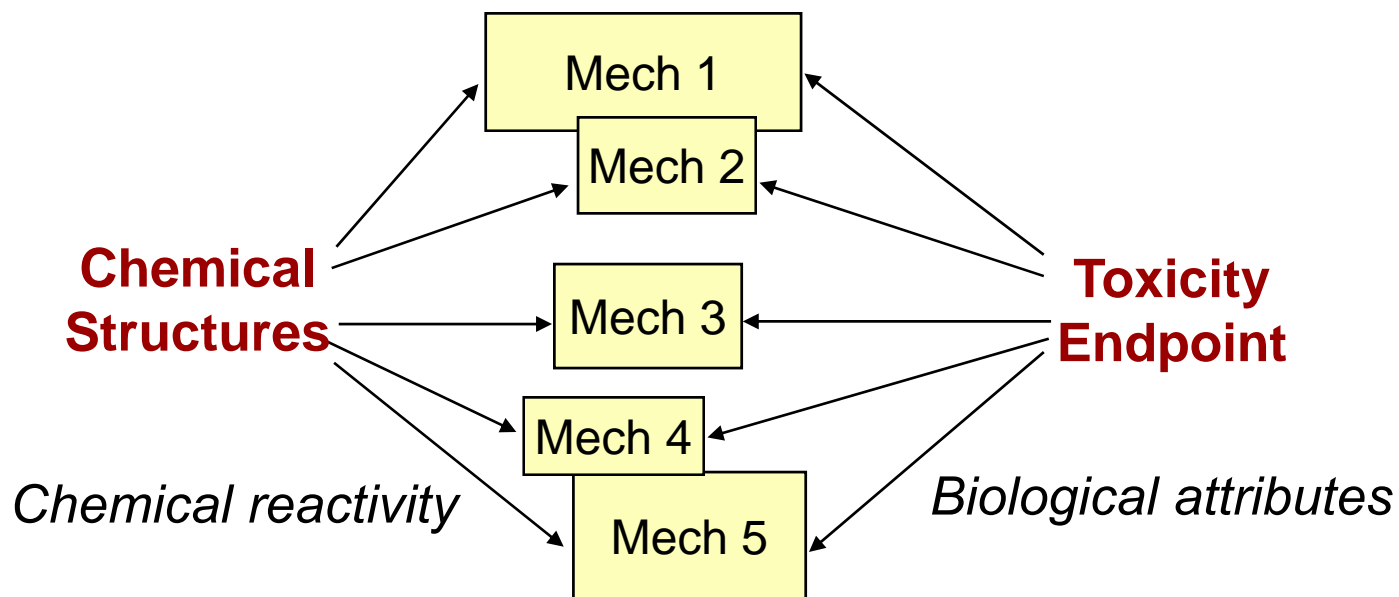
- Single therapeutic target
- Drug-like chemicals
- Some toxicity anticipated

- Multiple unknown targets
- Diverse structures
- Human and eco endpoints

Toxicity Prediction Problem



Global vs. Local SAR models



Classical QSAR

“We are to admit no more causes of natural things than such as are both true and sufficient to explain their appearances.”

- Isaac Newton



Quantitative Structure-Toxicity Relationships for a Series of Alcohols in a Mammalian Viral Host Cell Reactivation Assay

Benane SG, Richard AM, Blackman CF, Lytle CD (1993) InVitroToxicol 6(4):267-277.

Alcohol	Formula	HCR-inhibiting Concentration [mM]	LogP(o/w)
methanol	CH ₃ OH	230.00	-0.77
ethanol	CH ₃ CH ₂ OH	100.00	-0.31
1-propanol	CH ₃ CH ₂ CH ₂ OH	19.00	0.25
1-butanol	CH ₃ (CH ₂) ₃ OH	8.00	0.8
1-pentanol	CH ₃ (CH ₂) ₄ OH	2.20	1.56
1-hexanol	CH ₃ (CH ₂) ₅ OH	0.44	2.03
1-heptanol	CH ₃ (CH ₂) ₆ OH	0.19	2.41
1-octanol	CH ₃ (CH ₂) ₇ OH	0.08	2.97
2-propanol	CH ₃ CH(OH)CH ₃	44.00	0.05
2-butanol	CH ₃ CH ₂ CH(OH)CH ₃	12.00	0.61
2-methyl-1-propanol	CH ₃ CH(CH ₃)CH ₂ OH	9.60	0.76

Congeneric
series of
chemicals

Reasonable to
assume common
mechanism of
action

LogP(o/w) major
determinant in
many QSARs

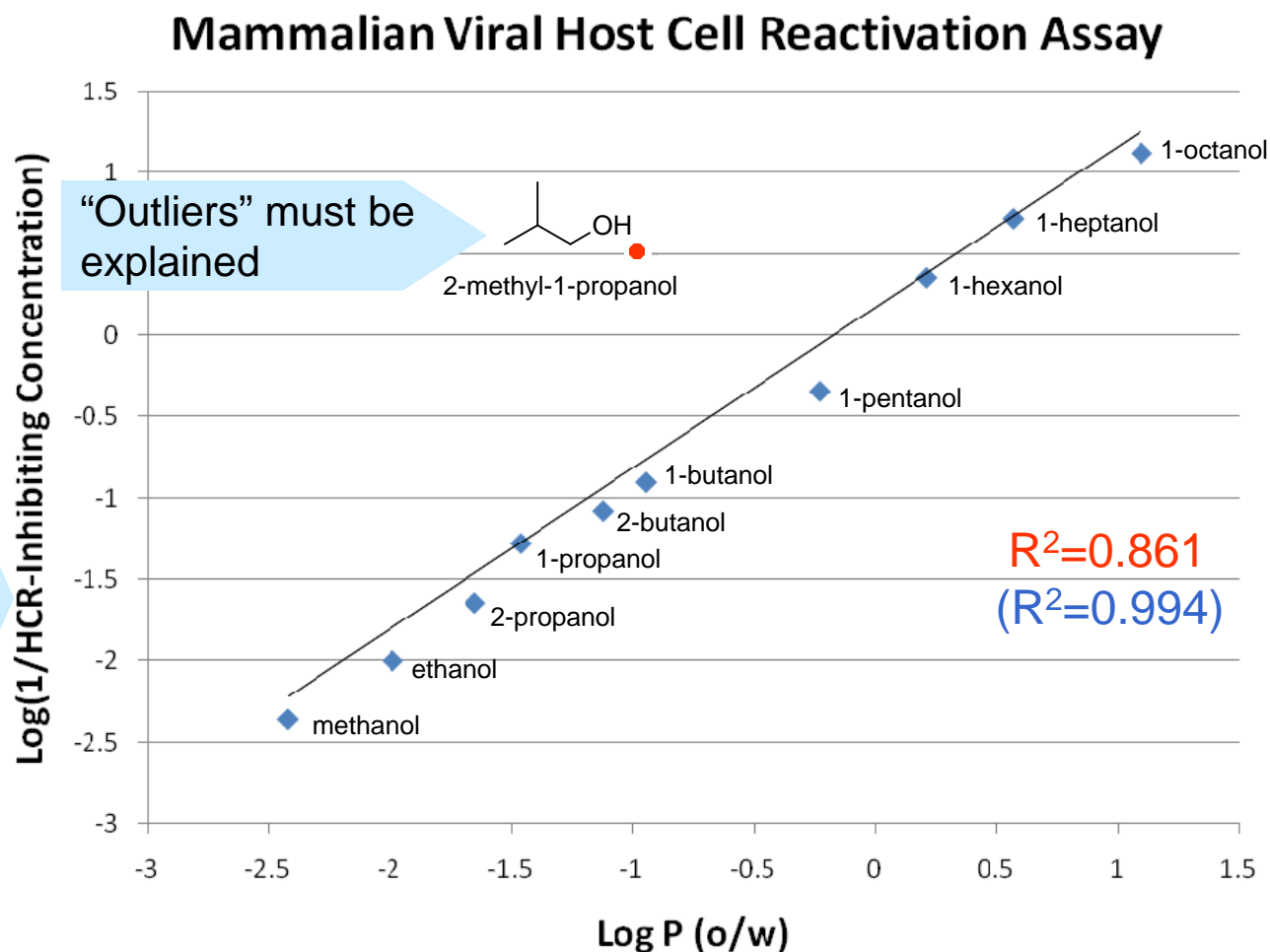
Does inhibition of DNA repair for a series of alcohols exhibit typical “narcosis” activity, or a structure-activity cutoff (C7) as reported for permeability of bacterial membranes?

Quantitative Structure-Toxicity Relationships for a Series of Alcohols in a Mammalian Viral Host Cell Reactivation Assay

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Linear QSAR
relates to log
[1/Activity(molar
concentration)]

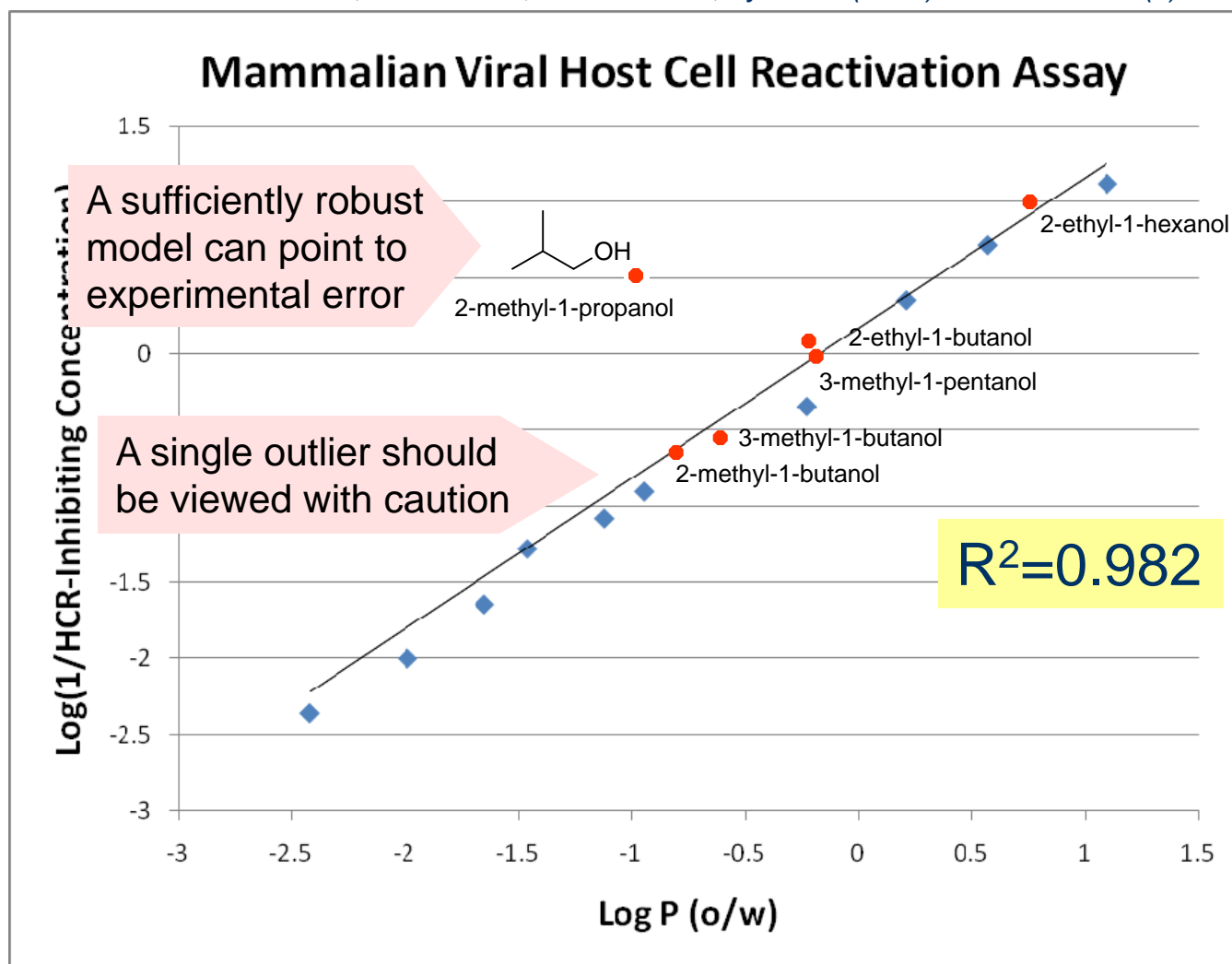
Activity spans
several orders
of magnitude



Does inhibition of DNA repair for a series of alcohols exhibit typical “narcosis” activity, or a structure-activity cutoff (C7) as reported for permeability of bacterial membranes?

Quantitative Structure-Toxicity Relationships for a Series of Alcohols in a Mammalian Viral Host Cell Reactivation Assay

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Do branched alcohols (similar to valproic acid) exceed “baseline” activity due to, e.g., active transport? → Test series of branched alcohols.

If only we could combine apples & oranges...

"Simply stated, it is sagacious to eschew obfuscation."

- Norman R. Augustine

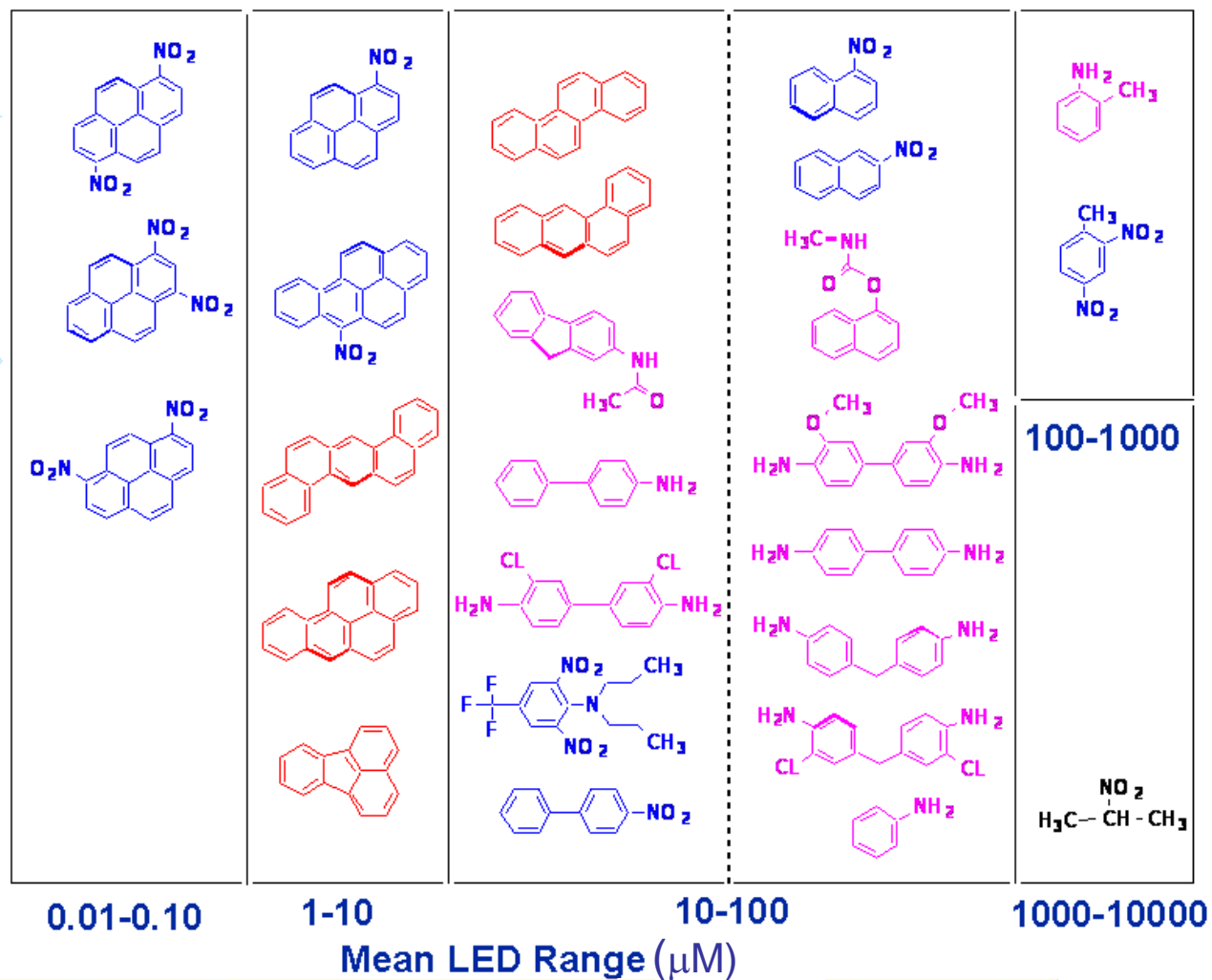


QSARs of mutagens & carcinogens: Case study illustrating problems in the construction of models for noncongeneric chemicals

Benigni R, Richard AM (1996) Mutation Res 371:29-46.

Diverse chemicals

Mean LED of
GeneTox
endpoints: SAL
TA100, TA98,
SCE, MLA, CHO



Question: Can a QSAR predict gross mean potency across multiple genotoxicity measures and diverse chemical space?

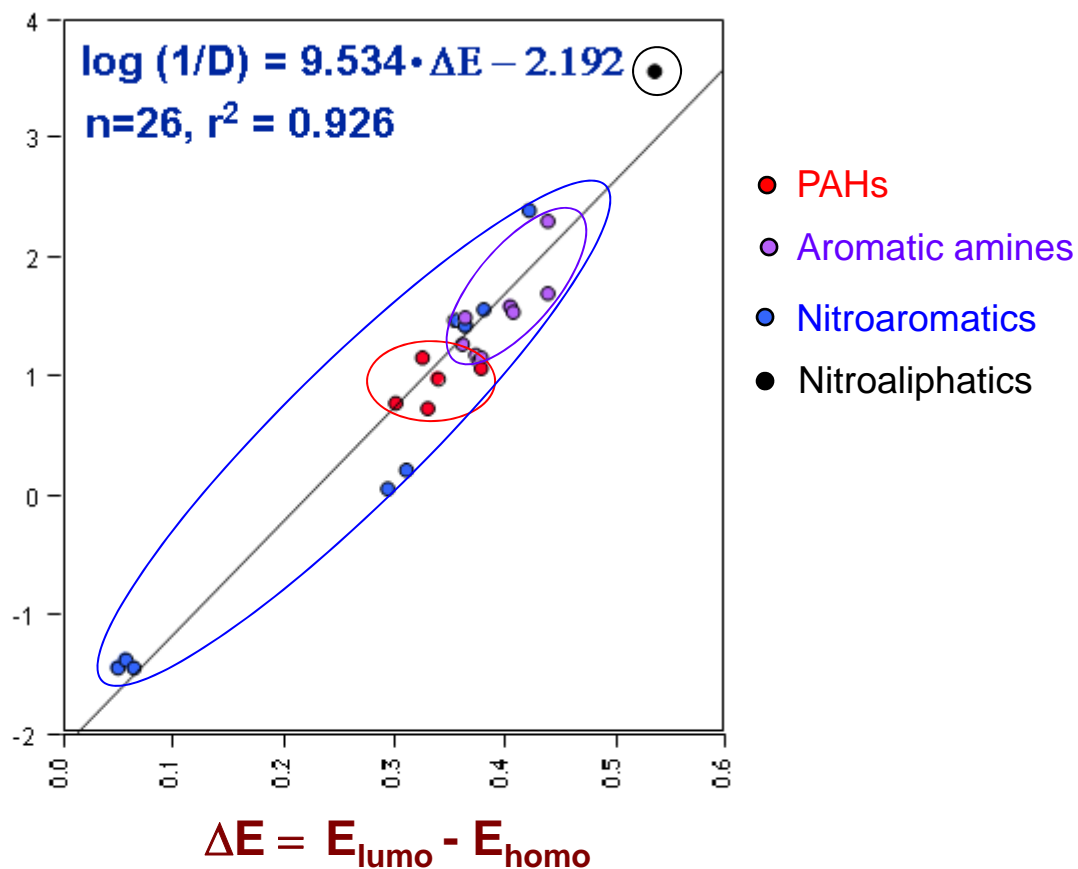
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Mean
LED



Question: Can a QSAR predict mean potency across multiple genotoxicity assays and chemical classes?

QSARs of mutagens & carcinogens: Case study illustrating problems in the construction of models for noncongeneric chemicals

Benigni R, Richard AM (1996) Mutation Res 371:29-46.

Diverse chemicals

Mean LED of
GeneTox
endpoints: SAL
TA100, TA98,
SCE, MLA, CHO

Good statistics of
initial QSAR
primarily due to
nitroaromatics in
SAL TA100

Activity	NO ₂	PAH	NH ₂	n=26	n=60
SA0	0.93 0.85	0.43	0.21	0.89	0.49
SA9	0.93 0.94		0.30	0.93	0.62
GT5	0.89			0.85	0.0
SIC	0.77 0.70		0.16	0.56	0.11
Mean LED	0.95	0.38	0.49	0.93	

Question: *Can a QSAR predict mean potency across multiple genotoxicity assays and chemical classes?*

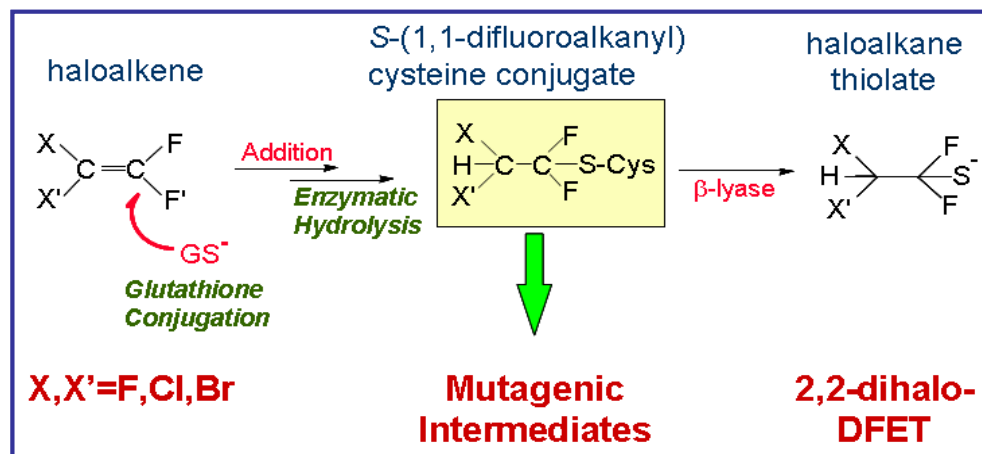
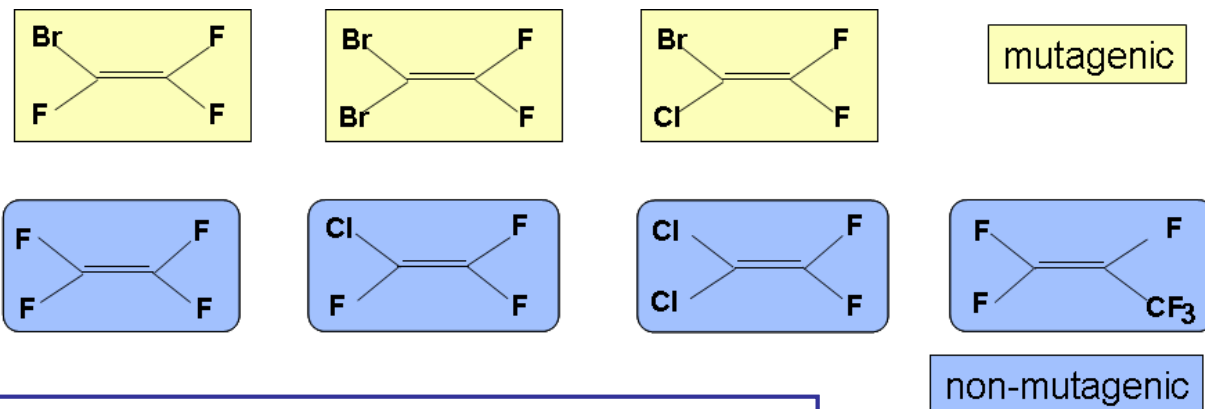
“Asking the right questions takes as much skill as giving the right answers.”

- Robert Half



Theoretical Evaluation of Two Plausible Routes for Bioactivation of S-(1,1-Difluoro-2,2-dihaloethyl)-L-cysteine Conjugates: Thiirane vs Thionoacyl Fluoride Pathway

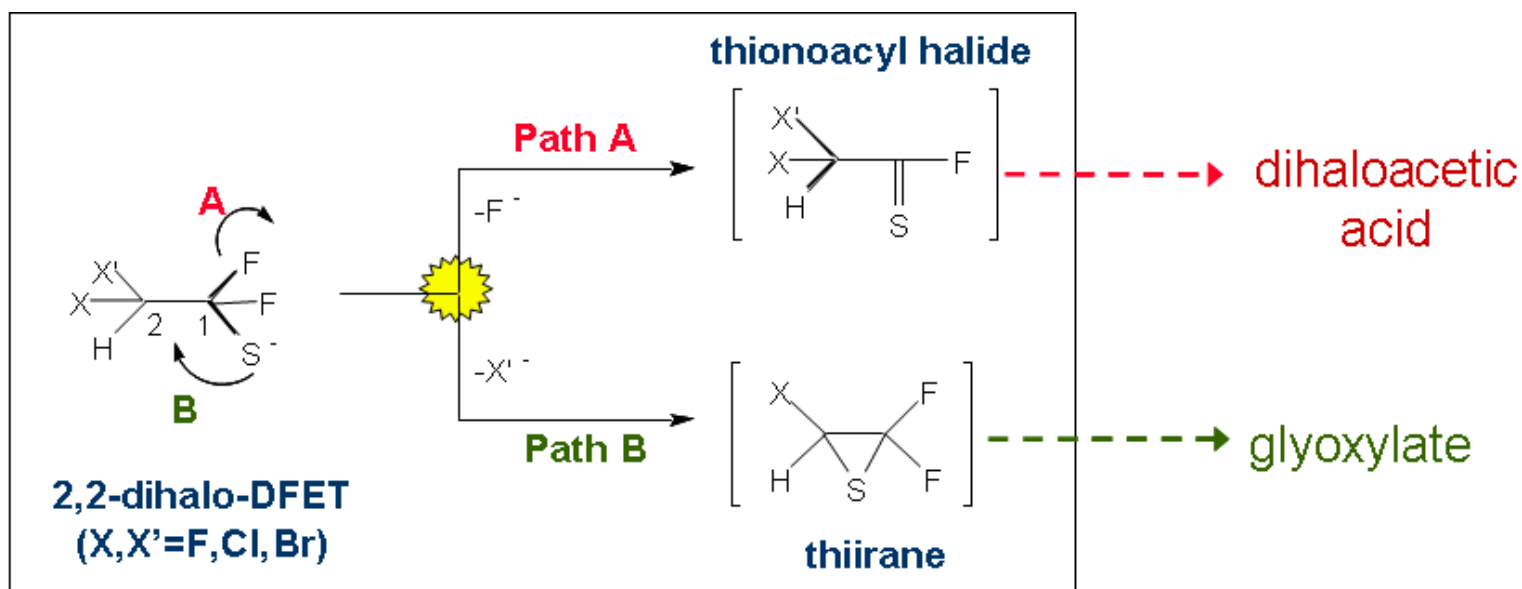
Shim JY, Richard AM (1997) *Chem Res Toxicol* 10: 103-110.



Given known glutathione activation mechanism, can different reactive intermediates account for the greater mutagenicity of brominated forms?

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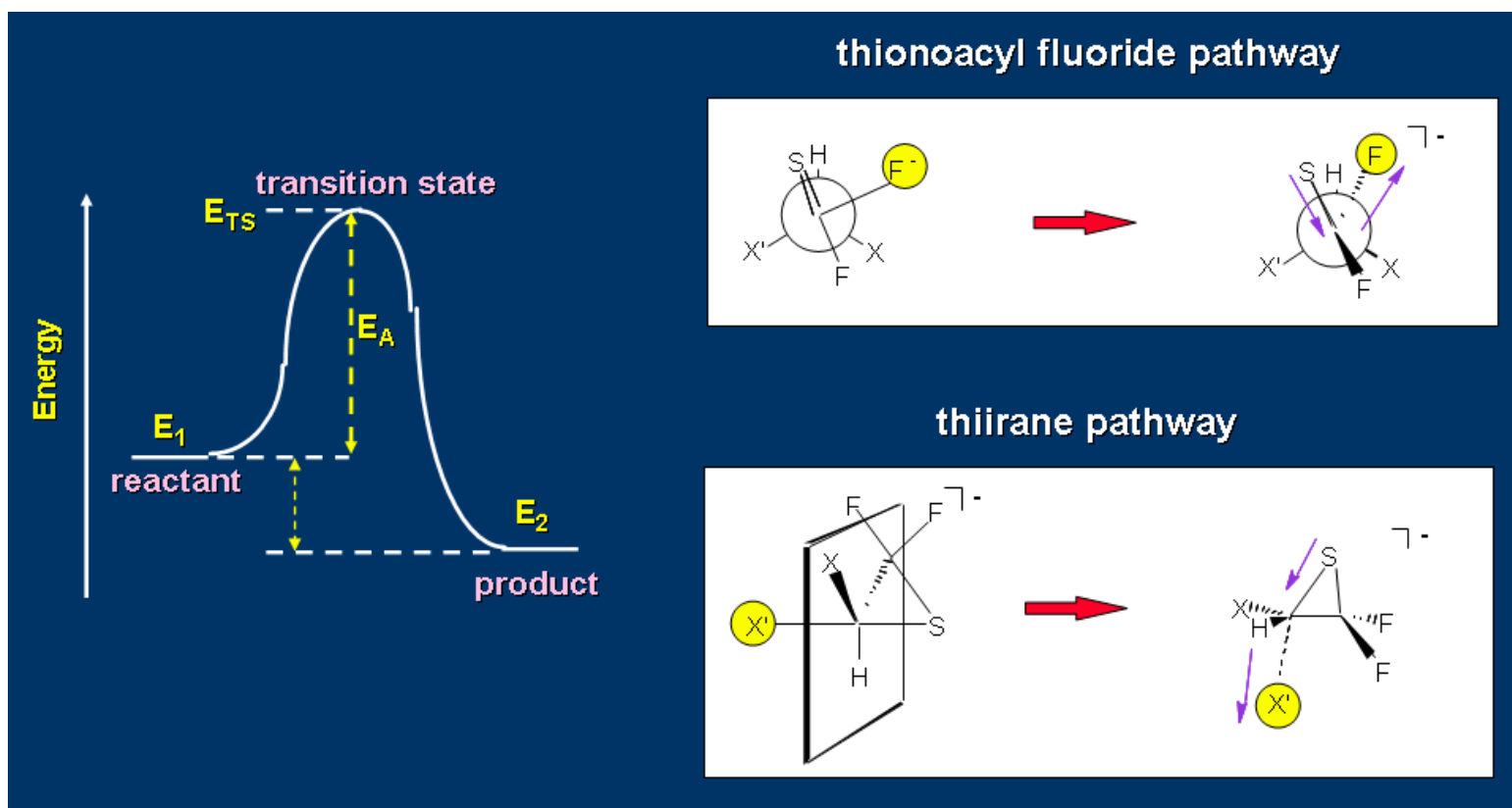
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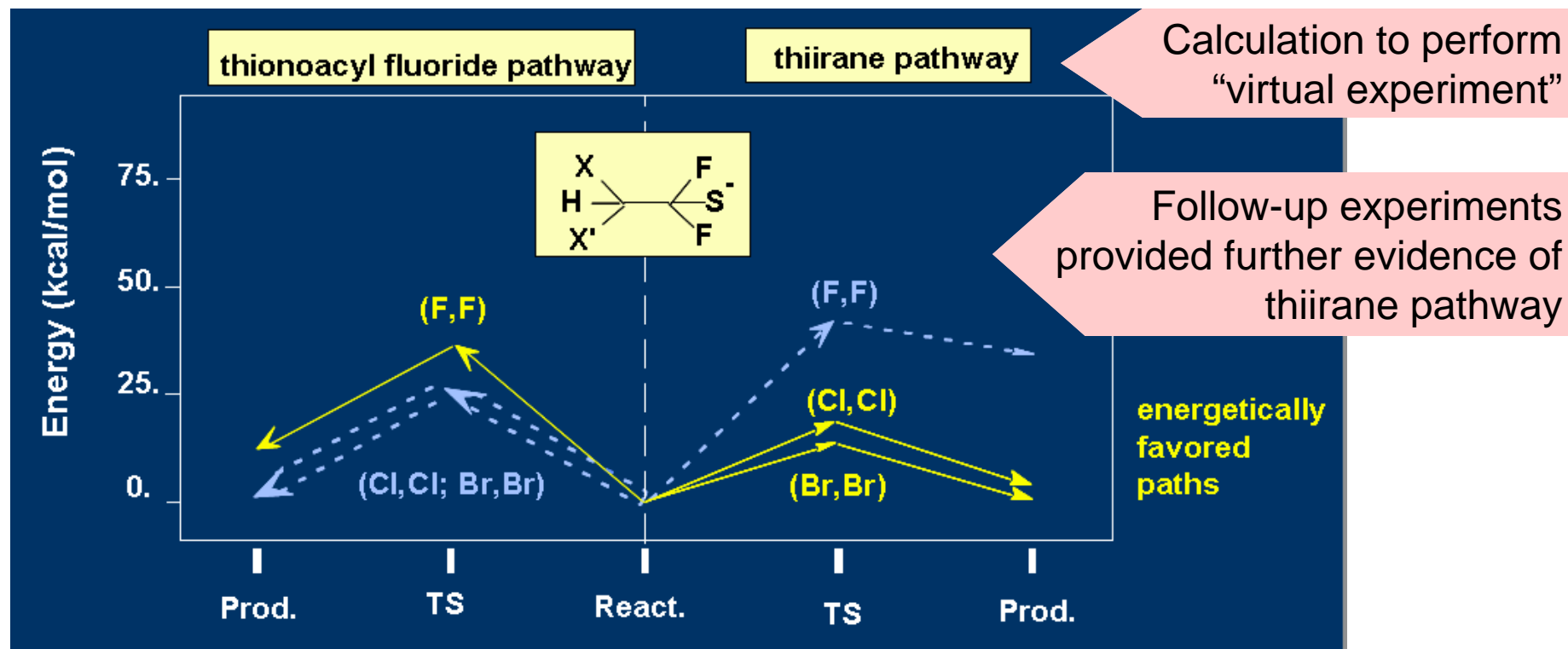
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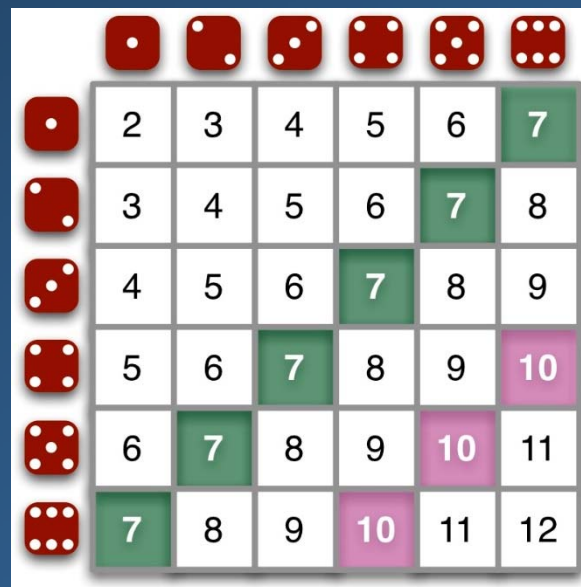
MP2/6-311+G**//HF/6-311G**













Given known glutathione activation mechanism, can different reactive intermediates account for the greater mutagenicity of brominated forms?

It all boils down to probabilities

“Important principles may and must be *flexible*.”

- Abraham Lincoln



						
	2	3	4	5	6	7
	3	4	5	6	7	8
	4	5	6	7	8	9
	5	6	7	8	9	10
	6	7	8	9	10	11
	7	8	9	10	11	12

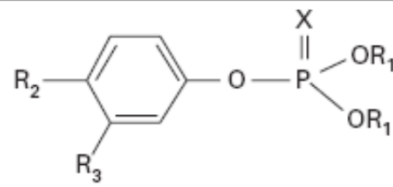
Interaction of Organophosphate Pesticides and Related Compounds with the Androgen Receptor

Tamura H, Yoshikawa H, Gaido KW, Ross SM, DeLisle RK, Welsh WJ, Richard AM (2003) EHP 111:1-8.

agonist: makes enzyme work

antagonist: prevents enzyme working

Competitive AR antagonists



Fenitrothion & Hydroxyflutamide are both weak agonists in the absence of DHT

Fenitrothion and Flutamide have similar antagonist potency

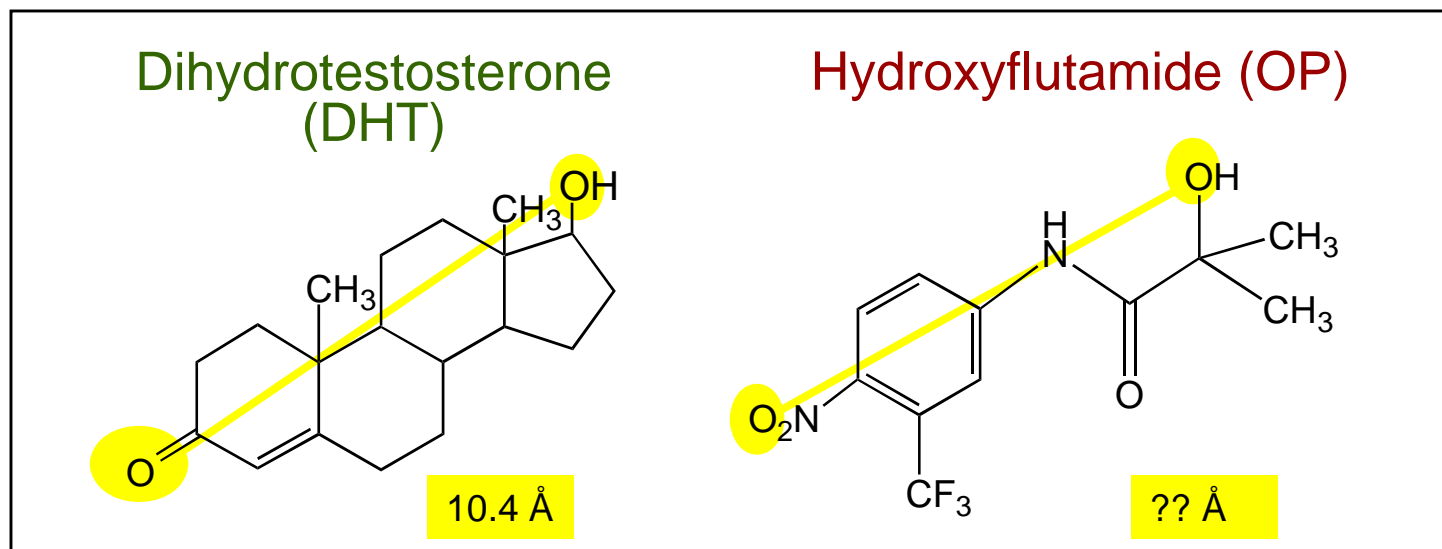
Chemical name ^a	No.	R ₁	R ₂	R ₃	X	K _B (x 10 ⁻⁸ M)
Fenitrothion	1	CH ₃	NO ₂	CH ₃	S	2.18 ^b
	2	CH ₃	NO ₂	CH ₃	O	ND ^c
Methylparathion	3	CH ₃	NO ₂	H	S	35.9
	4	CH ₃	NO ₂	H	O	ND
	5	C ₂ H ₅	NO ₂	CH ₃	S	16.5
Ethylparathion	6	C ₂ H ₅	NO ₂	H	S	ND
	7	C ₂ H ₅	CH ₃	H	S	ND
	8	C ₂ H ₅	H	CH ₃	S	ND
	9	C ₂ H ₅	(O-CH ₂ -O)		S	ND
	10	n-C ₃ H ₇	NO ₂	CH ₃	S	ND
Flutamide ^d						1.07 ^e
Hydroxyflutamide ^d						0.22
Linuron ^d						75.8 ^f

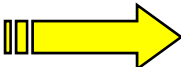
} Known antagonists

What distinguishes the AR antagonists-only from the antagonists/agonists within a series of organophosphates?

Interaction of Organophosphate Pesticides and Related Compounds with the Androgen Receptor

Tamura H, Yoshikawa H, Gaido KW, Ross SM, DeLisle RK, Welsh WJ, Richard AM (2003) EHP 111:1-8.



2D  **3D:**

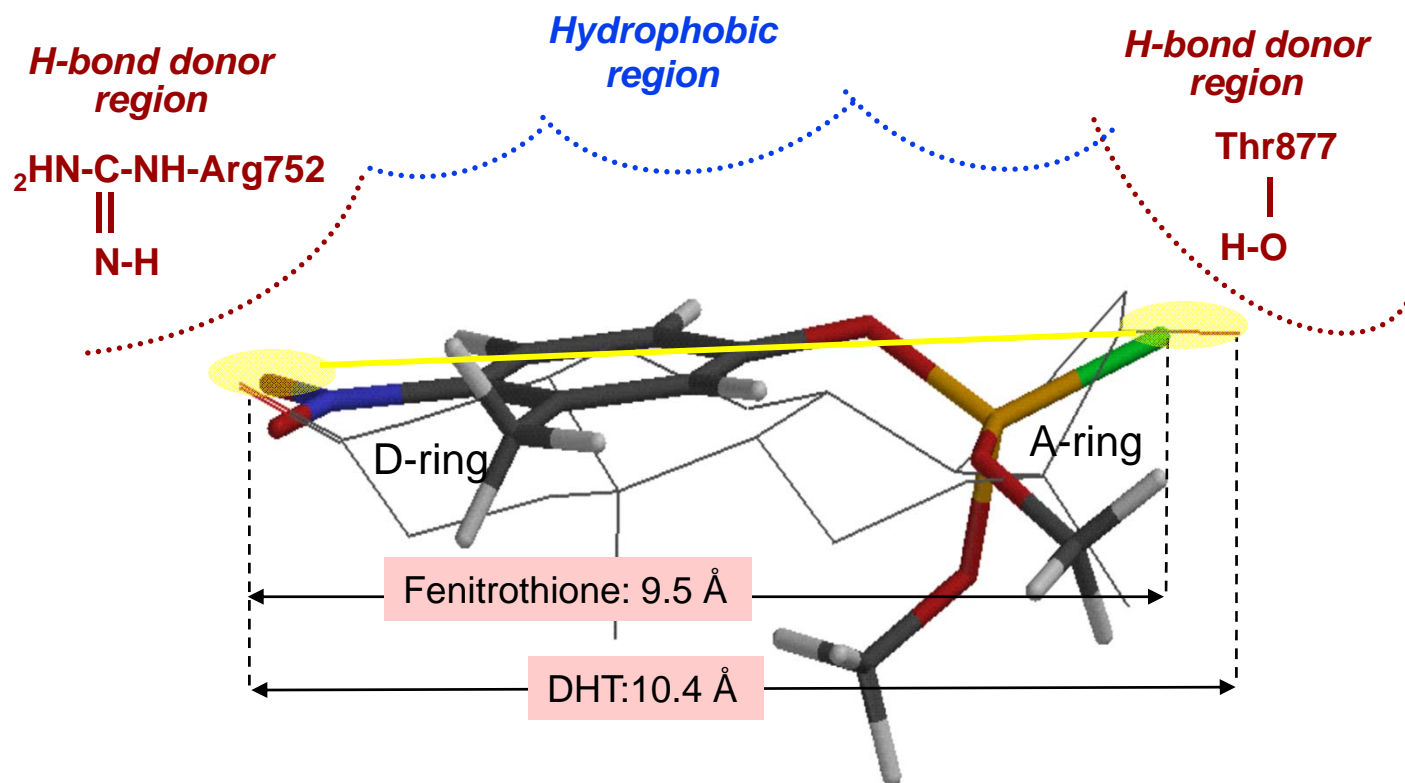
- Compute max distance between polar groups for OPs
- Compute ΔE to reach stretched conformation
- Compute H-bonding interaction energies & distances

Translate question to
computational problem

What distinguishes the AR antagonists-only from the antagonists/agonists within a series of organophosphates?

Interaction of Organophosphate Pesticides and Related Compounds with the Androgen Receptor

Tamura H, Yoshikawa H, Gaido KW, Ross SM, DeLisle RK, Welsh WJ, Richard AM (2003) EHP 111:1-8.



Is it feasible (i.e., low energy cost) for the OP to achieve the H-bonding configuration of DHT?

Interaction of Organophosphate Pesticides and Related Compounds with the Androgen Receptor

Tamura H, Yoshikawa H, Gaido KW, Ross SM, DeLisle RK, Welsh WJ, Richard AM (2003) EHP 111:1-8.

Agonists can achieve
DHT binding distance
and effective H-bonds

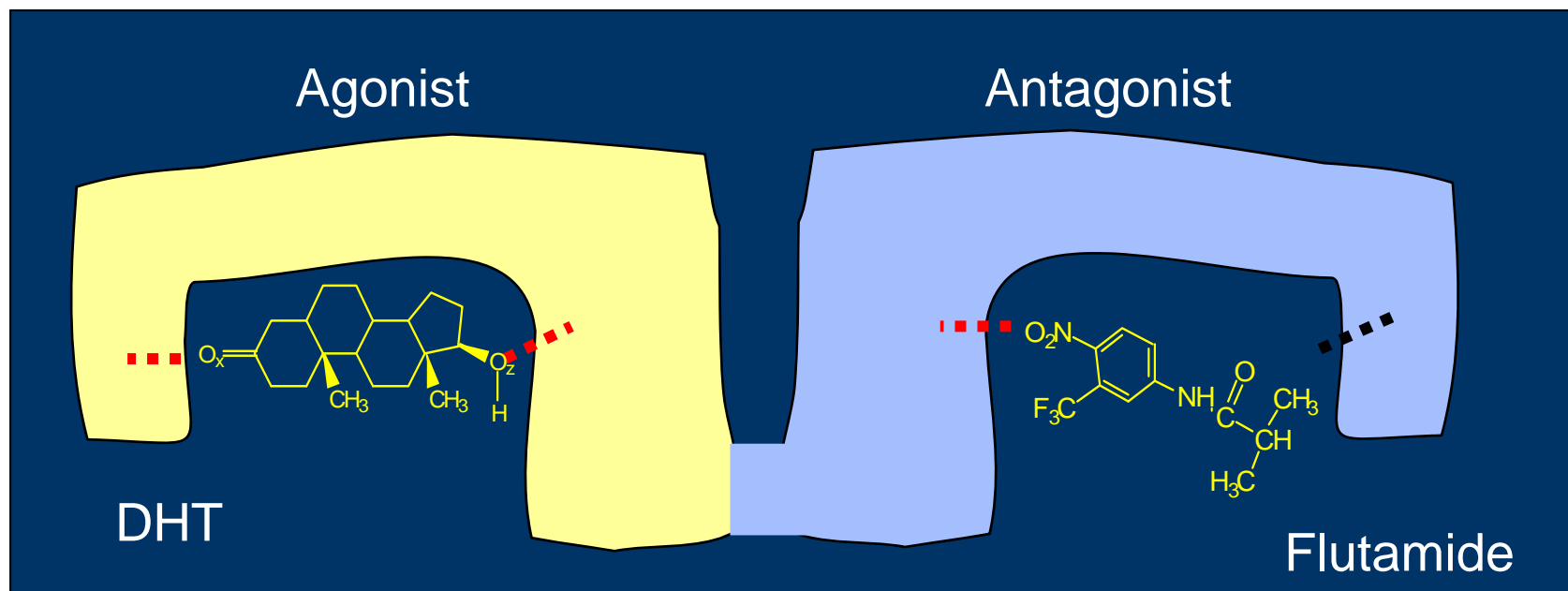
Antagonists can't

Chemical Structure Agonist/Antagonist	Energy (kcal/mol)	Distance(Å) x - - - z	H-bond (kcal/mol)		
			x	y	z
DHT 	0.00 0.36	10.48 10.00	-3.70 (1.81Å)		-3.14 (1.82Å)
Fenitrothion 	0.00 1.68	8.18 9.50 (8.09)	-3.33 (1.83Å)	-0.17 (1.88Å)	-2.17 (2.83Å)
Flutamide 	0.00 2.48	7.50 8.00	-2.91 (1.85Å)		-2.97 (1.82Å)
Hydroxyflutamide 	0.00 1.72	8.94 9.50 (7.27)	-2.96 (1.83Å)	-3.20 (1.81Å)	-2.95 (1.83Å)
Linuron 	0.00 1.65	9.16 9.50 (7.00)	-2.06 (2.64Å)	-3.25 (1.82Å)	-2.85 (2.68Å)

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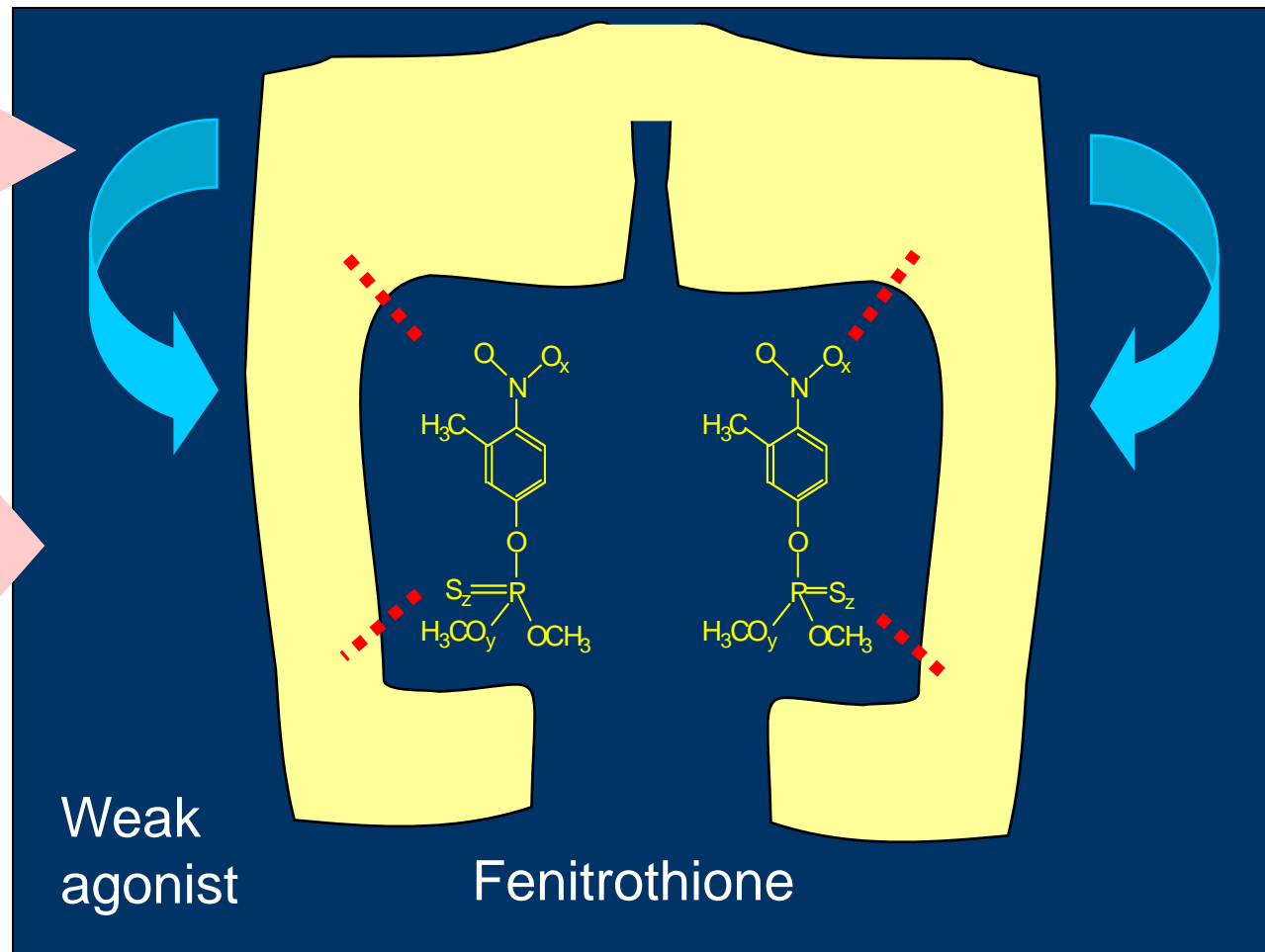
Low dose α
High probability event

Interaction of Organophosphate Pesticides and Related Compounds with the Androgen Receptor

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High dose α
Low probability event

Relatively
unsophisticated
calculations can lend
insight into target
interaction



Lessons learned ...

- Important for modelers to collaborate with “domain” experts (e.g., toxicologists)
- Computational chemistry & QSAR approaches can be effective partners to experiment
- SAR works best with similar chemicals and clear mechanisms
- Importance of asking the right questions, and using the appropriate level of theory for the problem

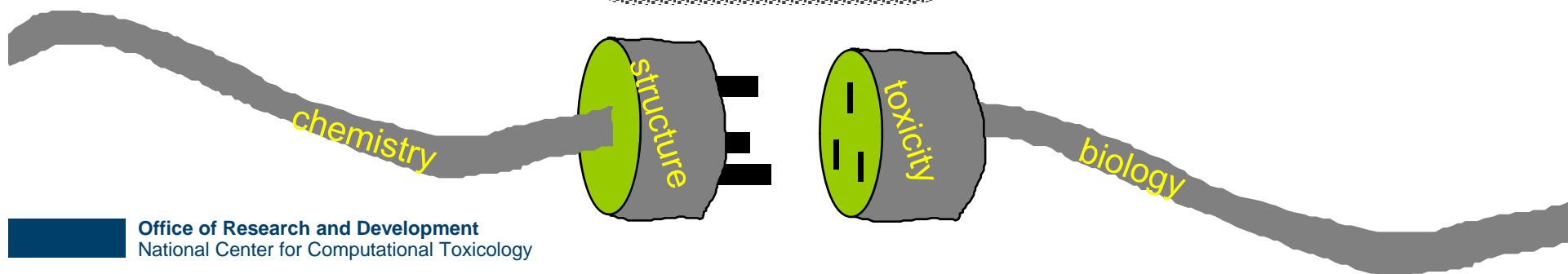
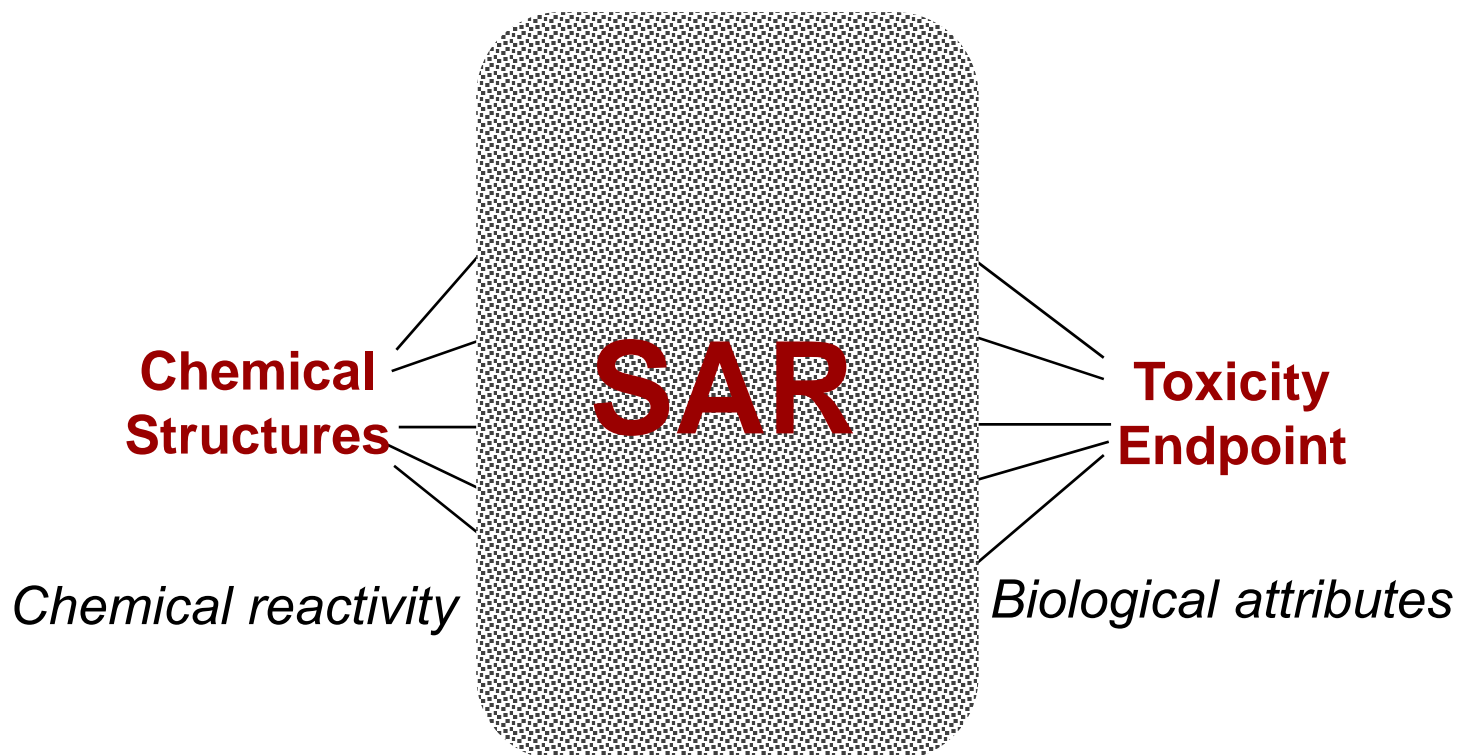
Toxicity prediction is not easy!

Part II:

Computational Toxicology

*Data challenges &
cheminformatics approaches
to predicting toxicity*

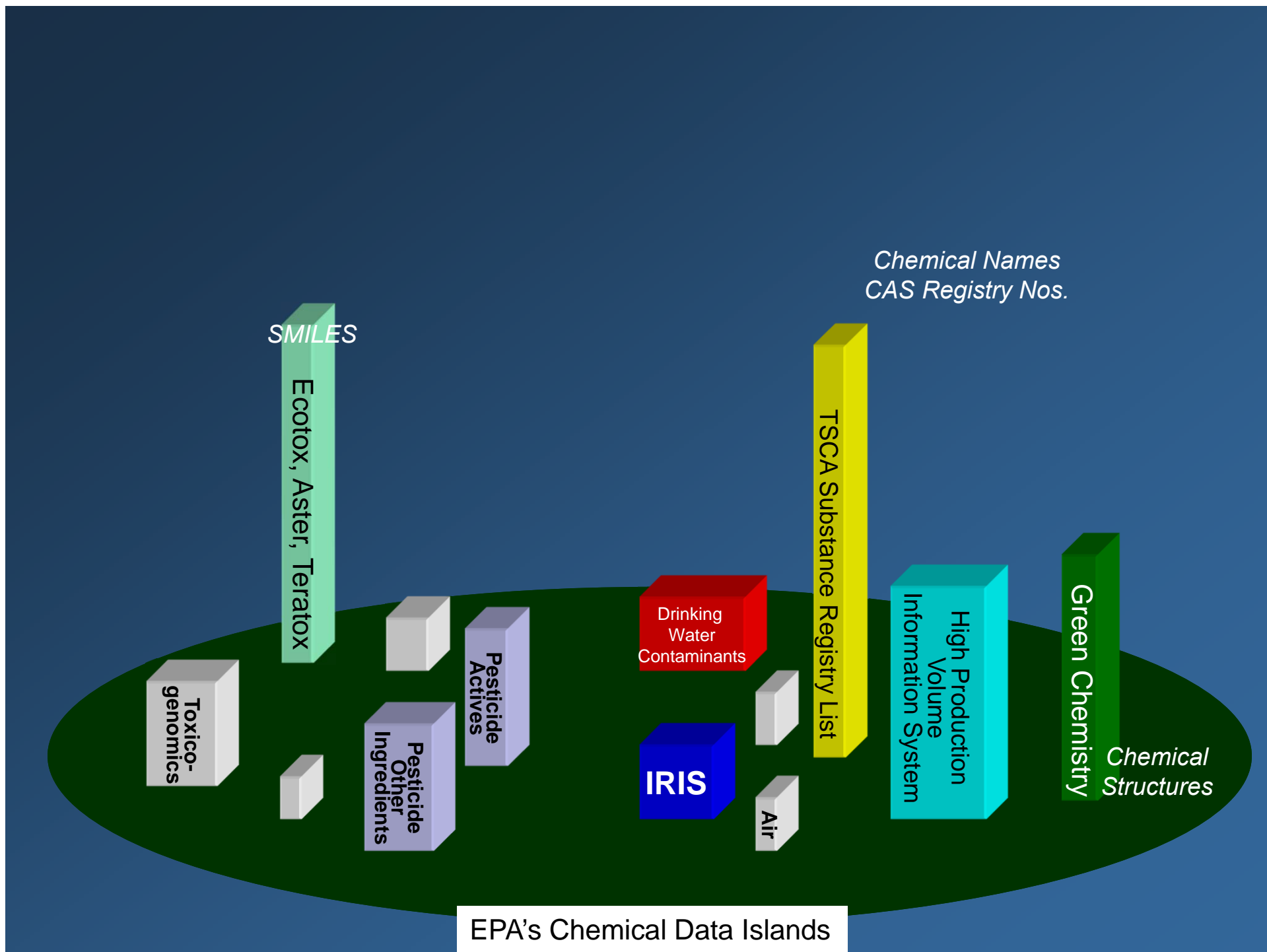
Global vs. Local SAR models

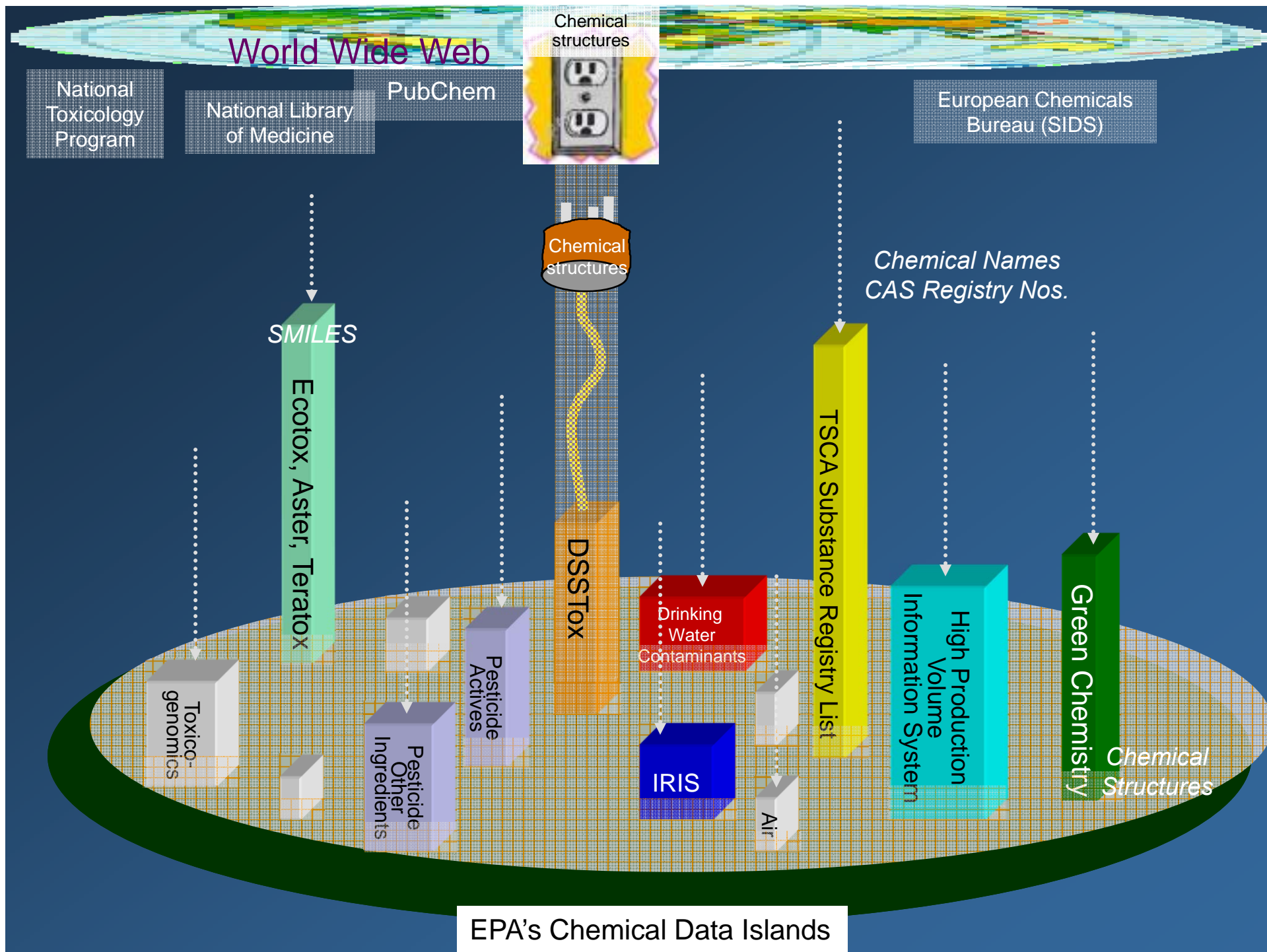


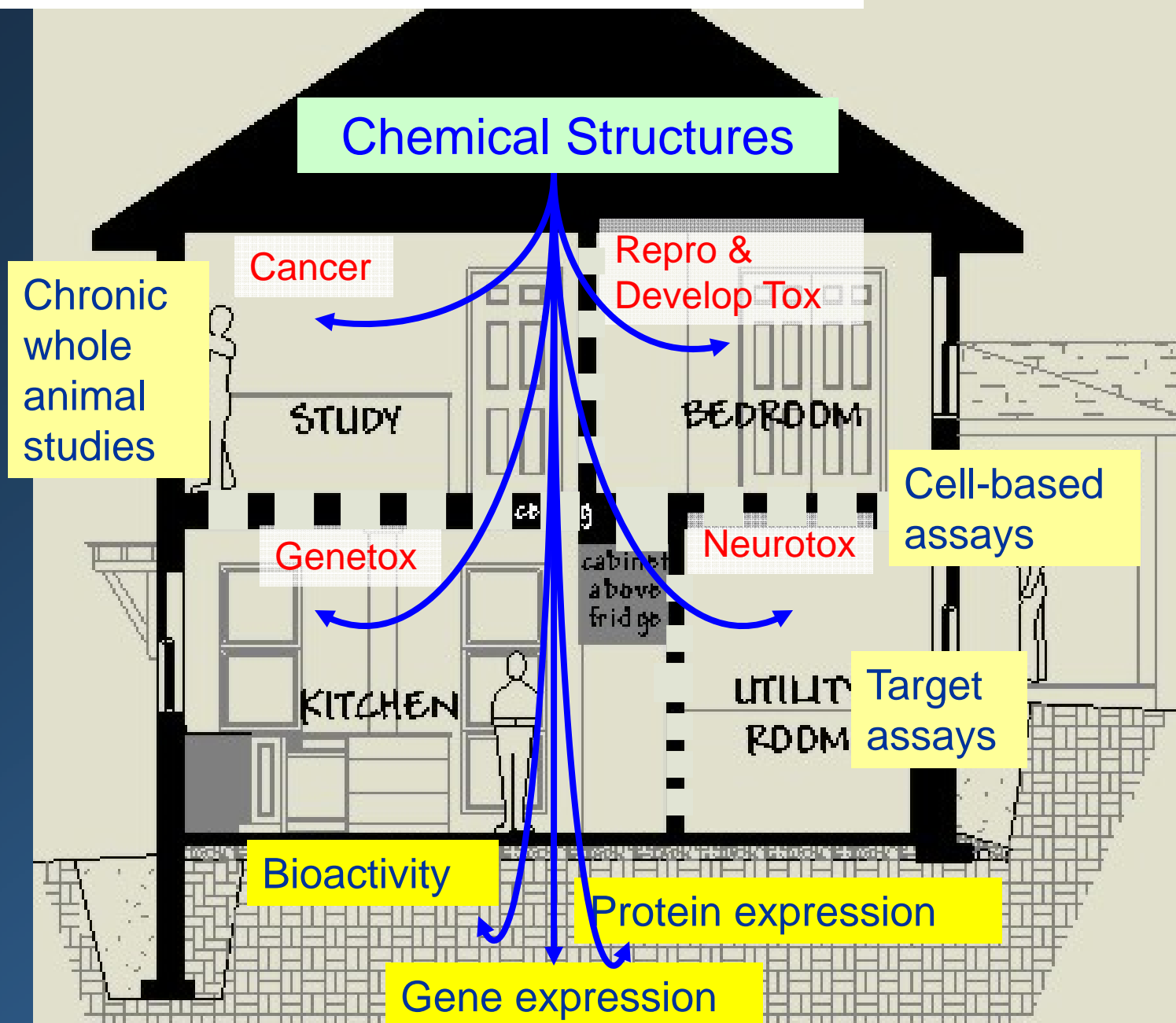
The bigger challenge -
predict potential toxicity of any chemical

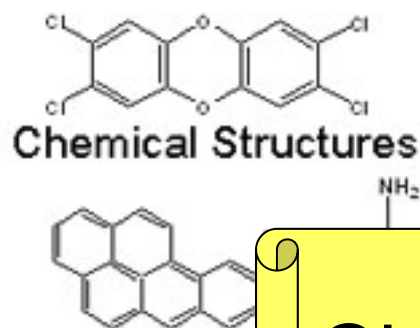


*What are the chemicals of concern?
Where are the data to develop models??*

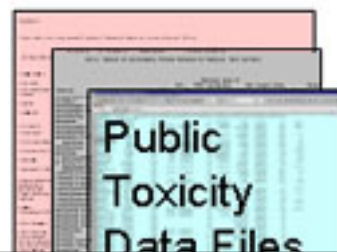








+



Chemical structure-annotation

Distributed
Structure-Searchable
Toxicity
 Public
 Database
 Network




Data standards and integration

Analog
Searching

Port into User
Database
Applications

Improved
Toxicity
Prediction
Models

EPA's DSSTox Public Website – Launched 2004



U.S. Environmental Protection Agency

Distributed Structure-Searchable Toxicity (DSSTox) Public Database Network

About DSSTox

Work in Progress

Frequent Questions

Structure Data Files

Central Field Definition Table

Apps, Tools & More

DSSTox Community

Site Map

Glossary of Terms

Help

Recent Additions | Contact Us | Print Version Search: **Go**

[EPA Home](#) > [Research & Development](#) > [Computational Toxicology Research](#) > Distributed Structure-Searchable Toxicity (DSSTox) Public Database Network

DSSTox

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 chemical structure files associated with toxicity data.

[More>](#)

Recent Additions: 08 June 2006

*****Revised Standard Chemical Fields for all DSSTox files:**

- Revised [DSSTox Standard Chemical Fields](#)
- [Chemical & Substance ID fields](#) to index all unique DSSTox structures and substances
- Updated IUPAC names and [InChI codes](#) (v. 1.0)
- Major [Chemical Information Quality Review](#) of all DSSTox structure data files

*****New DSSTox Structure Data Files:**

- New [Structure Data Files Index](#) and [SD File Types](#)

• [IRISSI](#): EPA Integrated Risk Information System Structure-Index Locator File
 • [NTPBSI](#): National Toxicology Program Bioassay Structure-Index Locator File
 • [HPVCSI](#): EPA High Production Volume Challenge Program Structure-Index File
 • [NTPHTS](#): National Toxicology Program High-Throughput Screening Structure-Index File
 • [DSSToxMaster](#): DSSTox Master Structure-Index File

*****Expanded Carcinogenic Potency Database - All Species (CPDBAS):**

- Added chemical records and revised data entries,
- Activity Category fields, URL links to chemically indexed data pages on CPDB Source website -- see [CPDBAS](#)

Chemical Structures + **Toxicity Data**



DSSTox SDF Files

Standardized
Documented
Structure-Searchable
Application-independent

• [DSSTox Graphic Flowchart](#)

• [DSSTox Project Goals](#)

• [DSSTox Publications](#)

Database Files: [More](#)

CPDBAS_v3b_1481	10Apr2006	**updated
DBPCAN_v3b_208	10Apr2006	**updated
EPAFHM_v3b_617	10Apr2006	**updated
FDAMDD_v2b_1217	10Apr2006	**updated
NCTREER_v3b_232	10Apr2006	**updated

Structure-Index Locator Files: [More](#)

IRISSI_v1a_544	10Apr2006	**New
NTPBSI_v1a_2415	10Apr2006	**New

Structure-Index Files: [More](#)

HPVCSI_v1a_3548	10Apr2006	**New
NTPHTS_v1a_1408	10Apr2006	**New

DSSToxMaster_v1a_8804_10Apr2006 **New

Quick & Easy File Downloads:

• [FTP Download Instruction](#)

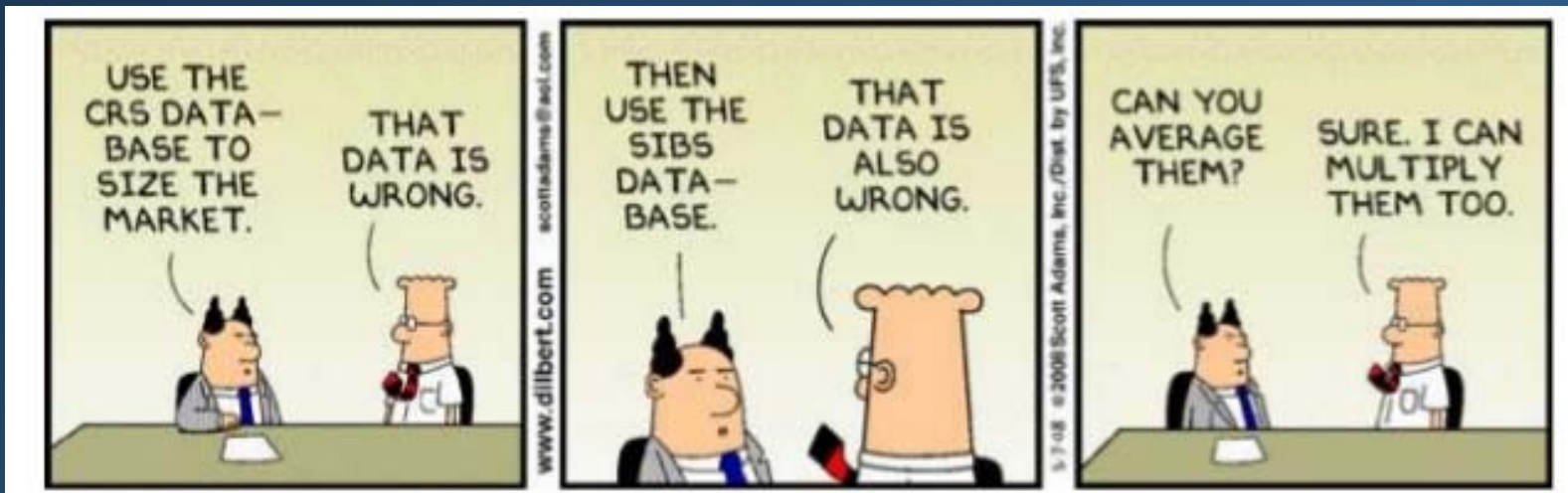
- Focus on environmental chemicals & EPA lists
- Toxicity datasets for building SAR models
- High quality, manually curated data-structure associations
- Downloadable structure files

Distributed structure-searchable toxicity (DSSTox) database network: A proposal. Richard, A.M., Williams, C.R. *Mut. Res.*, 499:27-52, **2002**.

Improving structure-linked access to publicly available chemical toxicity information. Richard, A.M., Williams, C.R., Cariello, N. *Curr. Opinion Drug Devel Discov.*, 5:136-143, **2002**.

DSSTox Website launch: Improving public access to databases for building structure-toxicity prediction models. Richard, A.M. *Preclinica*, 2:103-108, **2004**.

A prediction model is only as good as
the data that goes into it ...

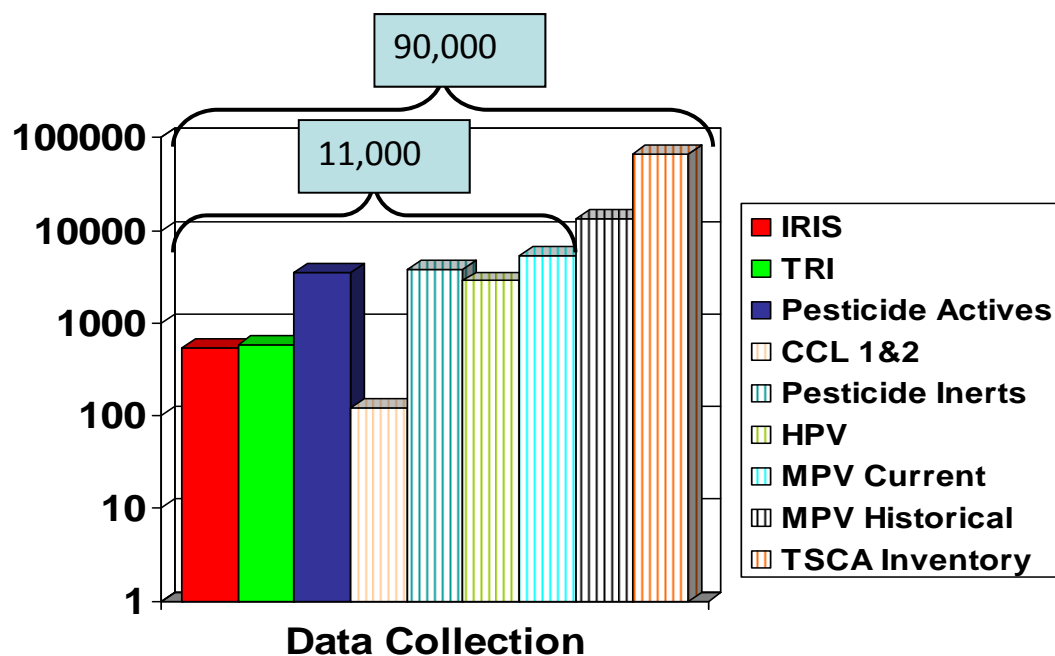


Data quantity,
Data quality!

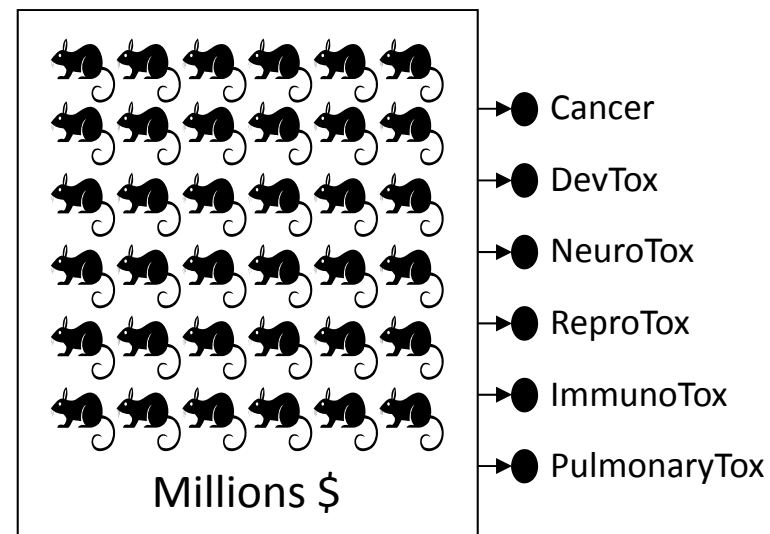
The Big Problem

Too Many Chemicals

Too High a Cost



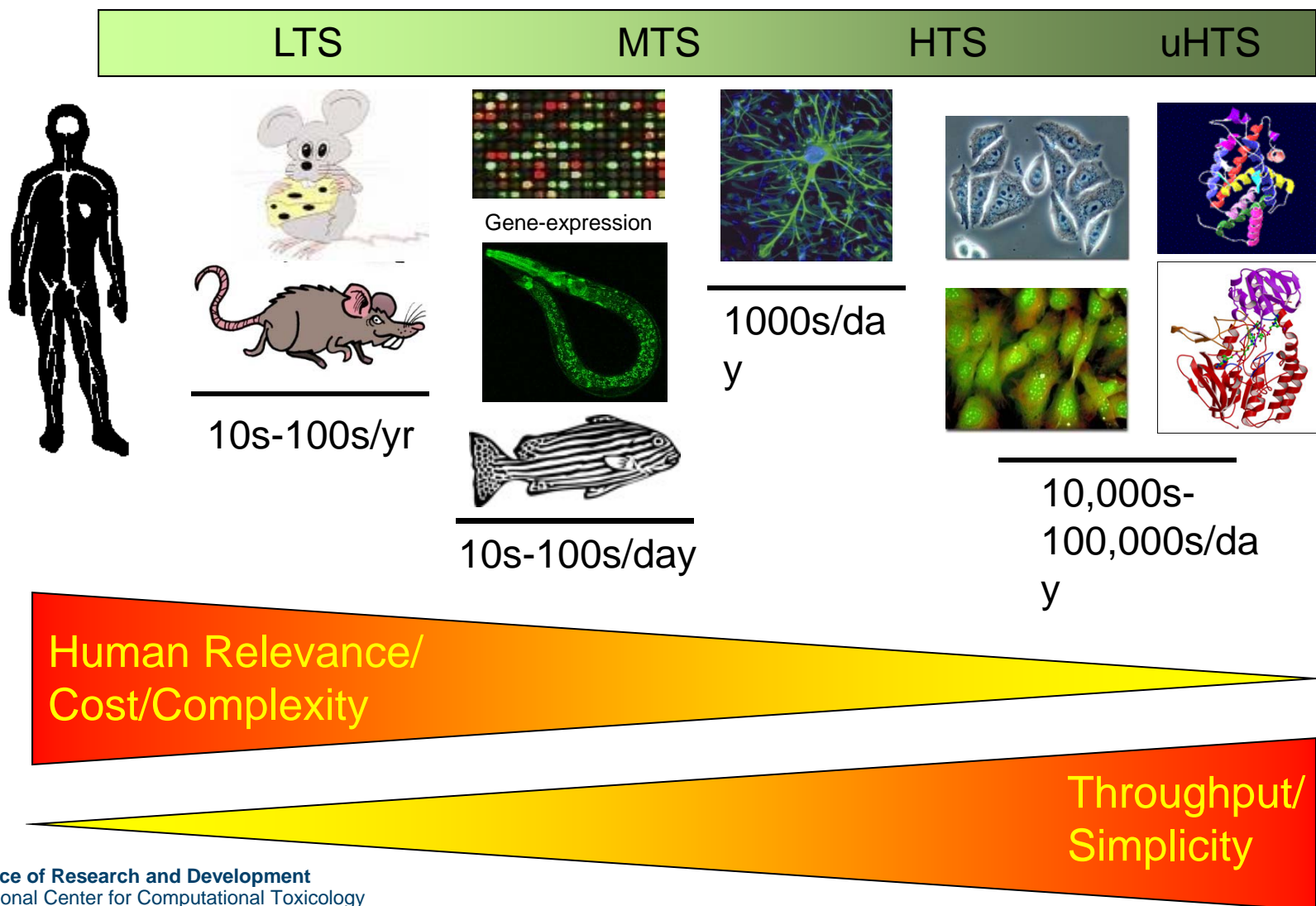
...and not enough data.



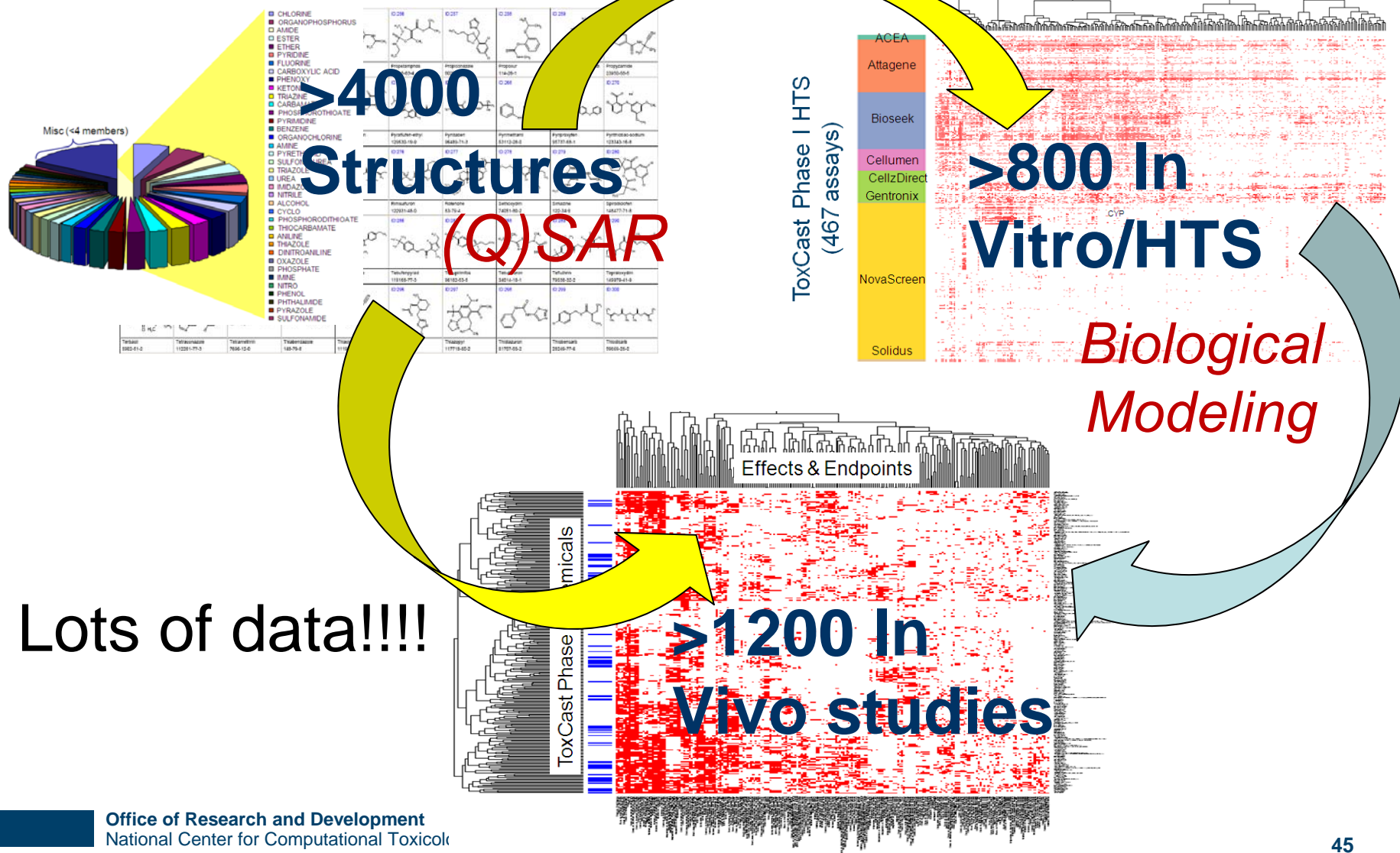
Too many endpoints
Too many mechanisms

High-Throughput Screening Assays

*batch testing of chemicals for pharmacological/toxicological endpoints
using automated liquid handling, detectors, and data acquisition*

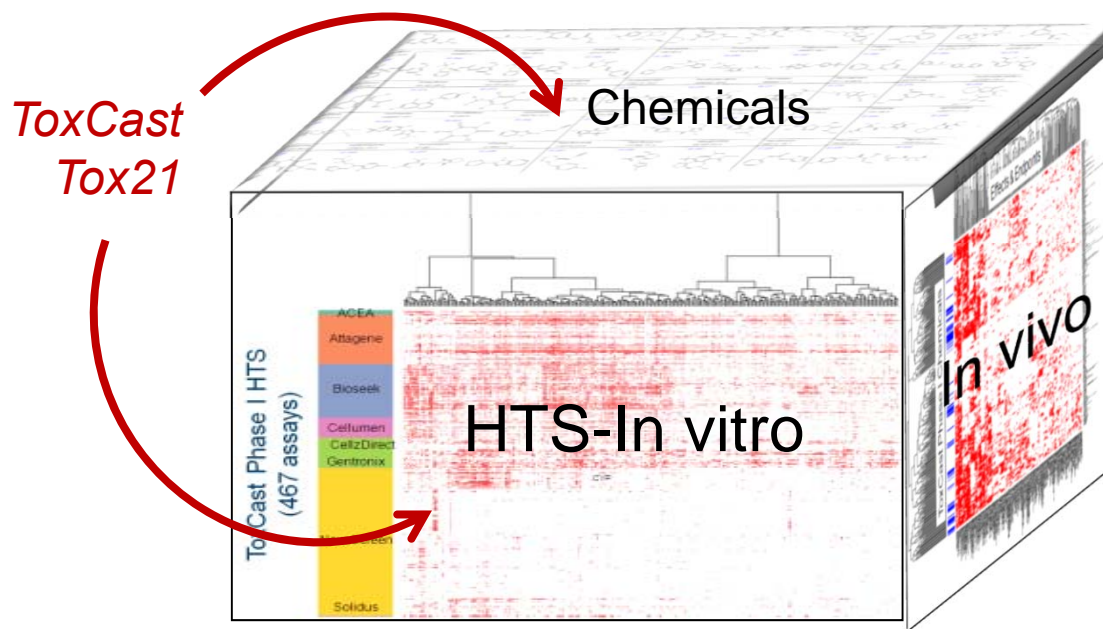


EPA's ToxCast Program

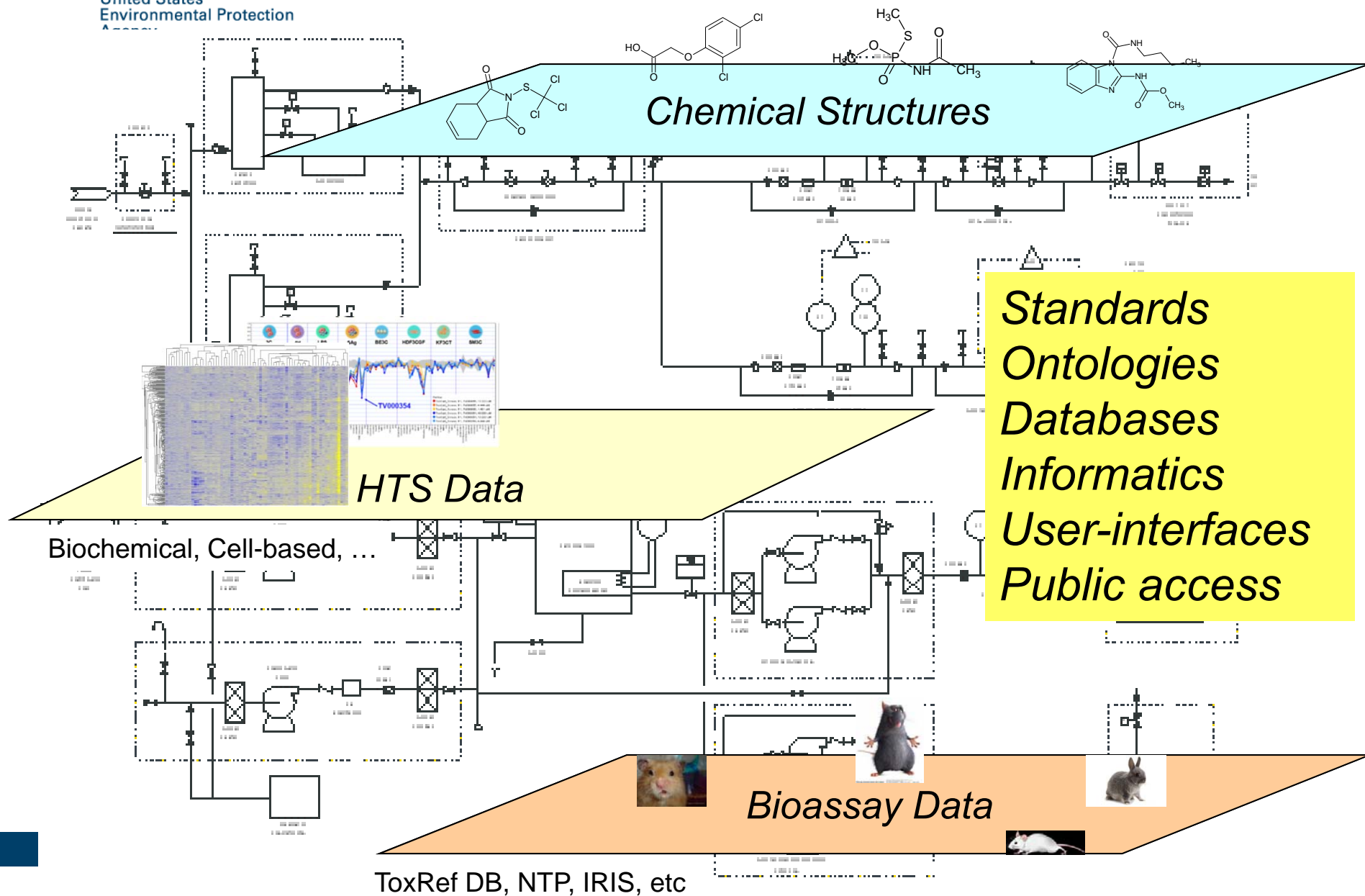


Chemical “probes” of biological activity

- Use existing knowledge & SAR to mine HTS data
- Use HTS data to inform & refine SAR models & approaches
- Use all of these data to improve ability to model toxicity



ToxCast: “Big Data” Informatics Challenges

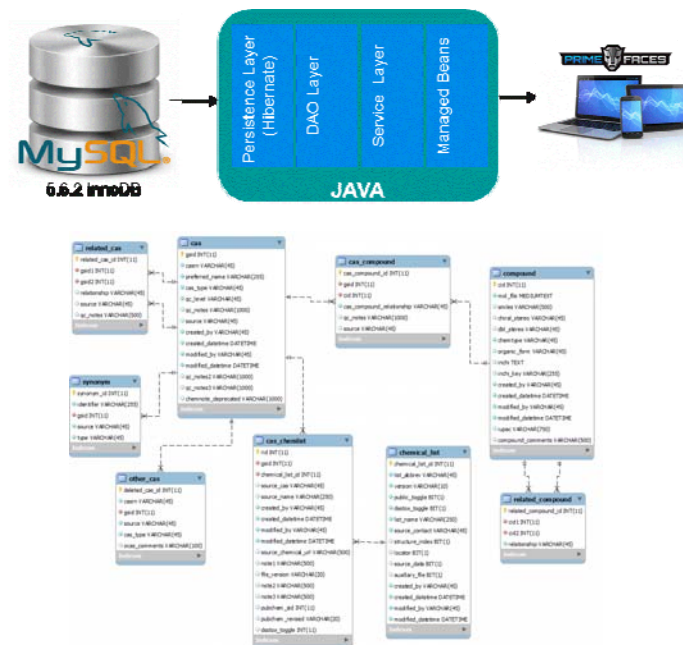


DSSTox v1



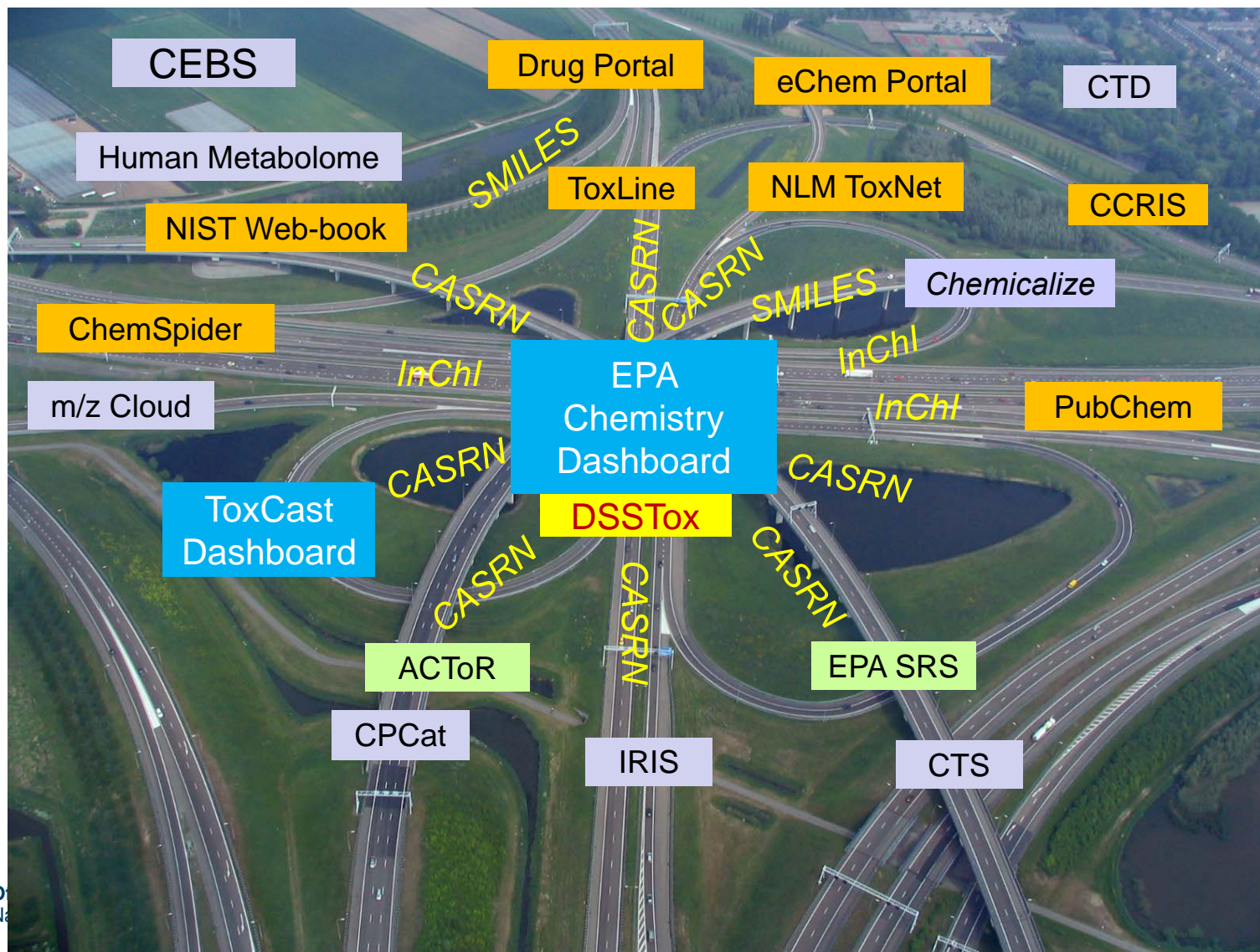
DSSTox v2

- Convert DSSTox tables to MySQL
- Develop curation interface & cheminformatics workflow
- Expand chemical content to 750K
- Web-services & Dashboard access

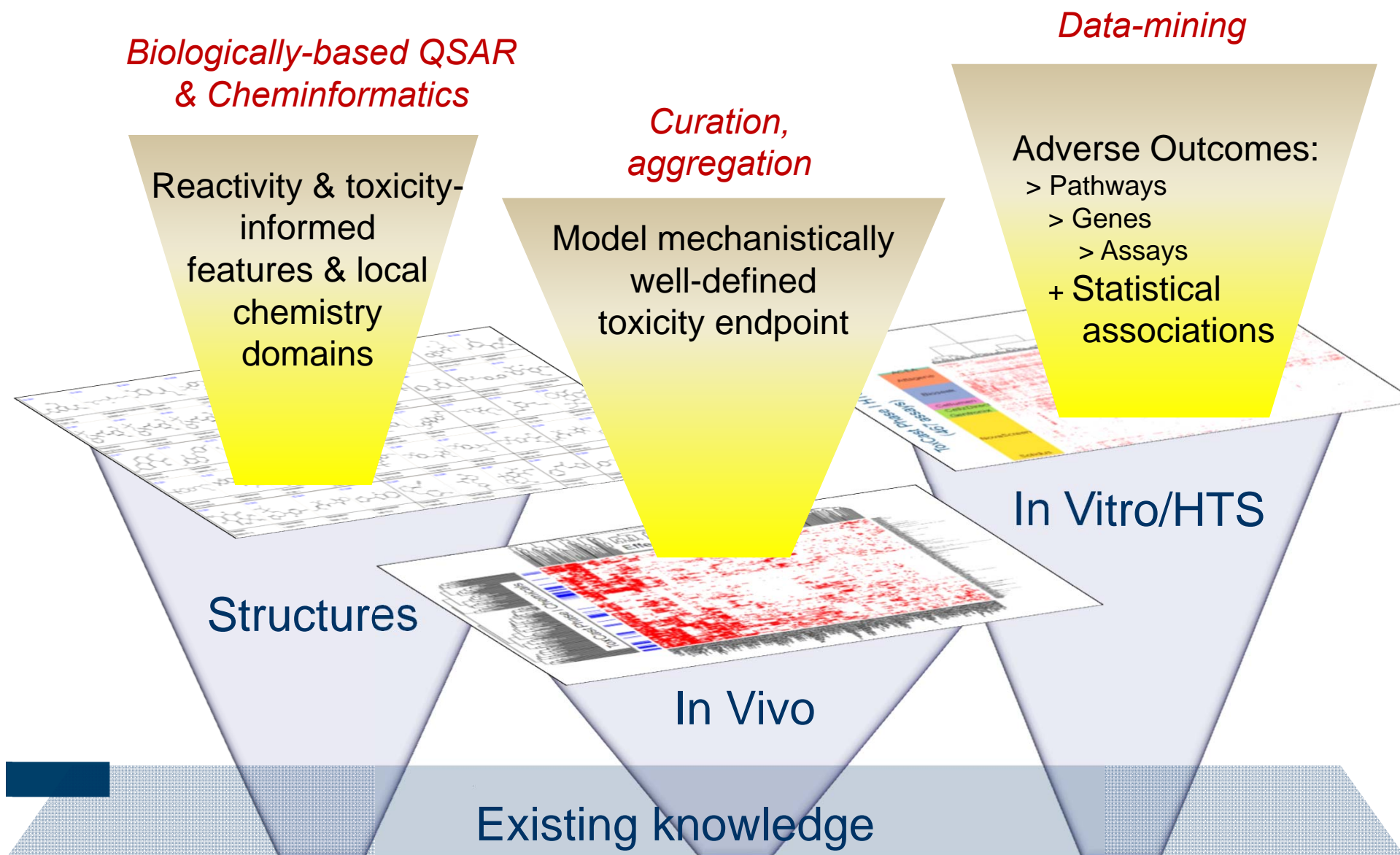


- Manually curated 25K substance records
- EPA-focus, environmental tox datasets
- Emphasis on accurate CAS-name-structure annotations
- Public resource for high-quality structure-data files (SDF)

DSSTox is now EPA's chemical "hub"



Toxicity Prediction Challenge



Toxicity Prediction Challenge

Toxicity prediction is still hard!

Environmental-
exposure”
landscape,
metals,
mixtures

Limited data, large
knowledge gaps,
experimental
uncertainty

capability,
sample QC,
Noisy data!

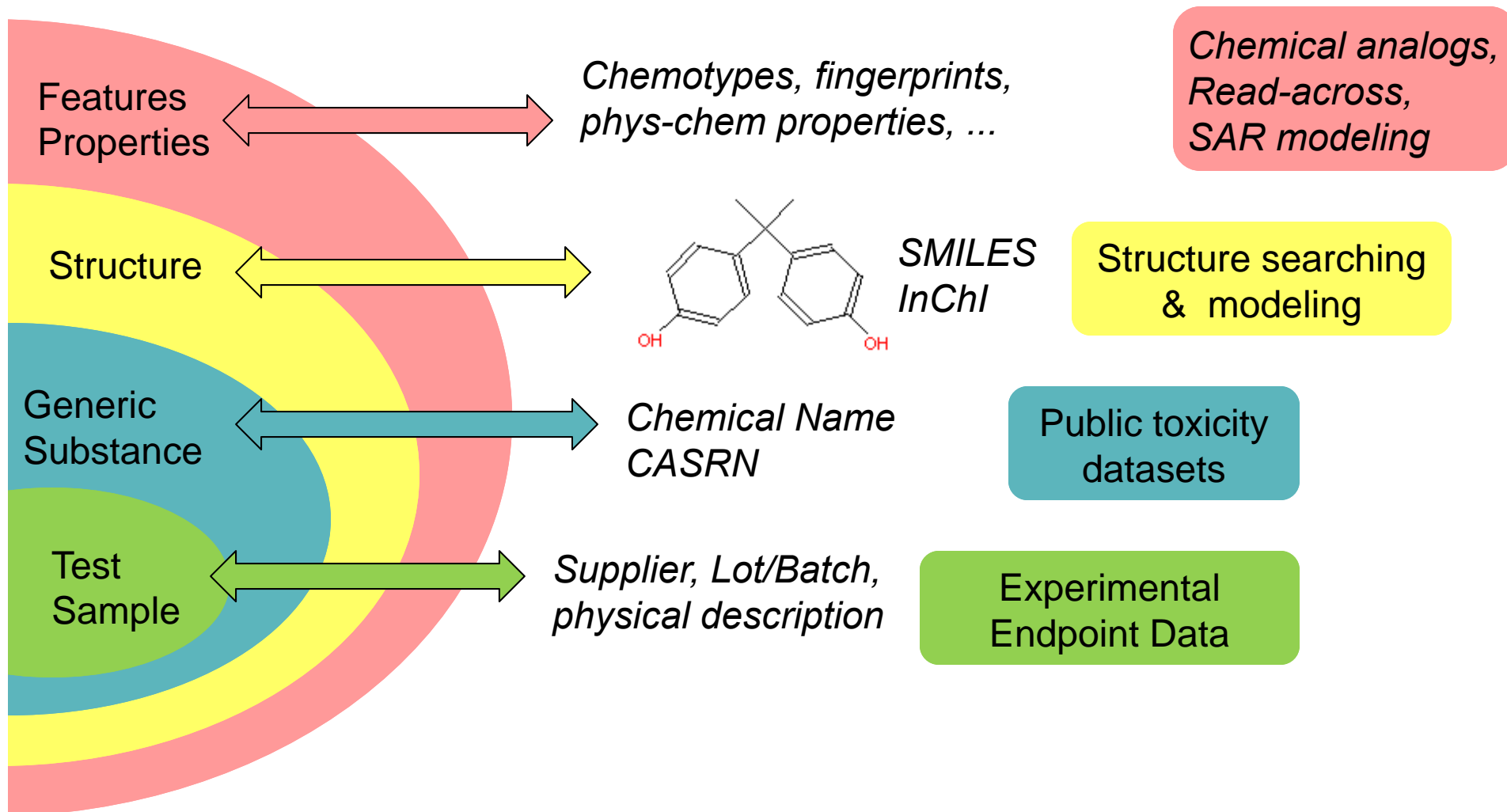
Structures

In Vitro/HTS

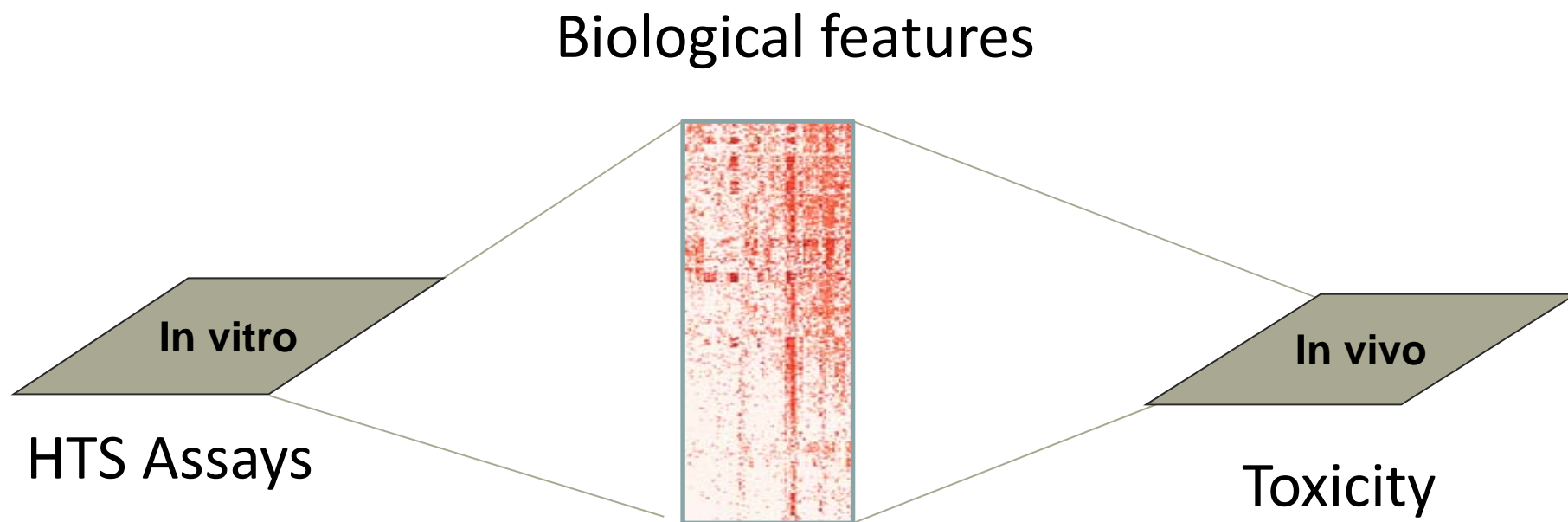
In Vivo

Existing knowledge

Chemical Representations supporting Data Integration

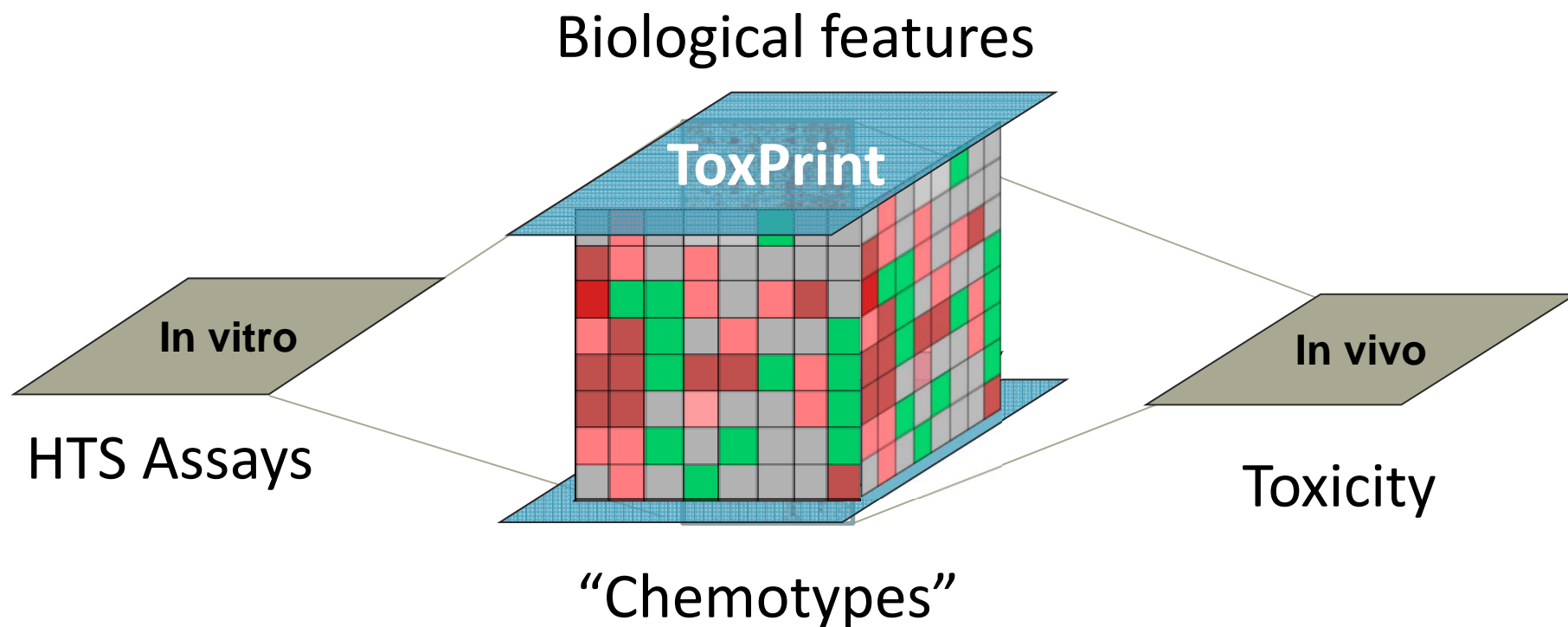


QSAR using biologically informed chemical features



HTS results are used to inform feature selection, linking chemical features, or “Chemotypes” to toxicity

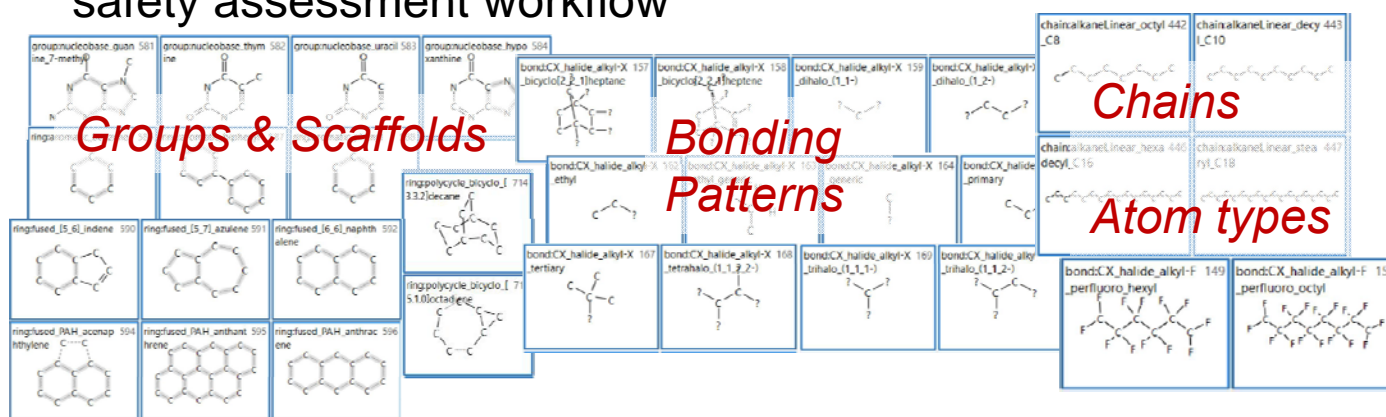
QSAR using biologically informed chemical features



HTS results are used to inform feature selection, linking chemical features, or "Chemotypes" to toxicity

ToxPrints: <http://www.toxprint.org>

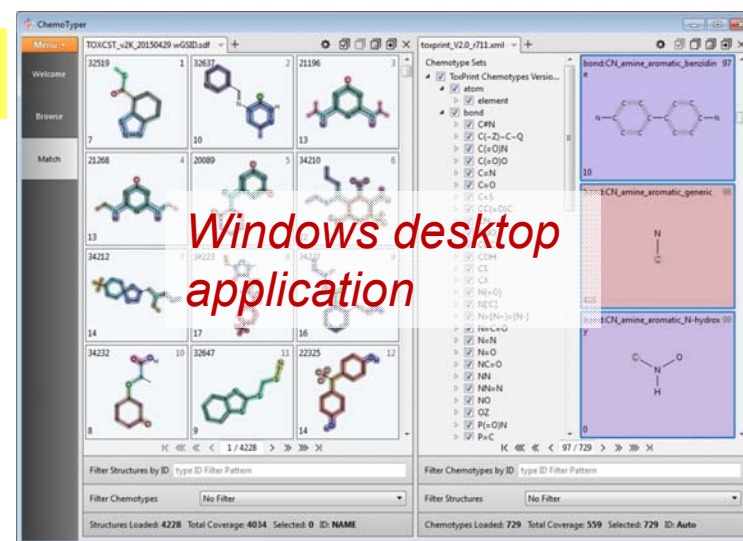
729 features important to EPA & FDA's "chemical exposure" landscape and safety assessment workflow



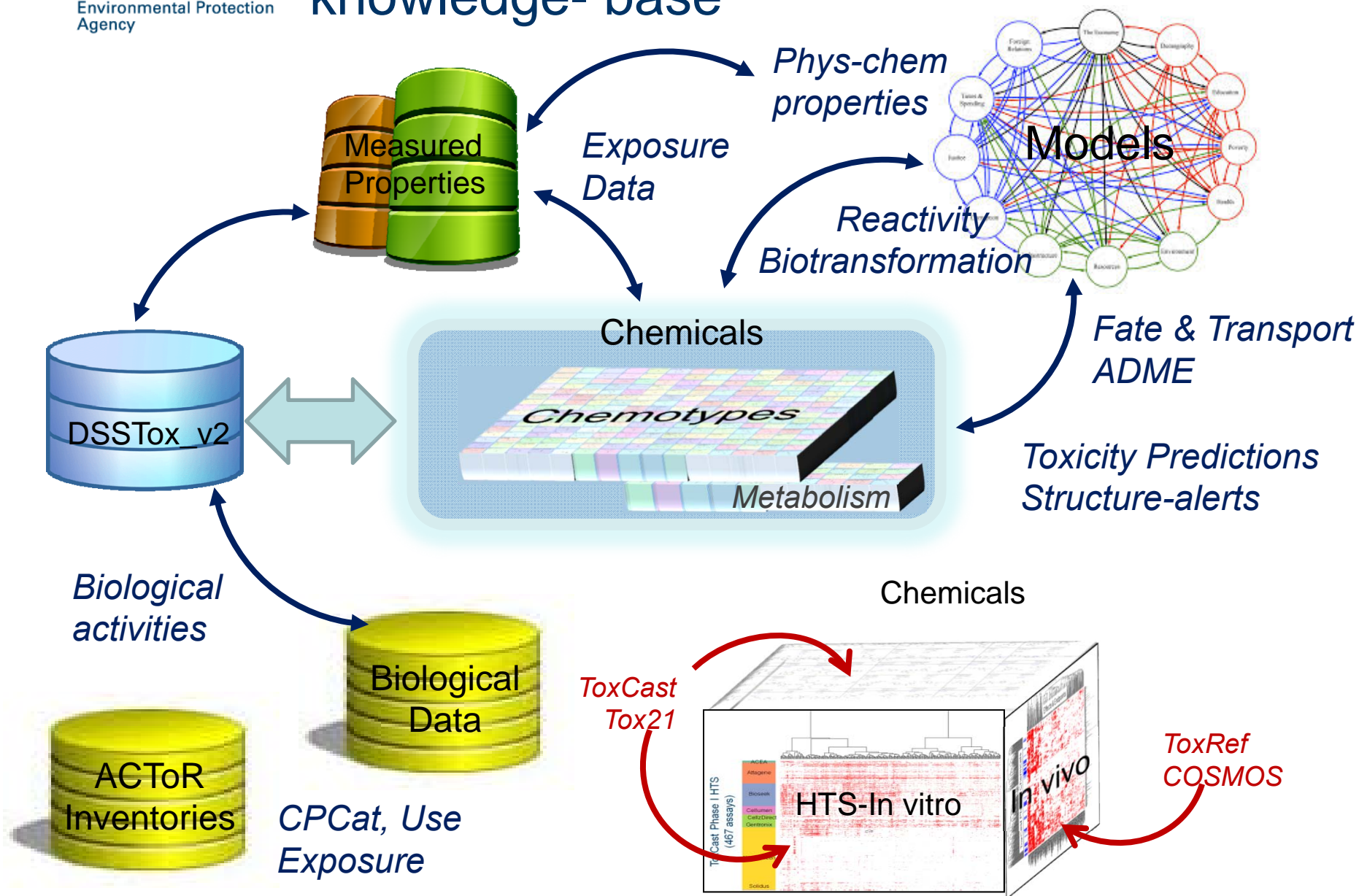
Chemotyper: <http://www.chemotyper.org>

[illegible]

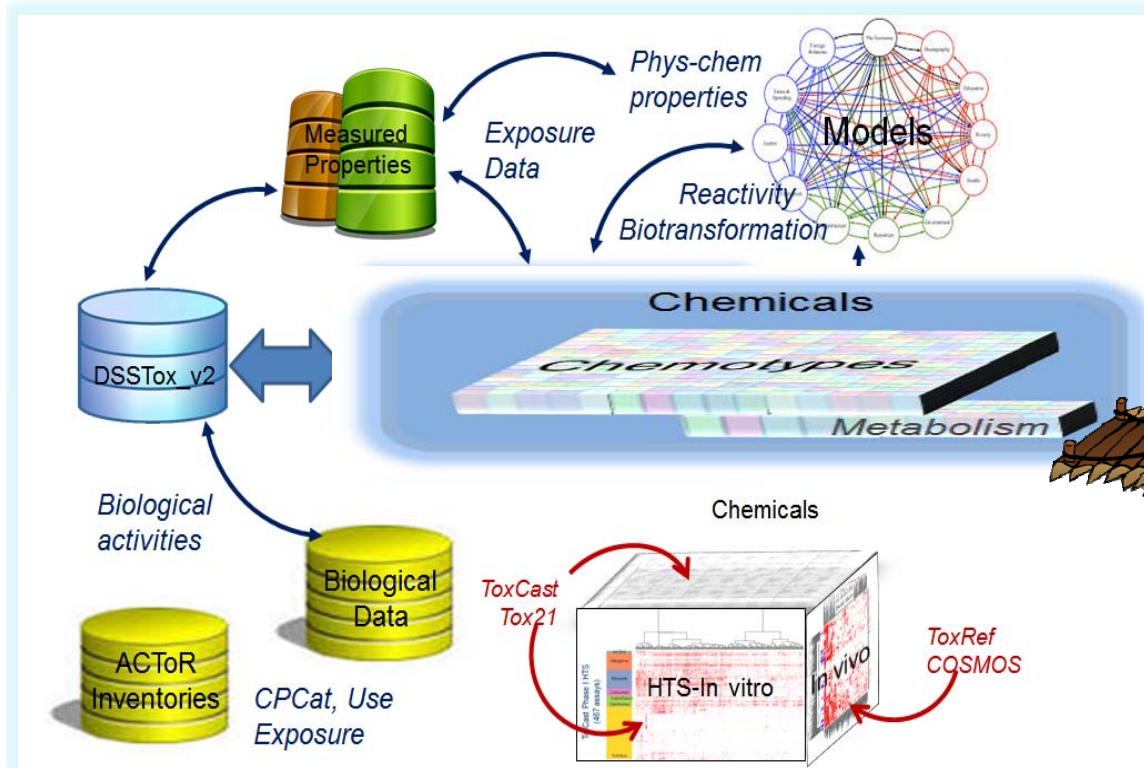
Binary fingerprint file



Building a public chemotype “knowledge- base”



Chemotypes: Build bridges to domain experts & knowledge resources



- Toxicologists
- SAR modelers
- Chemists
- Bioinformaticists
- EPA Programs
- Risk assessors

Office of Research and Development
National Center for Computational Toxicology

EPA's Chemistry Dashboard

<https://comptox.epa.gov/dashboard>

The screenshot displays the EPA Chemistry Dashboard interface. The top navigation bar includes the EPA logo, "United States Environmental Protection Agency", and links for "Home" and "Advanced Search". The main header reads "Chemistry Dashboard".

The search results page for "Atrazine" is shown. The search criteria are "1912-24-9 | DTXSID9020112". The search results indicate "Searched by Approved Name: Found 1 result for 'Atrazine'".

The chemical structure of Atrazine is displayed, showing a triazine ring with a chlorine atom at position 4, an isopropylamino group at position 1, and an ethylamino group at position 6. The structure is labeled with "H₃C", "CH₃", "NH", "N", "N", "NH", "CH₃", and "CH₃".

Key properties listed include:

- Molecular Formula:** C₈H₁₄ClN₅
- Average Mass:** 215.69 g/mol
- Monoisotopic Mass:** 215.093773 g/mol

Other sections visible include "Wikipedia", "Intrinsic Properties", "Structural Identifiers", "Related Compounds (Beta)", "Presence in Lists", and "Record Information".

The footer contains links for "About", "Contact", "Privacy", "ACToR", "DSSTox", "Accessibility", "Help", and "Downloads".

EPA's Chemistry Dashboard

<https://comptox.epa.gov/dashboard>

Chemistry Dashboard

Submit Comment Share Copy Aa Aa

Chemistry Dashboard

Submit Comment Share Copy Aa Aa

Chemistry Dashboard

Submit Comment Share Copy Aa Aa

Chemistry Dashboard

Submit Comment Share Copy Aa Aa

Chemical Properties

Env. Fate/Transport

Synonyms

External Links

Toxicity Values (Beta)

Exposure

Bioassays

Similar Molecules (Beta)

Literature

Comments

Google Scholar

Abstract Sifter

PubChem Article

PubChem Pathway

IRIS

Select Term:

Exposure

Retrieve Articles

122 Articles (out of 122)

Add additional query terms to filter abstracts:

Search and Count

Edit the Query Before Retrieving Articles

("1912-24-9" OR "Atrazine" OR "Atrazine") AND (exposure OR near-field OR far-field OR SHEDS[tab] AND ENVIRONMENTAL MONITORING)

Te... Te... Te... To... PMID P... Title

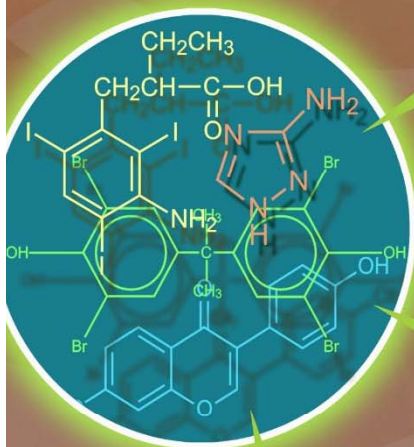
0 0 0 0 27957240 2016 Oral Exposure to Atrazine Induces Oxidative Stress and Calcium Homeostasis Disruption i...

Record: 1 of 122

Title: Oral Exposure to Atrazine Induces Oxidative Stress and Calcium Homeostasis Disruption in Spleen of Mice.

Abstract: The widely used herbicide atrazine (ATR) can cause many adverse effects including immunotoxicity, but the underlying mechanisms are not fully understood. The current study investigated the role of oxidative stress and calcium homeostasis in ATR-induced immunotoxicity in mice. ATR at doses of 0, 100, 200, or 400 mg/kg body weight was administered to Balb/c mice daily for 21 days by oral gavage. The studies performed 24 hr after the final exposure showed that ATR could induce the generation of reactive oxygen species in the spleen of the mice, increase the level of advanced oxidation protein product (AOPP) in the host serum, and cause the depletion of reduced glutathione in the serum, each in a dose-related

Thousands of
CHEMICALS
Environment and Products



CHEMISTRY DATA



Likelihood of Toxicity
Based on Chemical
Properties

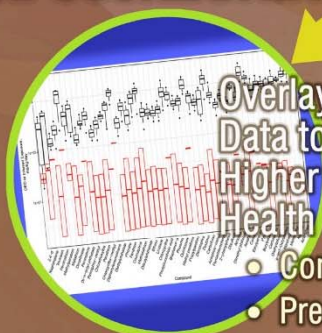
- Experimental and Predicted Values
- High-Quality Chemical Structures

TOXICITY DATA



- High-Throughput Screening on Thousands of Chemicals and Interactions with Biological Processes
- Animal Toxicity Studies when Available

EXPOSURE DATA



Overlay Toxicity and Exposure
Data to Identify Chemicals
Higher Likelihood of Potential
Health Effects

- Consumer Products
- Predicted Total Human Exposure
- Estimate Dose Values for Various Populations

CompTox Online Dashboard



SUPPORT TSCA ACTIVITIES



CORPORATE



CompTox Online Dashboard



Already
IN USE



ENDOCRINE DISRUPTION

- OLD: 50-100 Chemicals per Year at Approximately \$1M Each
- NEW: 1800 Chemicals in 3 Years at Approximately \$30K Total

NEAR-TERM
USE

CONTAMINATED SITE EVALUATION--RapidTox



- Data-Poor Chemicals Found on Site
- Integrate Related Chemical Properties Toxicity and Exposure

PESTICIDES



- Interpretation of New Data on Pesticides
- Begin Using New Models to Estimate Exposure and Dose

SUPPORT TSCA ACTIVITIES



CORPORATE



INTERNATIONAL



STATES



- CALIFORNIA Prioritization for Biomonitoring Pesticides
- MINNESOTA Water Contaminants

city

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ghput
n Thousands of
nd Interactions
ical Processes
city Studies
ble

ulations

Acknowledgements:

✦ EPA NCCT Chemistry Team

Chris Grulke (DSSTox, Chemotypes)

Indira Thillainadarajah (DSSTox)

Tony Williams (DSSTox, Chemistry Dashboard)

Grace Patlewicz (Read-across)

✦ Past & present collaborators

John Shim

ClarLynda Williams-Devane

Chihae Yang, Jim Rathman
and many more...

✦ Entire EPA ToxCast team >



Thank you for your attention



Question

OR



Comment

ToxCast Chemical Landscape

**Chemical
Research in
Toxicology**

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Perspective
pubs.acs.org/crt

ToxCast Chemical Landscape: Paving the Road to 21st Century Toxicology

Ann M. Richard,^{*,†} Richard S. Judson,[†] Keith A. Houck,[†] Christopher M. Grulke,[†] Patra Volarath,[‡] Inthirany Thillainadarajah,[§] Chihae Yang,^{||,⊥} James Rathman,^{⊥,#} Matthew T. Martin,[†] John F. Wambaugh,[‡] Thomas B. Knudsen,[†] Jayaram Kancharla,[▽] Kamel Mansouri,[▽] Grace Patlewicz,[†] Antony J. Williams,[†] Stephen B. Little,[†] Kevin M. Crofton,[†] and Russell S. Thomas[†]

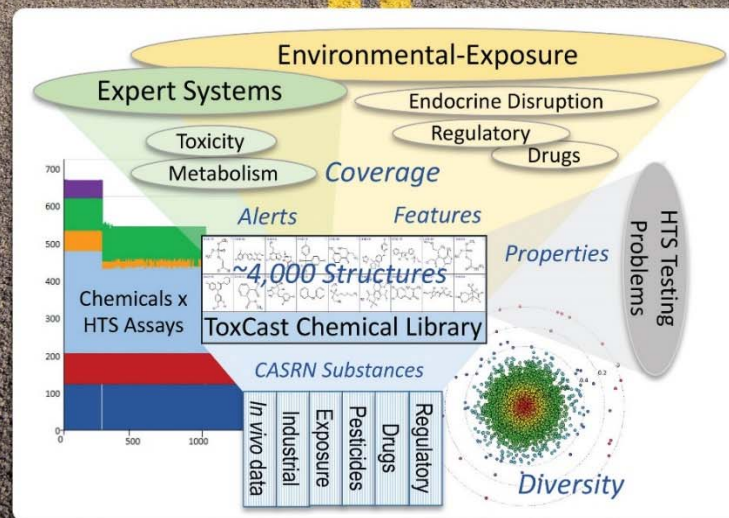
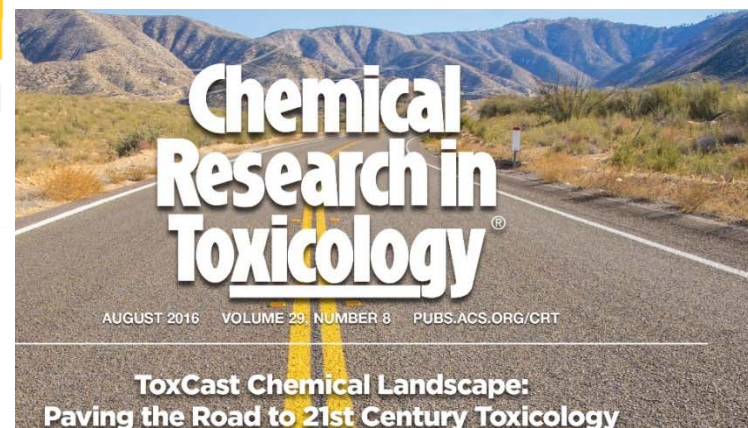
Open Access Perspectives article and Supporting Info files available for free download at:

<http://pubs.acs.org/doi/abs/10.1021/acs.chemrestox.6b00135>



DOI: 10.1021/acs.chemrestox.6b00135

ChemResToxicol., 2016, 29, 1225–1251





EPA Training Opportunities for recent BA graduates

<https://orise.orau.gov/epa/applicants/current-research-opportunities.aspx>

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