

The Evolution of Toxicology and Chemical Regulation

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Deputy Director
National Center for Computational Toxicology



Sitlington Lecture
Oklahoma State University
21 February 2017

Outline

- ☐ **What's the Problem?**
- ☐ **Who's your boss?**
- ☐ **Data, Data, Who's Got Data?**
- ☐ **If you build it, will they use it?**
- ☐ **Nothing is ever perfect**

Problem: The Chemical Hazard Universe

Toxicity Testing Strategies to Determine Needs and Priorities

Steering Committee on Identification of Toxic and Potentially Toxic
Chemicals for Consideration by the National Toxicology Program

Board on Toxicology and Environmental Health Hazards

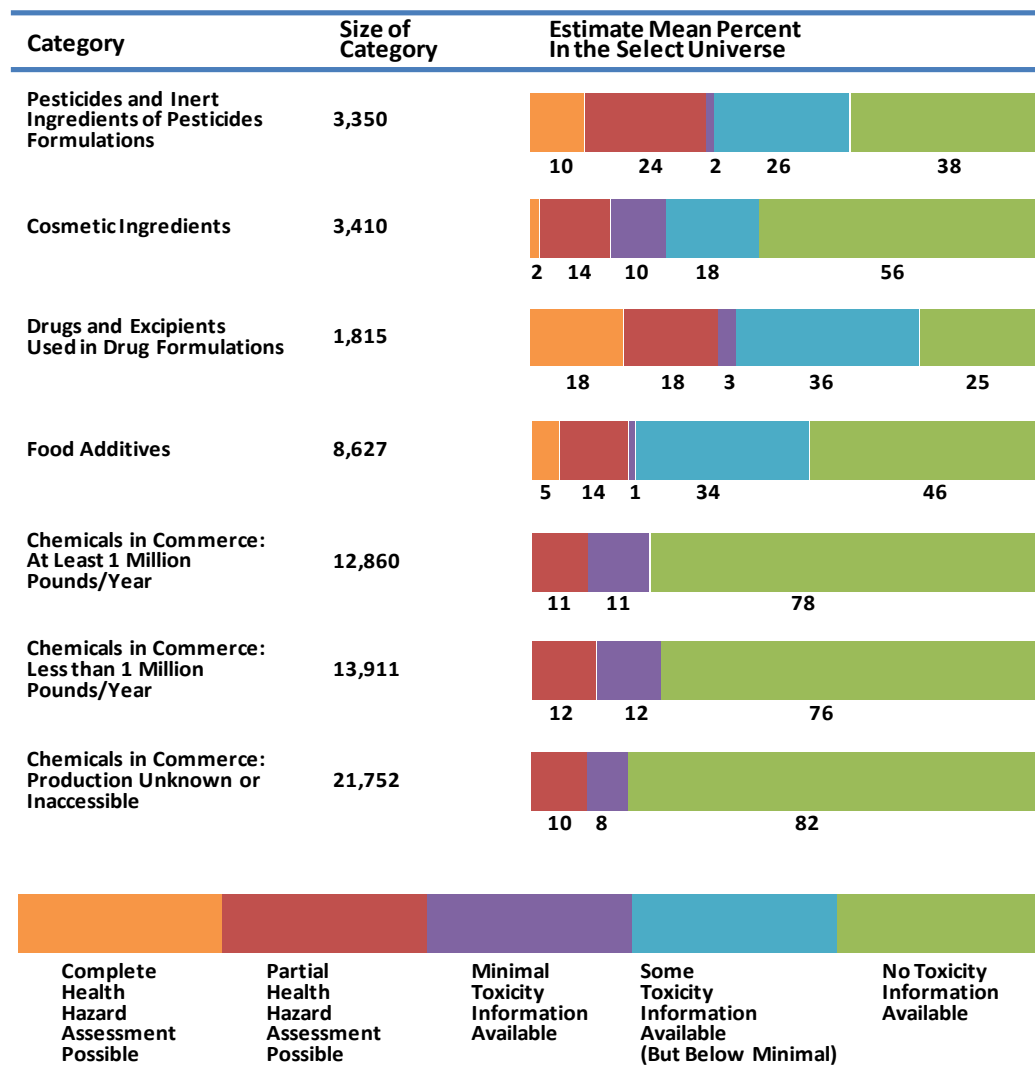
Commission on Life Sciences

National Research Council

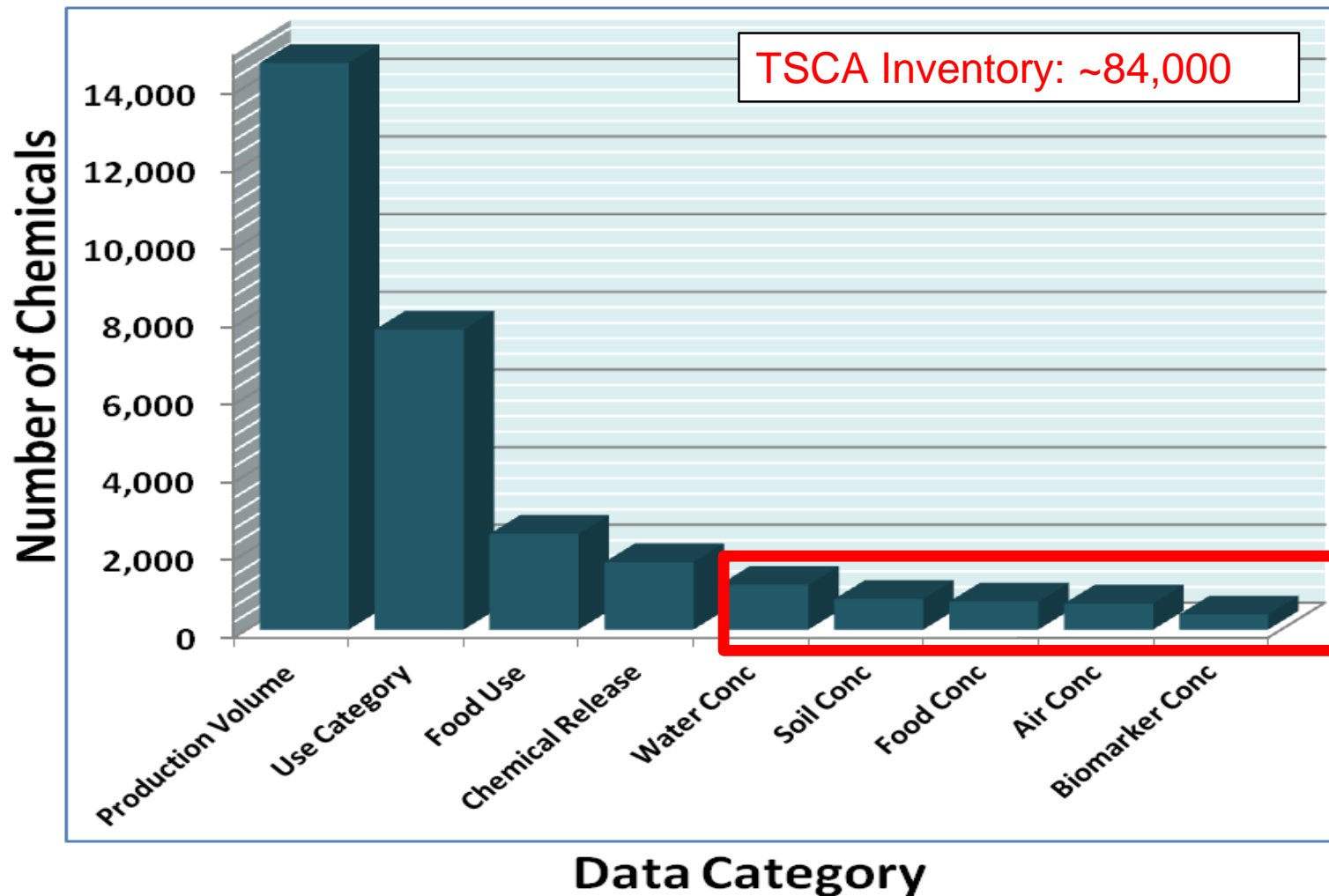
- Major challenge is too many chemicals and not enough data
- Total # chemicals = 65,725
- Chemicals with no toxicity data of any kind = ~46,000

NATIONAL ACADEMY PRESS
Washington, D. C. 1984

US National Research Council, 1984



Problem: The Chemical Exposure Universe

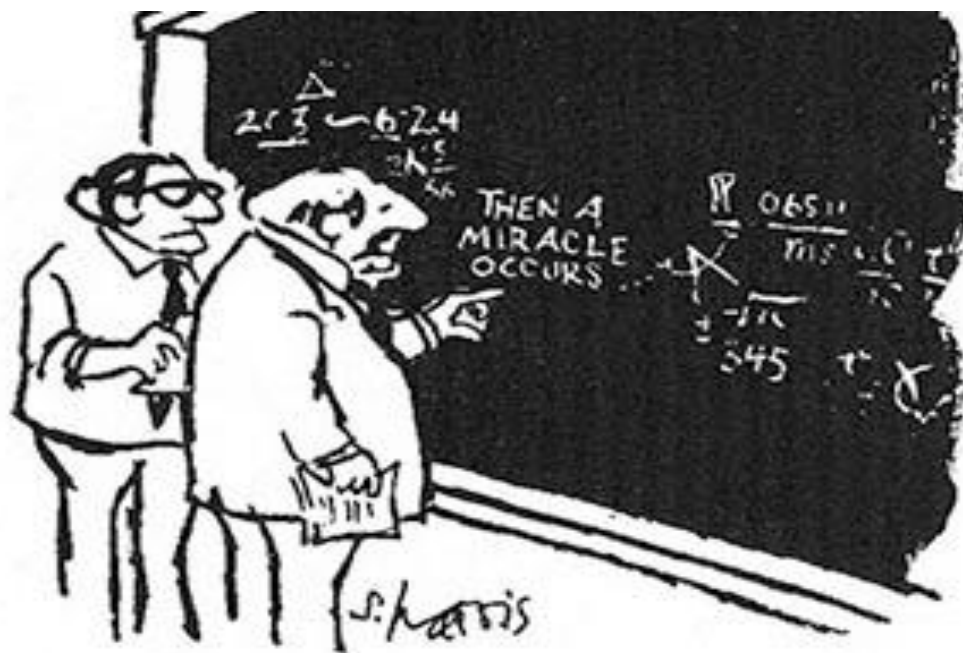


Who's Your Boss? Matching Data Type and Uncertainties to Decision Context



It is critical to understand the uncertainties in the data

And match them to the regulatory decision context

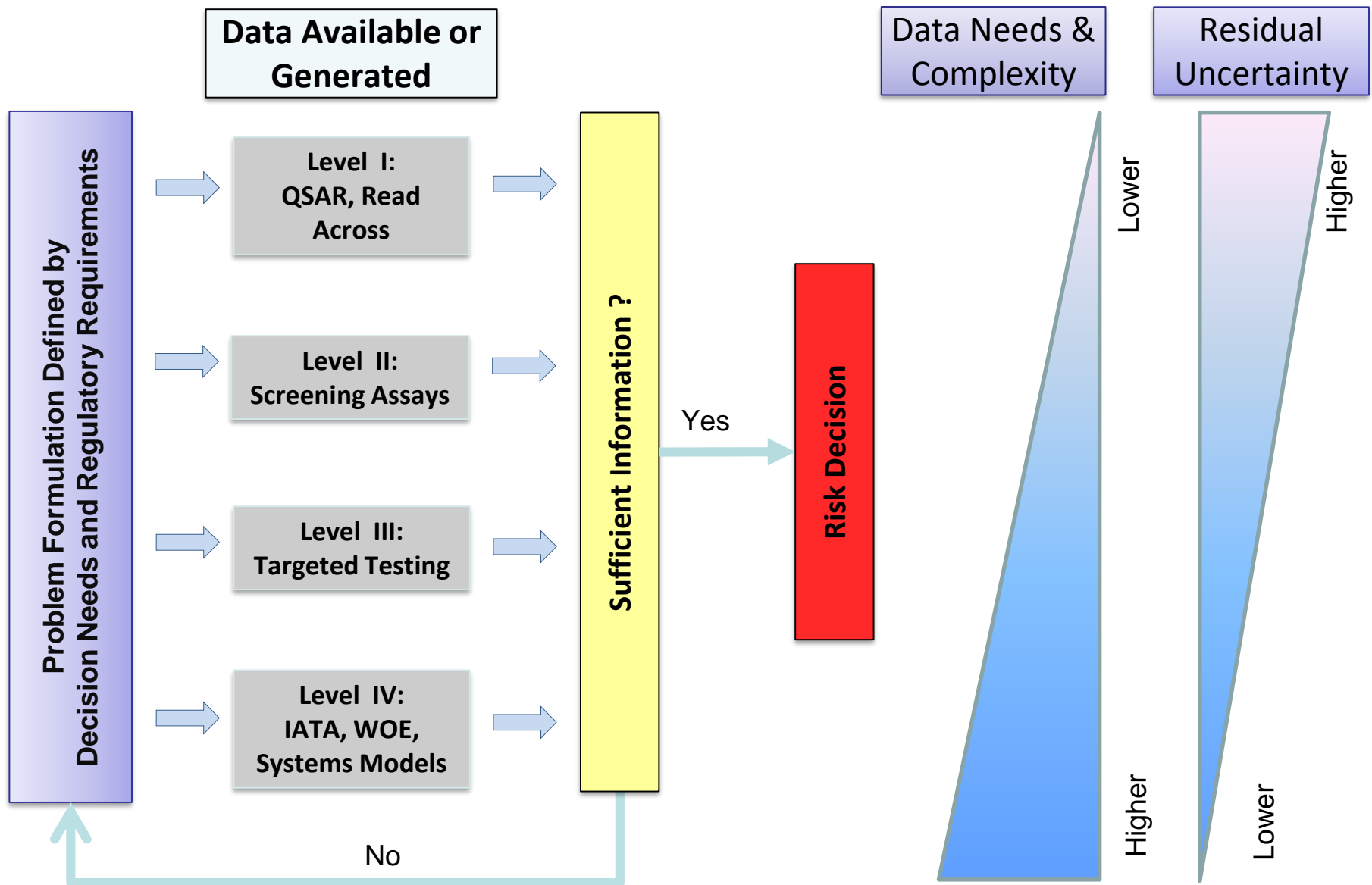


"I think you should be more explicit here in step two."

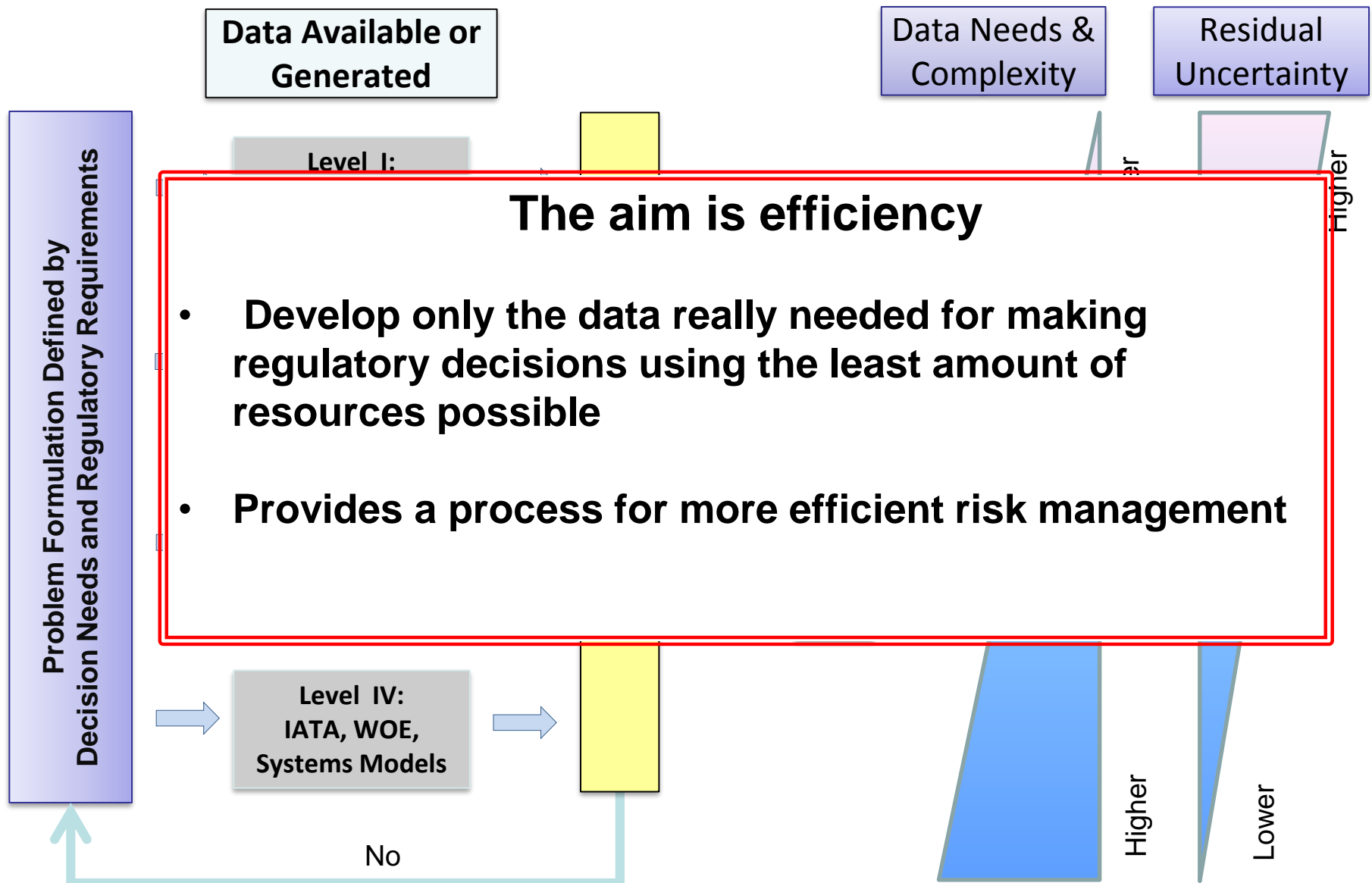
EPA Office	Assessment "Workflows"	Historical Throughput	
OPPTS	Premanufacture Notice (PMN) New chemicals Significant New Use Rule (SNUR) Existing chemicals	~1000/yr 90d/chem ~84,000 total	<div>~1000/year 90 days/chemical Very limited data. eg structure, LogP</div>
	Current Chemical Risk (<i>new program</i>)	~10 total	
	DFE / Green Chemistry	~2500	
OSCP	Endocrine Screening Program	~10-20/year	I, II, III
OPP	Pesticide registration (PR)	~10 new/yr ~50 old/yr	I
	Pesticide re-registration	~1000 24,576	
OW	Chemical Contaminant List	6yr ~6,000	<div>~10 chemicals/year Lots and lots of data \$ millions/chemical</div>
	Regulatory Actions on CCL	6yr 90 to	
	Unregulated Contaminant Monitoring	30/5yr	
	Drinking Water Health Advisories (MCLs)	~80 total	
ORD NCEA	IRIS	~3/yr ~540 total	I
	PPRTV	400-500	II, III

- I. Data rich – Extensive guideline studies
- II. Data partial – Some acute in vivo and in vitro data, SAR and exposure modeling
- III. Data minimal to none – only chemical structure, SAR and exposure modeling

Matching Data Type and Uncertainties to Decision Context



Matching Data Type and Uncertainties to Decision Context



The Beginnings of a Solution

What's Necessary to Begin Solving the Problem of Too Many Chemicals With No Exposure or Hazard Information

1. Chemical curation

- Everything starts with chemical structure

2. Prediction of hazard (or bioactivity)

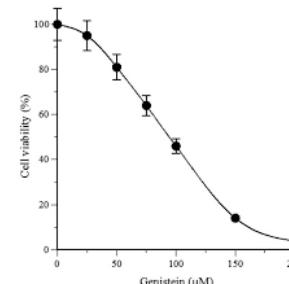
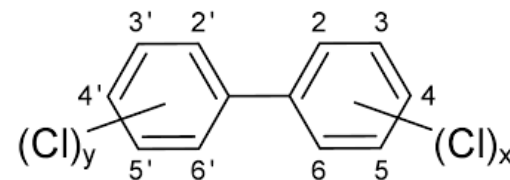
- Need fast efficient testing methods*

3. Predictions of exposure

- Need new models that predict or measure exposures

4. Putting it all together

- Models that integrate this into estimates of risk
- Tools that can be used by risk managers



CompTox Dashboard - Chemistry

DEVELOPMENT

An Integration Hub



~740,000 chemicals
Almost 15 years of data

CompTox Dashboard

Bisphenol

Bisphenol A

Bisphenol A (BPA)

BISPENOL A ANHYDRIDE

Bisphenol A bis(2-hydroxyethyl)ether

Bisphenol A bis(2-hydroxyethyl ether) diacrylate

Bisphenol A bis(2-hydroxyethyl ether) dimethacrylate

Bisphenol A bis(2-hydroxy-3-methacryloxypropyl) ether

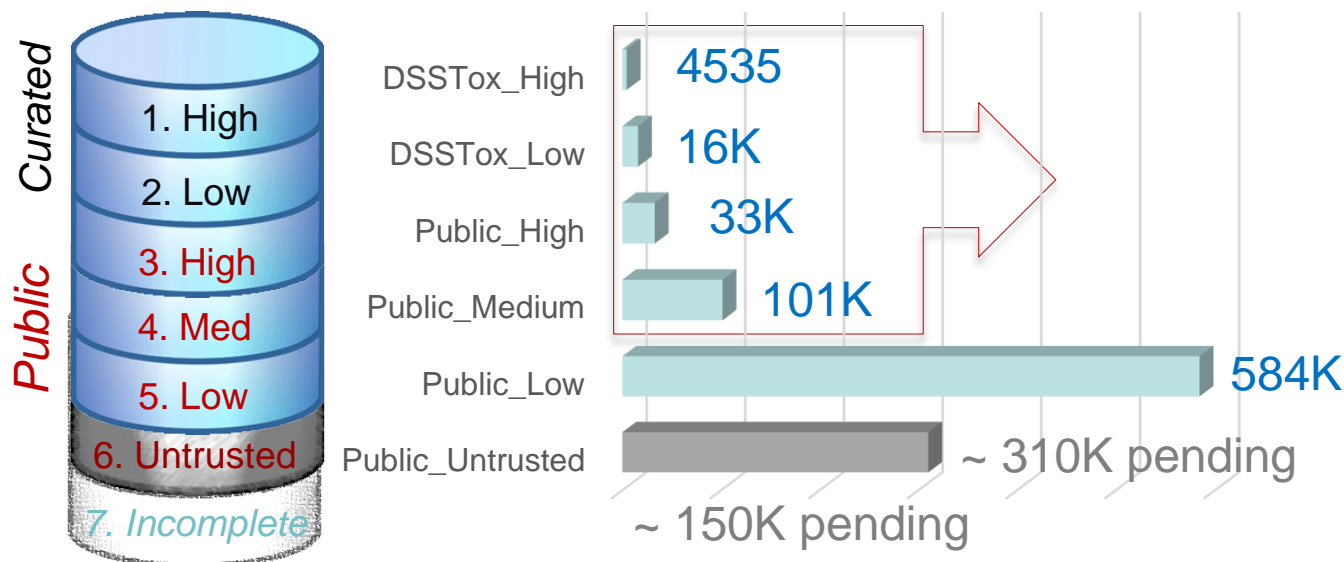
Bisphenol A bis(2-hydroxy-3-methacryloyloxypropyl ether)

q

Help

Even in Chemistry there is Uncertainty

Chemicals Information Ranked on “Confidence”



QC Levels


DSSTox_High:	Hand curated and validated
DSSTox_Low:	Hand curated and confirmed using multiple public sources
Public_High:	Extracted from EPA SRS and confirmed to have no conflicts in ChemID and PubChem
Public_Medium:	Extracted from ChemID and confirmed to have no conflicts in PubChem
Public_Low:	Extracted from ACToR or PubChem
Public_Untrusted:	Postulated, but found to have conflicts in public sources

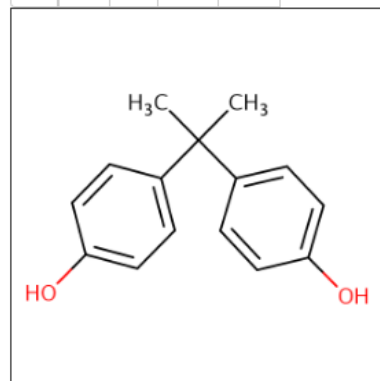
Dashboard Example

Bisphenol A

Bisphenol A

80-05-7 | DTXSID7020182

 Searched by Approved Name: Found 1 result for 'bisphenol A'.



Intrinsic Properties

Molecular Formula: C₁₅H₁₆O₂

[Find All Chemicals](#)



Average Mass: 228.291 g/mol



Monoisotopic Mass: 228.115030 g/mol



Structural Identifiers

Record Information

[Chemical Properties](#)[External Links](#)[Synonyms](#)[Product Composition](#)[ToxCast in Vitro Data](#)[Exposure](#)[Analytical](#)[PubChem](#)[Comments](#)[About](#)[Contact](#)[ACToR](#)[DSSTox](#)[Privacy](#)[Accessibility](#)[Help](#)[Chemical Properties](#)[External Links](#)[Synonyms](#)[Product Composition](#)[ToxCast in Vitro Data](#)[Exposure](#)[PubChem](#)[Comments](#)

Generating Bioactivity Data

ToxCast and Tox21 Programs

- **ToxCast** – EPA program
 - Multi-year research program started in 2007
 - Use automated in vitro chemical screening technologies to expose living cells or isolated proteins to chemicals where changes in biological activity may suggest potential toxic effects
 - Chemical library
 - ~3400 environmentally relevant chemicals

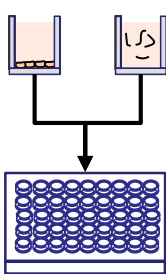
<http://www.epa.gov/ncct/toxcast/>
- **Tox21** – Collaborative project
 - US EPA, NIH/NCATS, NIH/NIEHS/NTP and FDA
 - aimed at developing better toxicity assessment methods using HTS.
 - Chemical library
 - ~8,500 chemicals, including environmental chemicals, food additives and pharmaceuticals

<http://www.ncats.nih.gov/research/reengineering/tox21/tox21.html>

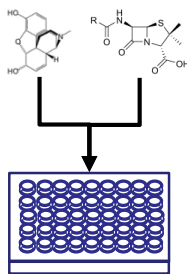
Increased Throughput Required Shift to Molecular/Pathway Approaches

ToxCast

~600 Cell & biochemical assays

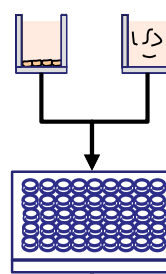


~1,000 Chemicals

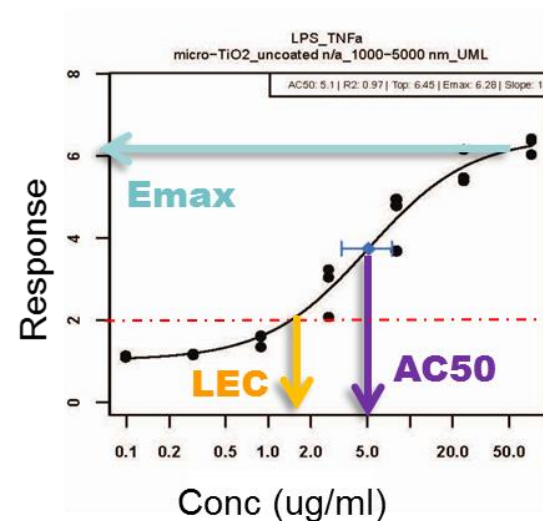
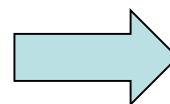
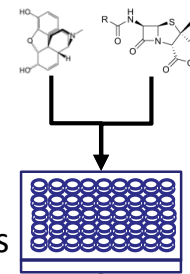


Tox21



~30 Cell & biochemical assays



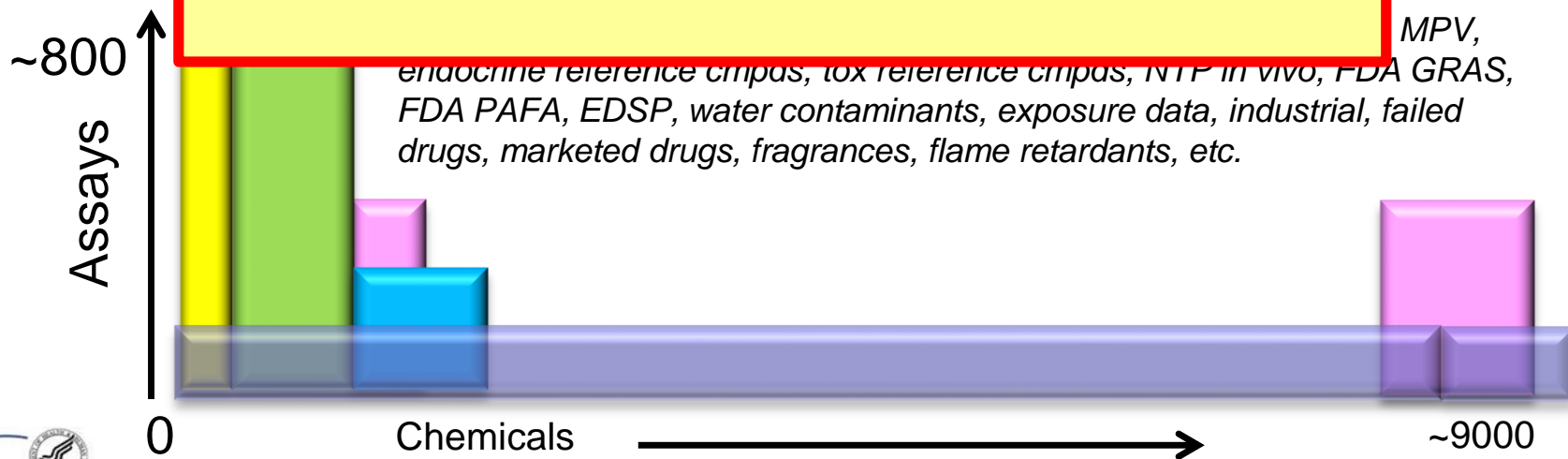
~8,000 Chemicals



ToxCast & Tox21: Chemicals, Data and Release Timelines

Set	Chemicals	Assays	Endpoints	Completion	Available
ToxCast Phase I	 293	~600	~700	2011	Now
ToxCast Phase II	 767	~600	~700	03/2013	Now
ToxCast E1K					Now
Tox21					Ongoing
ToxCast Phase III					2016

72 million data points
2.8 million conc response curves

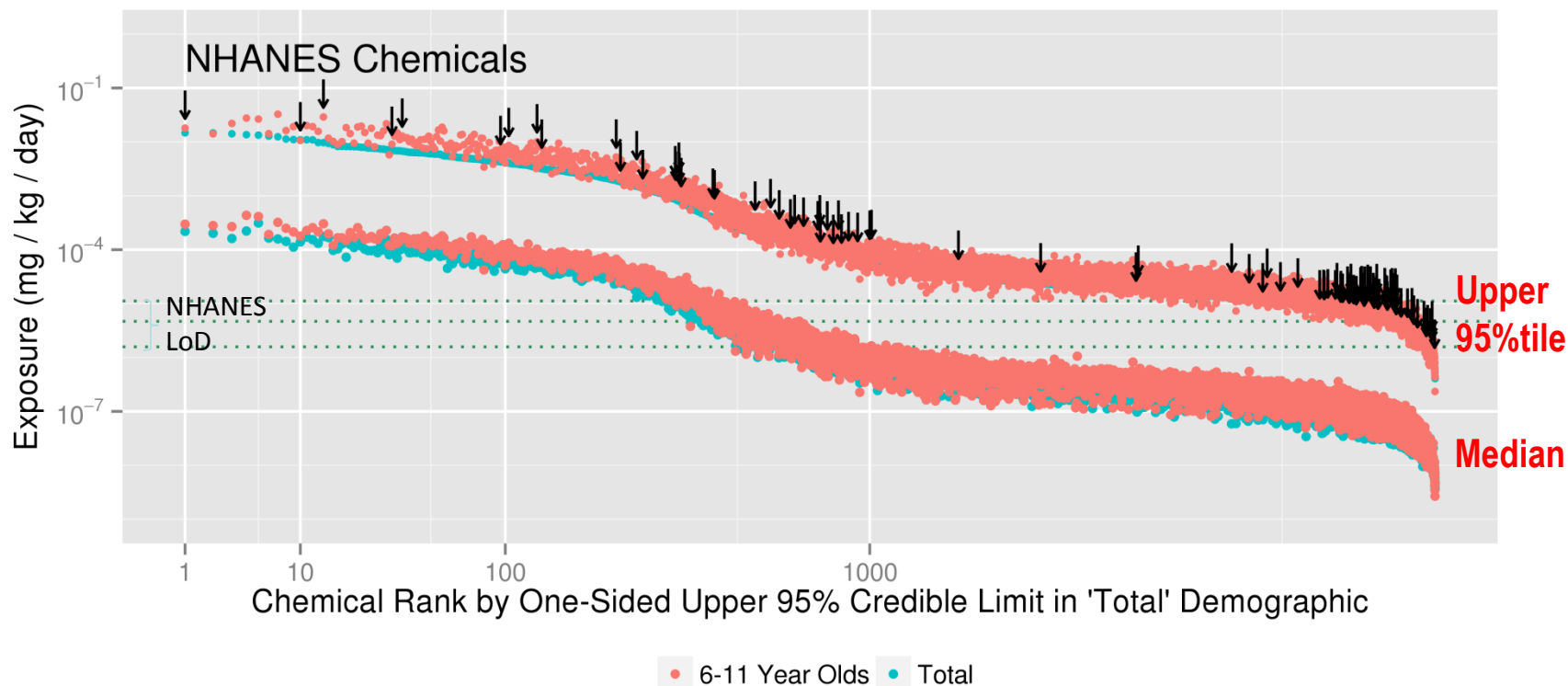


ExpoCast

HTP Exposure Predictions

- **For years exposure science has lagged behind**
 - Most models require extensive information on production, use, fate and transport and rely on empirical data (*no measurement = no exposure?*)
- **ExpoCast**
 - Exposure predictions based on:
 - pChem, production values, fate and transport, and product use categories (e.g., industrial, pesticide use, consumer personal care)
 - Industrial vs consumer use
 - Yields *predictions of exposure estimates* and Bayesian confidence

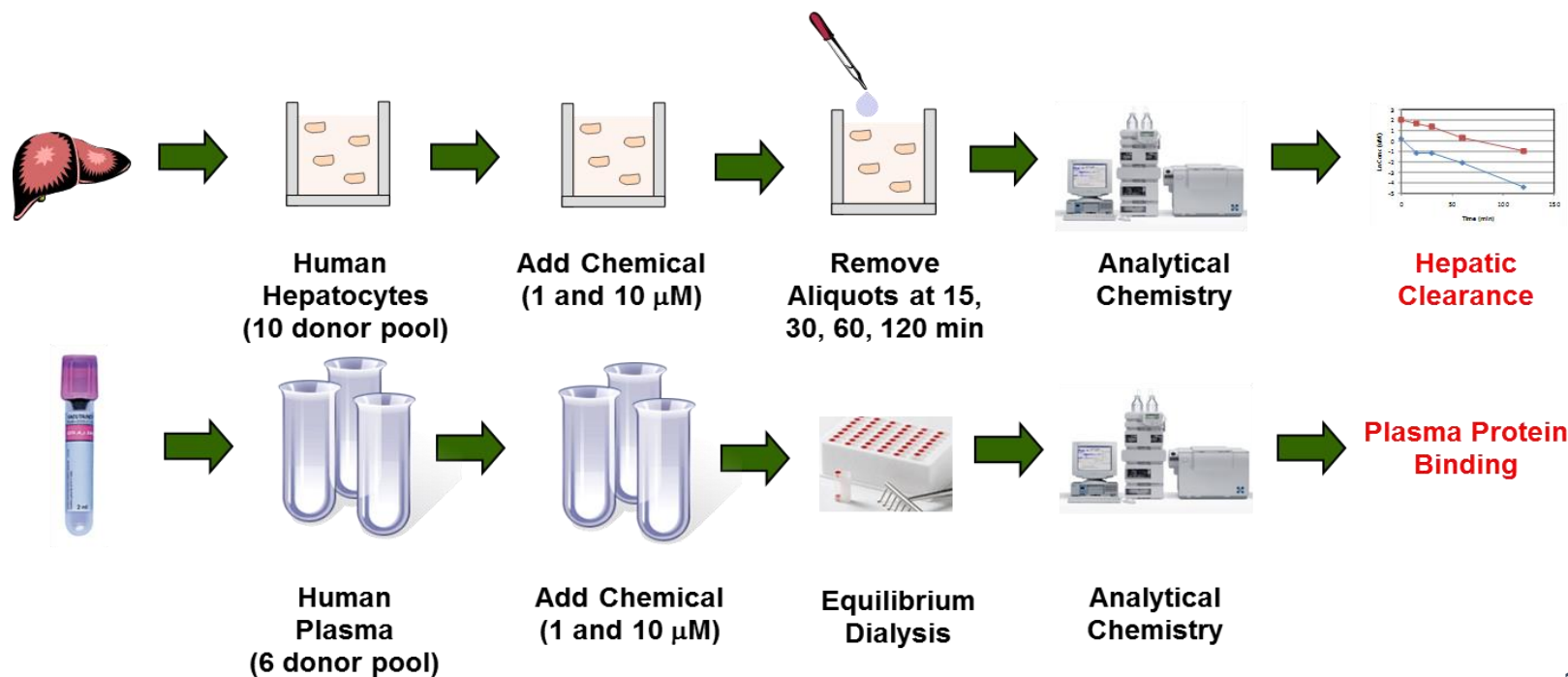
Exposure Predictions for 7968 Chemicals & Comparison to NHANES



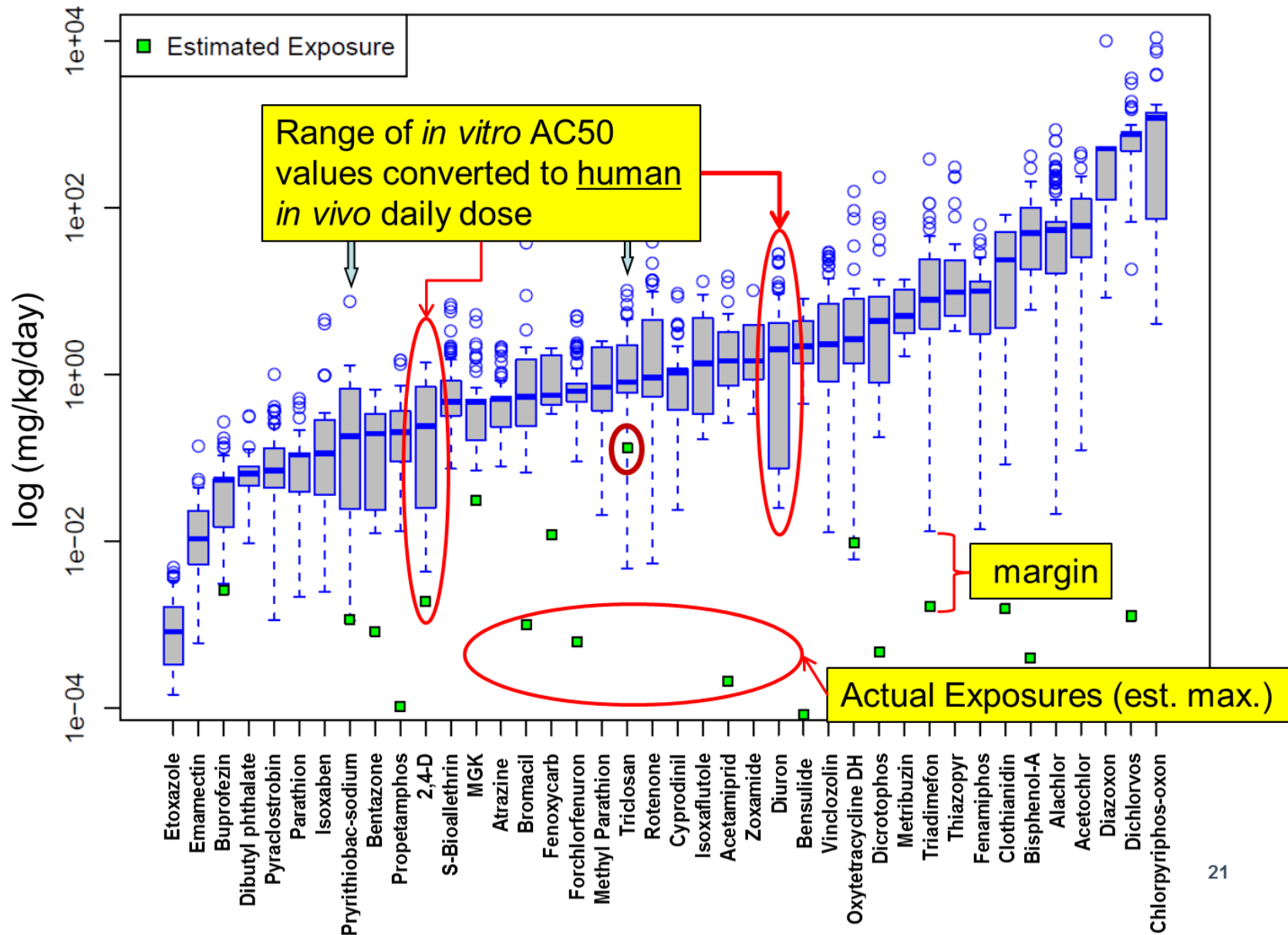
- NHANES – US National Study – measures exposures in human serum and urine
- Chemicals currently monitored by NHANES are distributed throughout the predictions
- Shows accuracy of the prediction model

Estimating Daily Dose with Reverse ToxicoKinetics (rTK)

- VERY SIMPLE biokinetics models – *measure only 2 parameters*
 - in vitro hepatic clearance disappearance of parent compound
 - serum protein binding values
- Provides scaling from concentration in which there is in vitro biological activity to in vivo activity dose (mg/kg/day)



Estimating Exposures for *in vitro* bioactivity

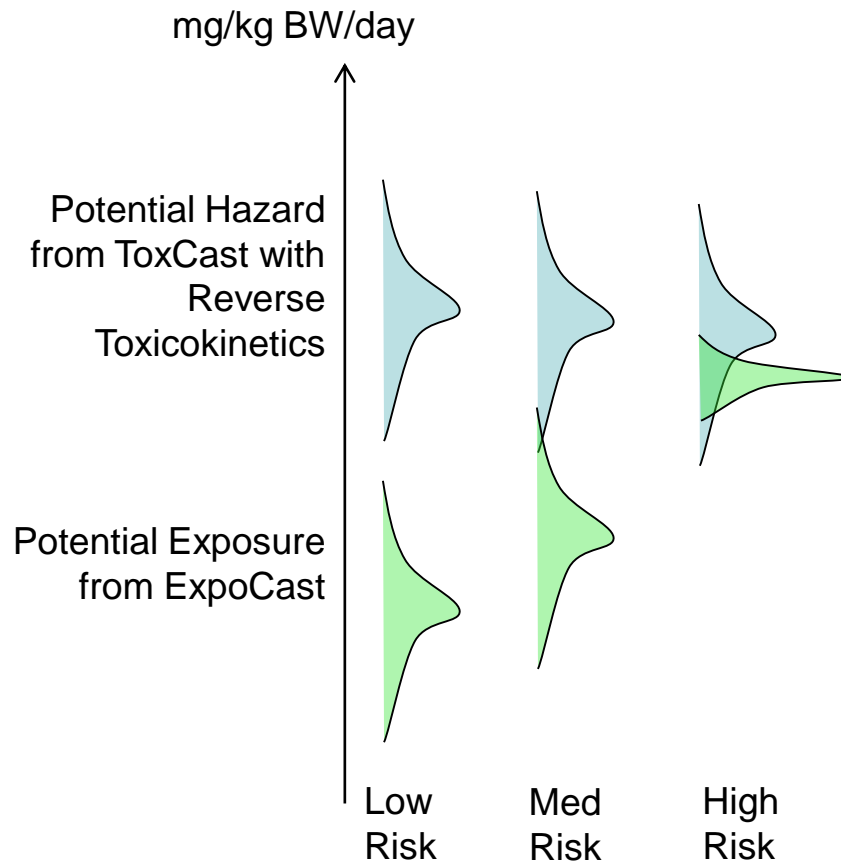


Putting It All Together HT Prioritization

Risk is the product of
hazard and exposure

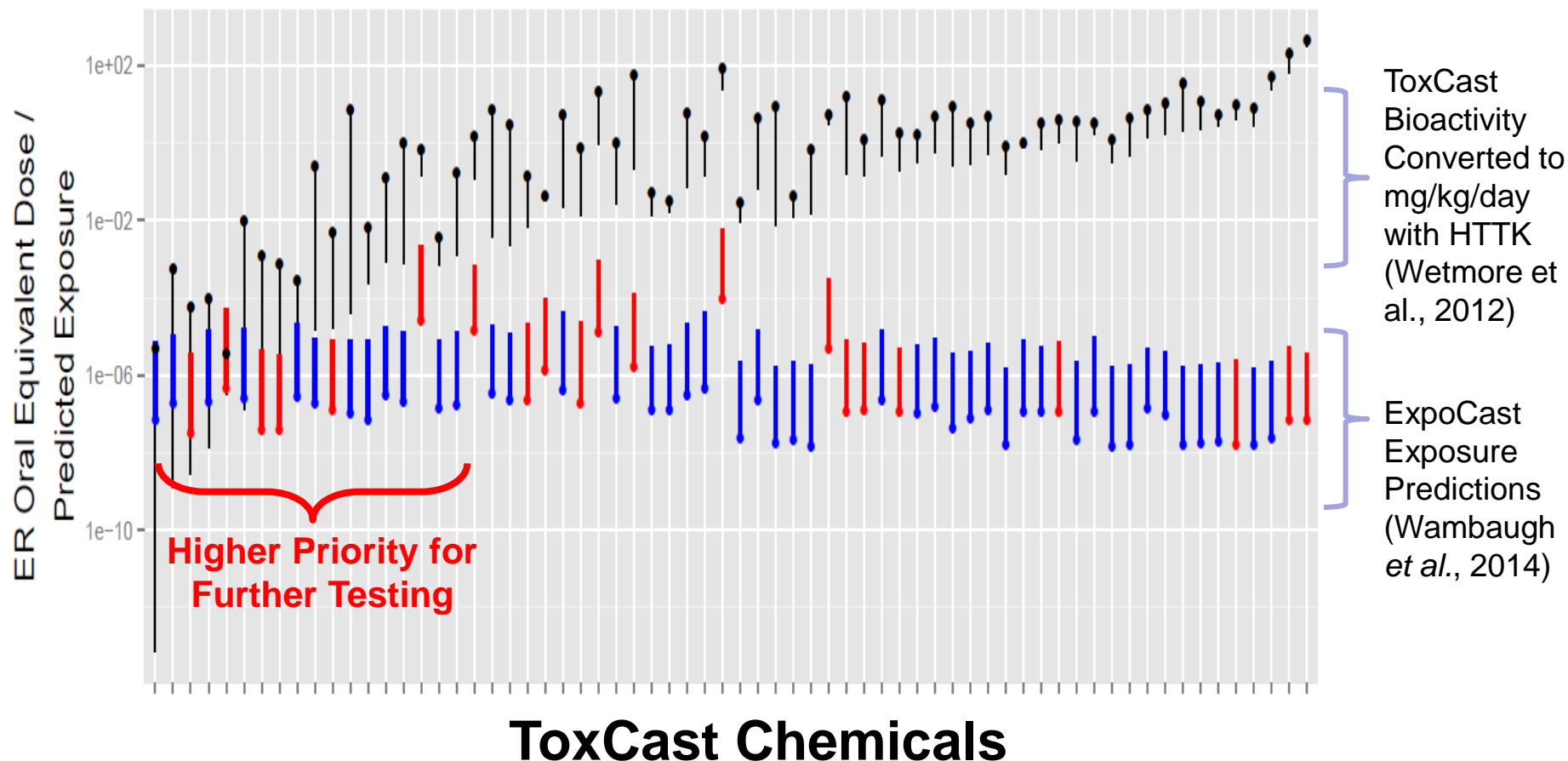
Use rTK convert
bioactive concentrations
to daily dose

Combine with exposure
prediction



Judson *et al.*, (2011)
Chemical Research in Toxicology

Combining Bioactivity-Base Dose and Exposure Estrogen Active Chemicals



Prioritization = test the chemicals that might be the worst, first!

If You Build It, Will They Use It?

Peer Review of New Approaches by FIFRA Science Advisory Panel and Public Led to Adoption by Regulatory Partners

Prioritization of the Endocrine Disruptor Screening Program Universe of Chemicals for an Estrogen Receptor Adverse Outcome Pathway Using Computational Toxicology Tools

U.S. Environmental Protection Agency
Endocrine Disruptor Screening Program

Jointly developed by:

- Office of Chemical Safety and Pollution Prevention, Office of Chemical Safety and Pollution Prevention, Office of Pesticide Programs (OPP), Office of Pollution Prevention and Control (OPPC)
- Office of Water (OW), Washington, DC 20460
- Office of Research and Development, National Environmental and Effect Mid-Continent Ecology Division (MCE), Toxicity Assessment Division (TAD)
- National Center for Computational Research Triangle Park, NC 27709

Exposure SAP White Paper

December 2011

New High-throughput Methods to Estimate Chemical Exposure

Scientific Advisory Panel Meeting, July 2014

December 2014

Integrated Bioactivity and Exposure Ranking: A Computational Approach for the Prioritization and Screening of Chemicals in the Endocrine Disruptor Screening Program

U.S. Environmental Protection Agency
Endocrine Disruptor Screening Program

Integrated Bioactivity and Exposure Ranking: A Computational Approach for the Prioritization and Screening of Chemicals in the Endocrine Disruptor Screening Program

U.S. Environmental Protection Agency
Endocrine Disruptor Screening Program

Federal Register / Vol. 80, No. 118 / Friday, June 10, 2015 / Notices

35350

may claim all or part of a response confidential. EPA will disclose information that is covered by a claim of confidentiality only to the extent permitted by, and in accordance with, the procedures in TSCA section 14 and 20 CFR part 2.

Burden statement: The annual public reporting and recordkeeping burden for this collection of information is estimated to average 31.5 hours per response. Burden is defined in 5 CFR 1320.3(b).

The ICR, which is available in the docket along with other related materials, provides a detailed explanation of the collection activities and the burden estimate that is only briefly summarized here.

Respondents/affected entities: Entities potentially affected by this ICR are companies that manufacture, process or import chemical substances, mixtures or categories.

Estimated total annual burden hours: 31.5 hours.

Frequency of response: On occasion.

Estimated total average number of responses for each respondent: 1.

Estimated total annual burden hours: 31.5 hours.

Estimated total annual costs: \$2,388. This includes an estimated burden cost of \$2,388 and an estimated cost of \$0 for capital investment or maintenance and operational costs.

III. Are There Changes in the Estimates from the Last Approval?

There is a decrease of 916 hours in the total estimated respondent burden compared with that identified in the ICR currently approved by OMB. This decrease reflects additional both adjustment changes from a reduction in the assumed number of FAIR reports filed annually, and program changes resulting from mandatory electronic submissions of FAIR reports. In recent years (FY 2011–FY 2014), EPA has received no FAIR submissions and, for the purposes of this analysis, EPA assumed an annual rate of one submission per year. At the time OMB last renewed this ICR, EPA estimated an average of 31 reports from 14.8 submitters based on fiscal year 2006–2010 data. The ICR supporting statement provides a detailed analysis of the change in burden estimate. This change is both an adjustment and a program change.

IV. What is the Next Step in the Process for this ICR?

EPA will consider the comments received and amend the ICR as appropriate. The final ICR package will then be submitted to OMB for review and approval pursuant to 5 CFR 1320.12. EPA will issue another Federal Register document pursuant to 5 CFR 1320.5(a)(1)(iv) to announce the submission of the ICR to OMB and the opportunity to submit additional comments to OMB. If you have any questions about this ICR or the approval process, please contact the technical person listed under **FOR FURTHER INFORMATION CONTACT**.

Authority: 40 U.S.C. 3501 et seq.

Dated: June 10, 2015.

James Jones,
Assistant Administrator, Office of Chemical Safety and Pollution Prevention.
(P) 202-554-1400; (F) 202-554-1401; (E) james.jones@epa.gov

ENVIRONMENTAL PROTECTION AGENCY
(EPA-HQ-OPP-2015-0305, FRL-9038-90)
Use of High Throughput Assays and Computational Tools: Endocrine Disruptor Screening Program: Notice of Availability and Opportunity for Comment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This document describes how EPA is planning to incorporate an alternative scientific approach to screen chemicals for their ability to interact with the endocrine system. This will improve the Agency's ability to fulfill its statutory mandate to screen pesticide chemicals and other substances for their ability to cause adverse effects by their interaction with the endocrine system. The approach incorporates validated high throughput assays and a computational model, and based on current research, can serve as an alternative for some of the current assays in the Endocrine Disruptor Screening Program (EDSP) Tier 1 battery. EPA has partial screening results for over 1,800 chemicals that have been evaluated using high throughput assays and a computational model for the estrogen receptor pathway. In the future, EPA anticipates that additional alternative methods will be available for EDSP chemical screening based on further advancements of high throughput assays and computational models for other endocrine pathways. Use of these alternative methods will accelerate the pace of screening, decrease costs, and reduce animal testing. In addition, this approach advances the goal of providing sensitive, specific, quantitative, and

efficient screening using alternative test methods to some assays in the Tier 1 battery to protect human health and the environment.

DATES: Comments must be received on or before August 18, 2015.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA-HQ-OPP-2015-0305, by one of the following methods:

- **Federal eRulemaking Portal:** <http://www.regulations.gov>. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute.
- **Mail:** Document Control Office (7407M), Office of Pollution Prevention and Toxics (OPPT), Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC 20460-0001.
- **Hand Delivery:** To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at <http://www.epa.gov/epahome/contact-us/other-contacts/contacts.html>. Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at <http://www.epa.gov/dockets>.

FOR FURTHER INFORMATION CONTACT: For technical information contact: Jane Robbins, Office of Science Coordination and Policy (OSCP), Office of Chemical Safety and Pollution Prevention, Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC 20460-0001; telephone number: (202) 554-6625; email address: robbins.jane@epa.gov.

For general information contact: The TSCA Hotline, ABVI Goodwill, 422 South Clinton Ave., Rochester, NY 14620; telephone number: (202) 554-1400; email address: TSCA-Hotline@epa.gov.

SUPPLEMENTARY INFORMATION:

1. General Information

A. Does this action apply to me?

This action is directed to the public in general, and may be of interest to a wide range of stakeholders including those interested in endocrine testing of chemicals (including pesticides), and the EDSP in general. Since others also may be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action.

B. What is the agency authority for taking this action?

The EDSP is established under section 406(g) of the Federal Food, Drug and

Federal Register
Notice - Dec 2014

Proposal for use:
• Prioritization
• And for first time replacement!

If You Build It, Will They Use It?

Minnesota Dept Health Risk Assessments for Water Contaminants

MDH Minnesota Department of Health First Quarter Report
FISCAL YEAR 2016
July - September 2015

Drinking Water Contaminants of Emerging Concern Program

The mission of the Drinking Water Contaminants of Emerging Concern (CEC) program is to investigate and communicate the health and exposure potential of contaminants of emerging concern in drinking water. The CEC program supports the Clean Water Fund mission to protect drinking water sources and the Minnesota Department of Health (MDH) mission to protect, maintain, and improve the health of all Minnesotans.

Using ToxCast to Compare Activity of Pesticide Active Ingredients with their Environmental Degradates

Three chemicals were nominated to the CEC program this quarter:

- Anatoxin-a, a toxin produced naturally by blue-green algae (cyanobacteria),
- Bifenthrin, an insecticide known to be toxic to aquatic organisms, and
- Tetrahydrofuran, an industrial solvent.

Chemicals Screened by the CEC Program

IARC Monographs

Carcinogenicity of perfluorooctanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sultone

In June, 2014, 20 experts from nine countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of perfluorooctanoic acid (PFOA), tetrafluoroethylene (TFE), dichloromethane (DCM), 1,2-dichloropropane (1,2-DCP), and with 1,2-DCP in this industry). The working group considered the rarity of cholangiocarcinoma, the very high relative risk, the young ages of the patients, the absence of non-occupational risk factors, and the intensity of the exposure as indications that the excess of strong evidence that DCM metabolism via glutathione-S-transferase T1 (GSTT1) leads to the formation of reactive metabolites, that GSTT1 activity is strongly associated with genotoxicity of DCM in vitro and in vivo, and that GSTT1-mediated metabolism of DCM does occur in

Australian IMAP

Australian Government
Department of Health
National Industrial Chemicals
Notification and Assessment Scheme

Inventory Multi-tiered Assessment and Prioritisation (IMAP) Framework Review

April 2016

Prioritization for Biomonitoring CA

Possible Classes of Chemicals Used in UV Applications

Chemical identity	US production/import volume (lbs)	EPI Suite information ¹	Some toxicity information	Selected detections
Benzophenone-3 (BP-3) CASRN: 131-57-7 Synonyms: 2-hydroxy-4-methoxyphenyl-phenylmethanone; oxybenzone Metabolites include: BP-1, BP-2, BP-8	1986: >500K - 1M 1990: >1M - 10M 1994: >1M - 10M 1998: >1M - 10M 2002: 10K - 500K 2006: No data 2012: 100K - 500K	MW: 228.25 Log K _{ow} : 3.79 (exp) Water sol: 68.56 mg/L BCF: 38.24 L/kg Half-lives (hours): Air: 1.28 Water: 900 Soil: 1,800 Sediment: 8,100	• Indications of estrogenic, anti-estrogenic, and anti-androgenic activity • Cytotoxic in human neuroblastoma cells at environmentally relevant doses • ToxCast [®] endocrine activity; immune- and inflammation-related effects	• Urine • Serum • Breast milk • Adipose tissue • Aquatic organisms (fish, mussels, clams) • Dust
Benzophenone CASRN: 119-61-9 Synonym: diphenylmethanone Metabolites include: 4-hydroxy-benzophenone	1986: >1M - 10M 1990: >1M - 10M 1994: >1M - 10M 1998: >1M - 10M 2002: >1M - 10M 2006: 1 - <10M 2012: 3,967,158	MW: 182.22 Log K _{ow} : 3.18 (exp) Water sol: 103.3 mg/L BCF: 15.14 L/kg Half-lives (hours): Air: 72.2 Water: 360 Soil: 720 Sediment: 3,240	• Carcinogenicity (listed under Proposition 65) • Indications of estrogenic and anti-androgenic activity • ToxCast [®] endocrine activity; developmental toxicity in zebrafish	• Urine • Dust
4-Methylbenzophenone CASRN: 134-84-9 Synonym: (4-methylphenyl)phenylmethanone	1986: No data 1990: No data 1994: 10 - 500K 1998: 10 - 500K 2002: 10 - 500K 2006: No data 2012: Withheld	MW: 196.25 Log K _{ow} : 3.69 (est) Water sol: 32 mg/L BCF: 33.07 L/kg Half-lives (hours): Air: 39.2 Water: 900 Soil: 1,800 Sediment: 8,100	• Cytotoxic in human neuroblastoma cells at environmentally relevant doses • ToxCast [®] endocrine activity; immune- and inflammation-related effects	• None located

Health Canada

Government of Canada / Gouvernement du Canada

Chemical Substances
www.chemicalsubstances.gc.ca

Home > Chemicals Management Plan

Main Menu

- Canada's approach on chemicals
- Chemicals Management Plan**
 - Canada-United States Regulatory Cooperation Council
 - Initiatives
 - Monitoring & Surveillance
 - Resources
 - Science Committee

Chemicals Management Plan

Chemicals are part of everyday life, essential to our economy, our communities and our homes. While chemicals provide benefits, they may also have harmful effects if not properly managed.

The Chemicals Management Plan (CMP) is a Government of Canada initiative aimed at reducing the risks posed by chemicals to Canadians and their environment. The next phase of the CMP, launched in May 2016, will address the remaining 1550 priority chemicals out of the original 4300 chemicals identified as priorities during the categorization. The Minister of Health and the Minister of Environment and Climate Change have committed to addressing these chemicals by 2020. The CMP builds on previous initiatives by assessing chemicals used in Canada and by taking action on chemicals found to be harmful to human health and/or the environment.

Nothing is Ever Perfect

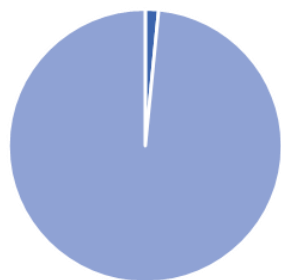
- You don't include metabolism in you in vitro assays
- You don't measure my favorite endpoint (or all of biology)
- In vitro assays are not normal biology
- Assay (x) in your battery did not get the right answer for my chemical
- My assay disagrees with your assay (x), so your approach is flawed
- You can't test my favorite chemicals because of limitations in your methods (e.g., solvents, high LogP)
- You can't possibly do RTK modeling with those simple models!
- You can't do HT Exposure predictions based on simple use models!

- If not this, then what? What other methods could we use for prioritization of thousands of chemicals?

Challenges: Increasing Biological Coverage

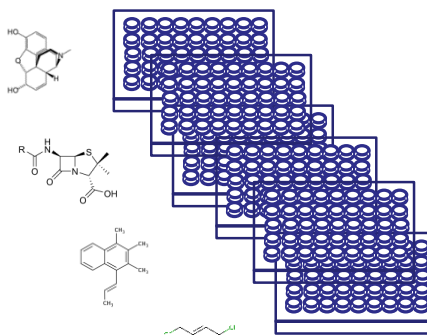
Next Generation Chemical Testing with New Sequencing Technologies

Gene Coverage

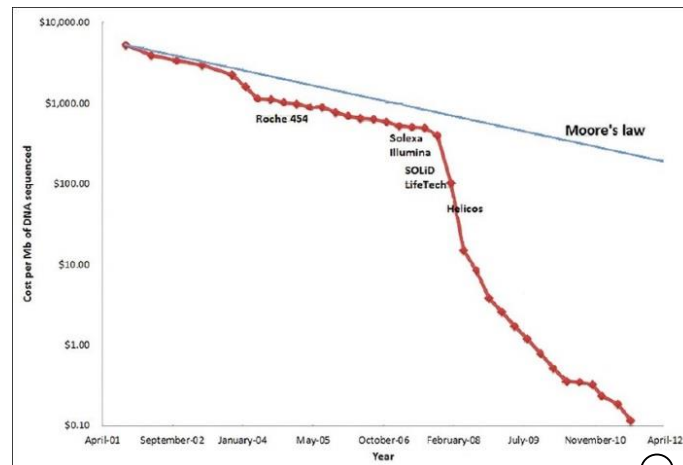


■ ToxCast
■ Not in ToxCast

Ongoing pilot projects using TempOSeq – a more **cost-efficient** whole gene sequencing platform



Sequencing Costs 2001-present

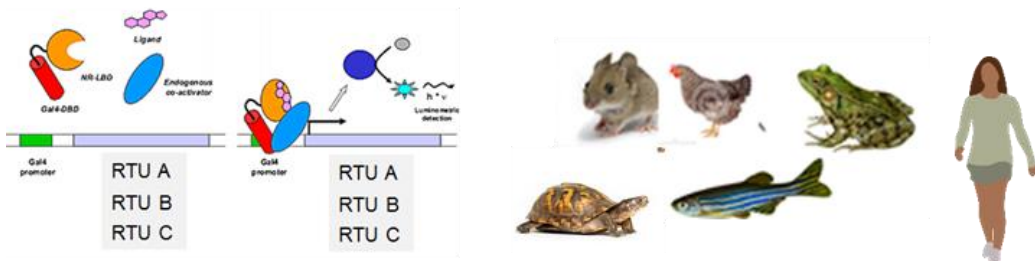


Assessing the effects of thousands of chemicals on all the genes in the genome

Challenges: Increasing Species Coverage

- ToxCast & Tox21 are mostly human based
- Pilot project using Attagene system – insert receptor ligand binding domains from multiple species
- Multiple readouts of nuclear receptor hits from one cell

Multispecies Attagene *Trans* Reporter Assay



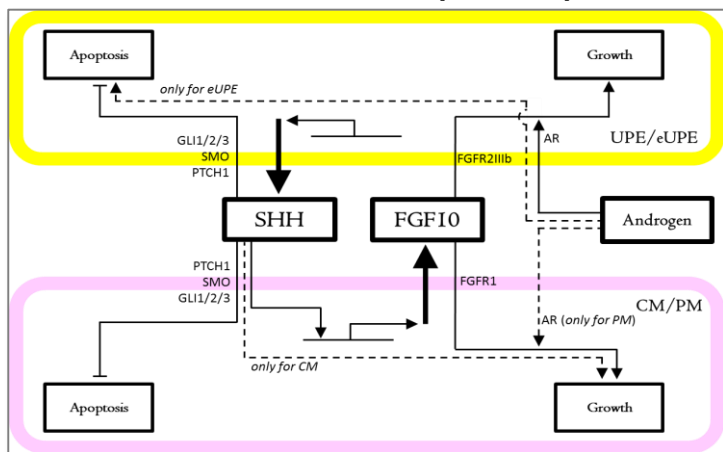
- Host cell: human HepG2
- 100 chemicals with ER, AR, TR, PPAR activity tested in concentration-response
- Pilot data using positive and negative reference chemicals is promising

Receptor Family	Receptor Name	Species
Estrogen Receptor	ERa	Human
Estrogen Receptor	ERb	Human
Estrogen Receptor	ER1	Zebrafish
Estrogen Receptor	ER2a	Zebrafish
Estrogen Receptor	ER2b	Zebrafish
Estrogen Receptor	ERa	Chicken
Estrogen Receptor	ER1	Frog
Estrogen Receptor	ER2	Frog
Estrogen Receptor	ERa	Turtle
Estrogen Receptor	AR	Human
Estrogen Receptor	AR	Chicken
Estrogen Receptor	AR	Turtle
Estrogen Receptor	AR	Frog
Estrogen Receptor	AR	Zebrafish
Peroxisome Proliferator Activated Receptor γ	PPAR γ	Mouse
Peroxisome Proliferator Activated Receptor γ	PPAR γ	Zebrafish
Peroxisome Proliferator Activated Receptor γ	PPAR γ	Human
Pregnane X Receptor	PXR	Mouse
Thyroid Receptor	TRa	Turtle
Thyroid Receptor	TRb	Zebrafish
Thyroid Receptor	TRb	Zebrafish
Thyroid Receptor	TRa	Frog
Thyroid Receptor	TRa	Human
Thyroid Receptor	TRb	Human
Controls	M-06	NA
Controls	GAL4	NA
Controls	M-19	NA
Controls	m-32	NA
Controls	m-61	NA

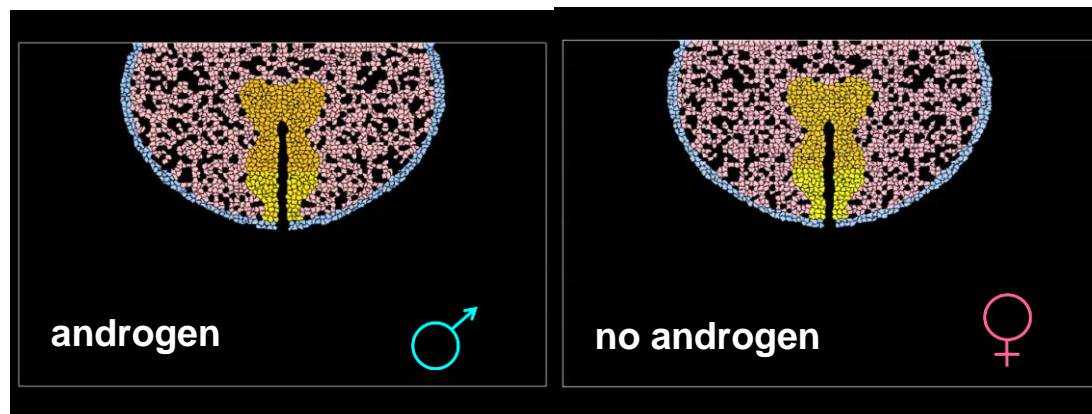
Challenges: Recapitulating Complex Biology in In Vitro and In Silico

An Example of Complex Systems Modeling

Signaling Network Underlying Virtual Genital Tubercle Model (Mouse)

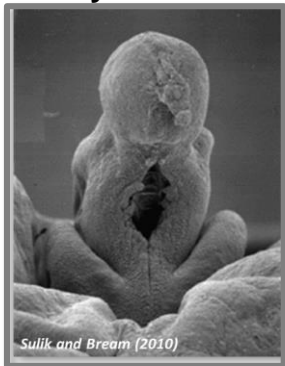


Simulation of Genital Tubercle Closure

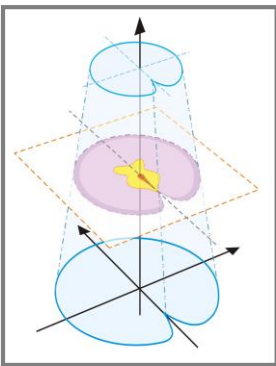


GD13.5 – 17.5

Embryonic GT



Abstracted GT



Androgenization

(*n* = 10 sims)

100%
67%
33%
0%

Phenotype (MCS 4000)

Septation

Fusion

Conden.

Closure Index

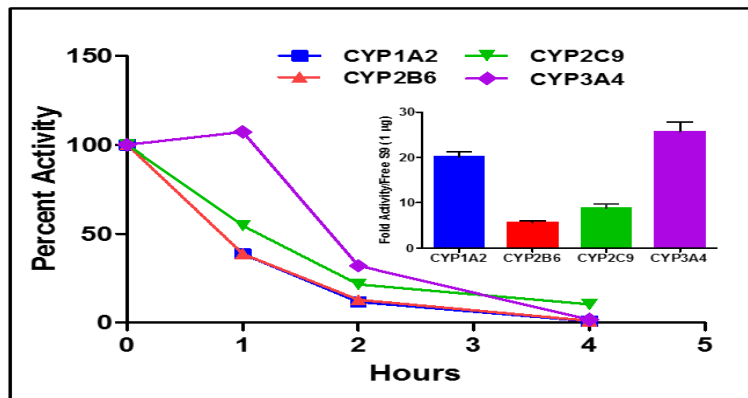
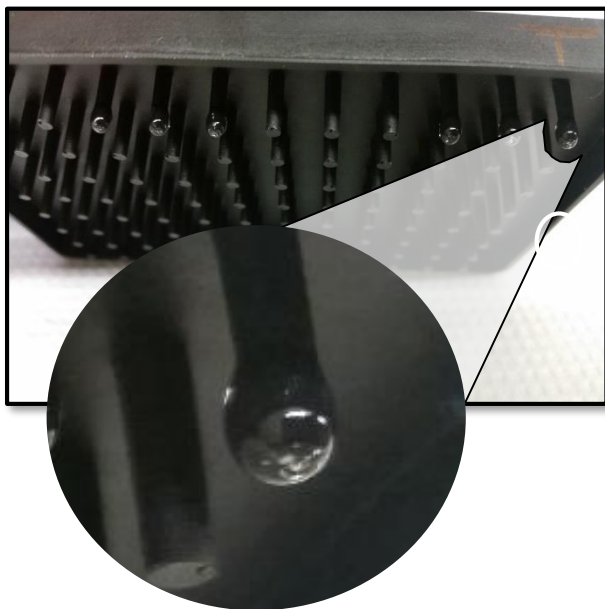
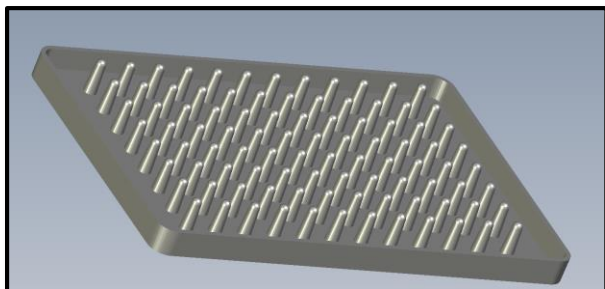
6/10
2/10
0/10
0/10

8/10
5/10
4/10
2/10

10/10
10/10
0/10
0/10

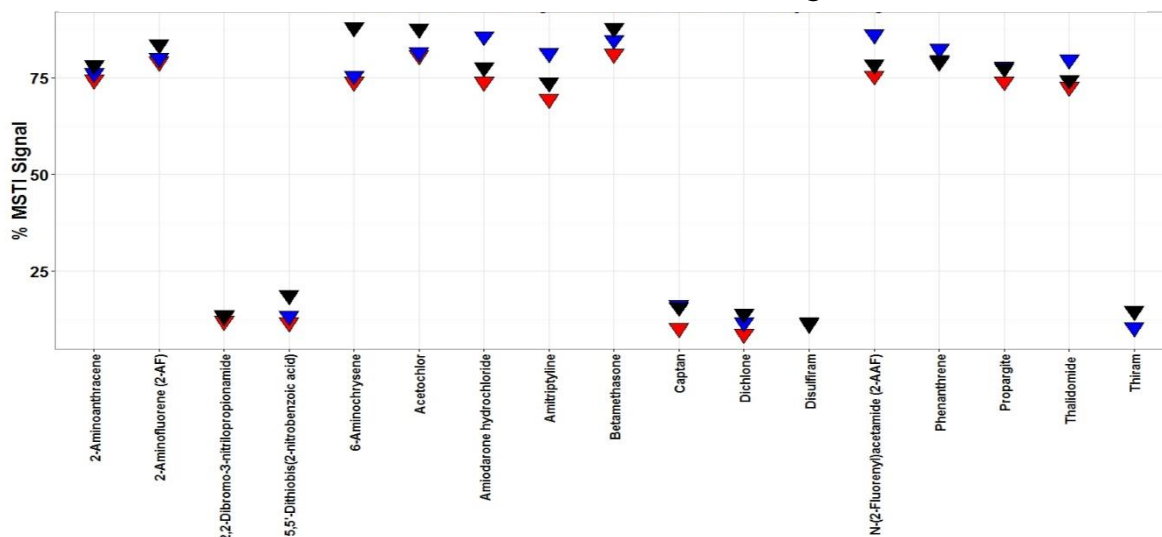
0.80
0.57
0.13
0.07

Challenges: Retrofitting Assays with Metabolic Activity

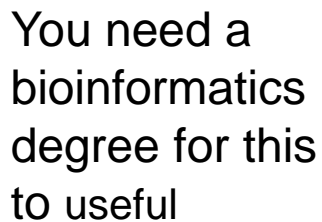


Cyp activity over time of encapsulated S9 fraction

MSTI Assay - An increase in electrophilicity was detected as a decrease in the fluorescent signal.



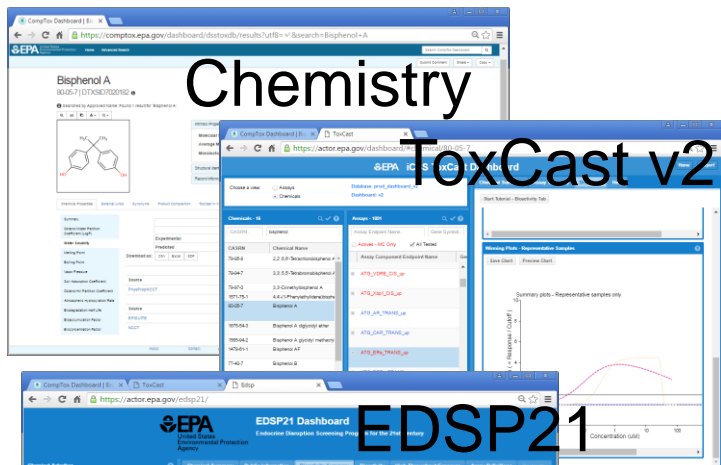
2013 Dashboard with Limited Search, Visualization, and Export Functionality



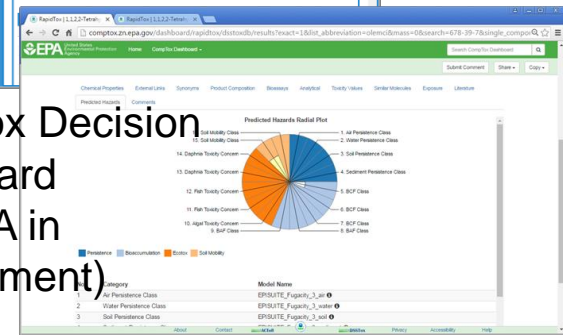
“Better, but still difficult to really get what you want without help from NCCT”



Chemistry ToxCast v2

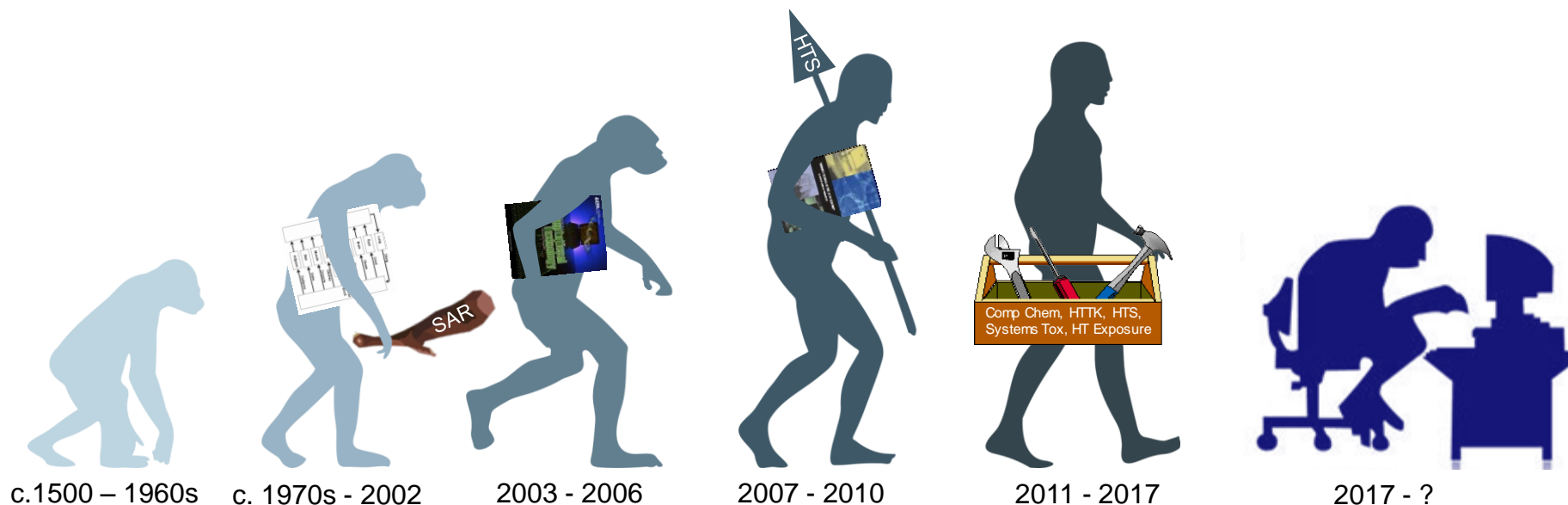


RapidTox Decision Dashboard (HTP RA in development)



Building data, analyses and visualization tools that allow for more rapid development of specific Decision Support Dashboards

Next Phase... Evolution Towards a Truly Predictive Science



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EPA's National Center for Computational Toxicology

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External Stakeholders

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CalEPA
EDF
EU Joint Research Center
European Chemicals Authority

