



Update on EPA's Endocrine Disruptor Screening Program

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1996 Legislative Mandate

1996 Federal Food, Drug and Cosmetic Act, section 408(p)

Requires the U. S. EPA to develop a screening program using appropriate validated test systems and other scientifically relevant methods to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effect as the Administrator may designate.

1996 Safe Drinking Water Act Amendments, section 1457

Testing of chemical substances that may be found in sources of drinking water, if substantial human populations may be exposed.



1998 Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC)

EDSTAC Key Recommendations:

- Expand Protection to Include Human Health and Wildlife
- Include Estrogen, Androgen and Thyroid Pathways
- Develop a Two-Tiered Screening and Testing Program:

EDSTAC Conceptual Framework:



Tier 1 Screening for *Potential* to Interact

Potential to interact with the estrogen, androgen or thyroid hormone systems

Tier 2 Testing to determine Interaction with the endocrine system

If endocrine-mediated adverse effects then quantify dose-response relationship



EDSP Implementation

- EPA has reviewed ~500 studies required on EDSP List 1
- Initiated WOE evaluations of 52 chemicals for estrogen, androgen and thyroid (E, A & T) interactions
 - Agency currently reviewing Tier 1 data and other scientifically relevant information (OSRI)
 - Initial WOE evaluation of 12 chemicals completed



Tier 1 Screening Assays

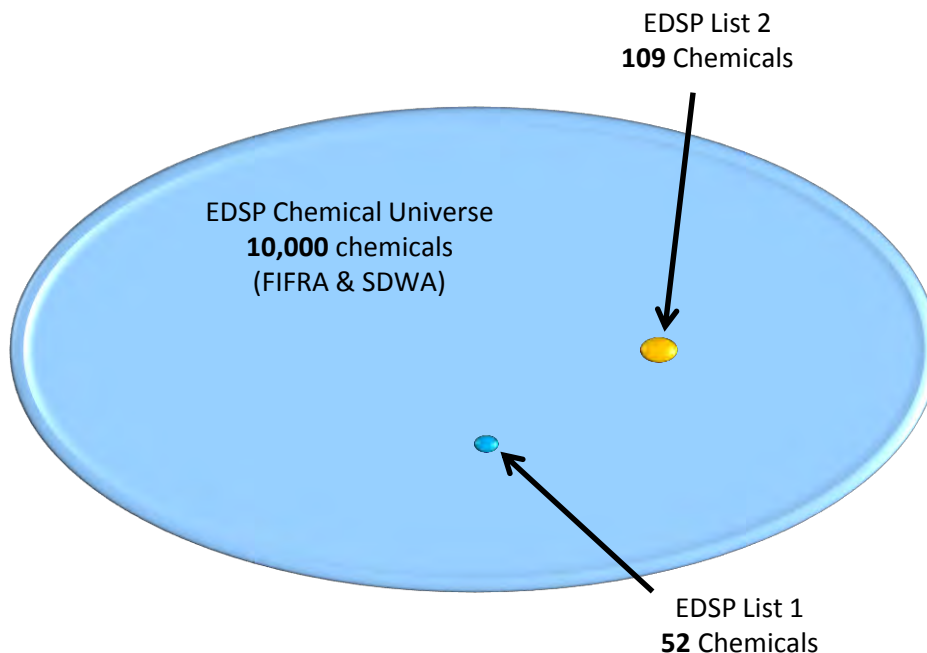
					Steroid Synthesis			
	E	E-	A	A-	T	E	HPG	HPT
<i>In vitro</i>								
ER Binding	X	X						
ER Transcriptional Activation	X							
AR Binding			X	X				
Steroidogenesis (H295R)					X	X		
Aromatase (Recombinant)						X		
<i>In vivo</i>								
Uterotrophic	X							
Hershberger			X	X				
Pubertal male			X	X	X		X	X
Pubertal female	X	X				X	X	X
Fish Reproductive Screen	X	X	X	X	X	X	X	
Amphibian Metamorphosis								X



EDSP Implementation

■ EDSP List 2 Chemicals

- Draft EDSP List 2 chemicals for Tier 1 screening released (2010)
- EPA issued revised EDSP List 2 with 109 chemicals (2013)
 - Selection based on registration review schedule of 41 pesticidal chemicals and 68 drinking water contaminants





Evolution of the EDSP

- Based on current pace it could take decades to screen all 10,000 chemicals for potential to interact with the endocrine system
- Recent advances in computational toxicology herald an important “evolutionary turning point” and an accelerated pace of screening and testing
- To address thousands of chemicals for potential to interact with the endocrine system, we must implement a more strategic approach to prioritize chemicals for targeted screening



Utility of Computational Toxicology

- Rapidly screen chemicals and use predictive models to evaluate thousands of chemicals for potential risk to human health and environment
- Increase capacity to prioritize, screen and predict chemical toxicity and exposure
- Overcome throughput limitations of traditional chemical toxicity testing, augmenting current data sources



Utility of Computational Toxicology

- Eventual replacement of some existing tests with non-animal alternatives
- Partner across EPA, with other federal agencies, state agencies, industry and non-governmental organizations to validate and apply tools
- Provide open access to data and adverse outcome pathways



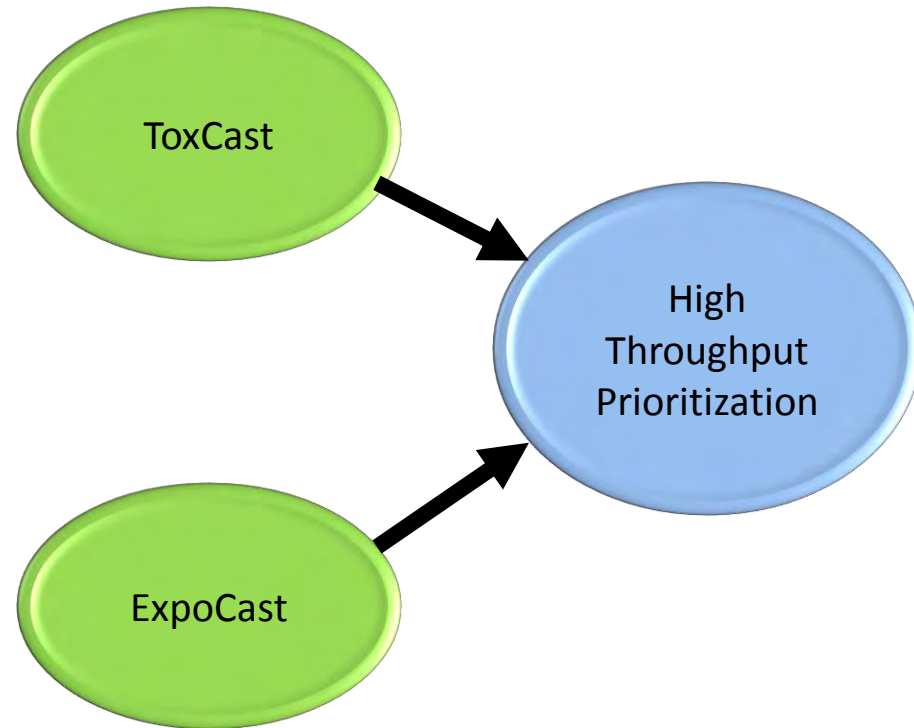
Screening and Prioritization

■ ToxCast

- Expanding use of CompTox (Phys-chem properties, QSARS, etc.) to support screening and prioritization
- Transparent and collaborative

■ ExpoCast

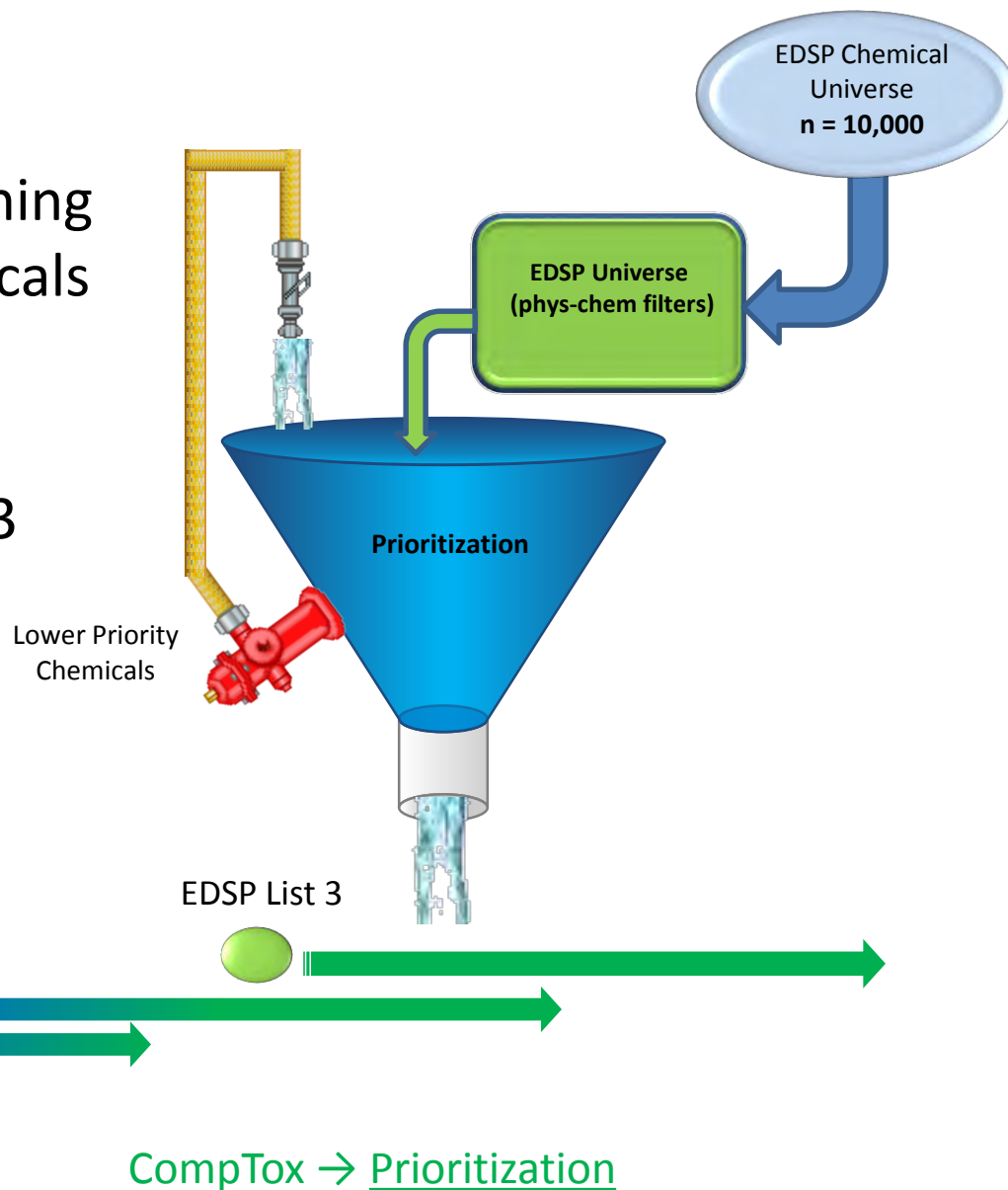
- Rapid exposure estimation based on readily available chemical use and production data
- Use toxicokinetics to bridge *in vitro*, concentration-based ToxCast data to *in vivo*, dose-based Exposures from ExpoCast





Prioritization

- Prioritize and target screening and testing of List 2 chemicals using new CompTox tools
- Prioritization of 10,000 chemical universe for List 3

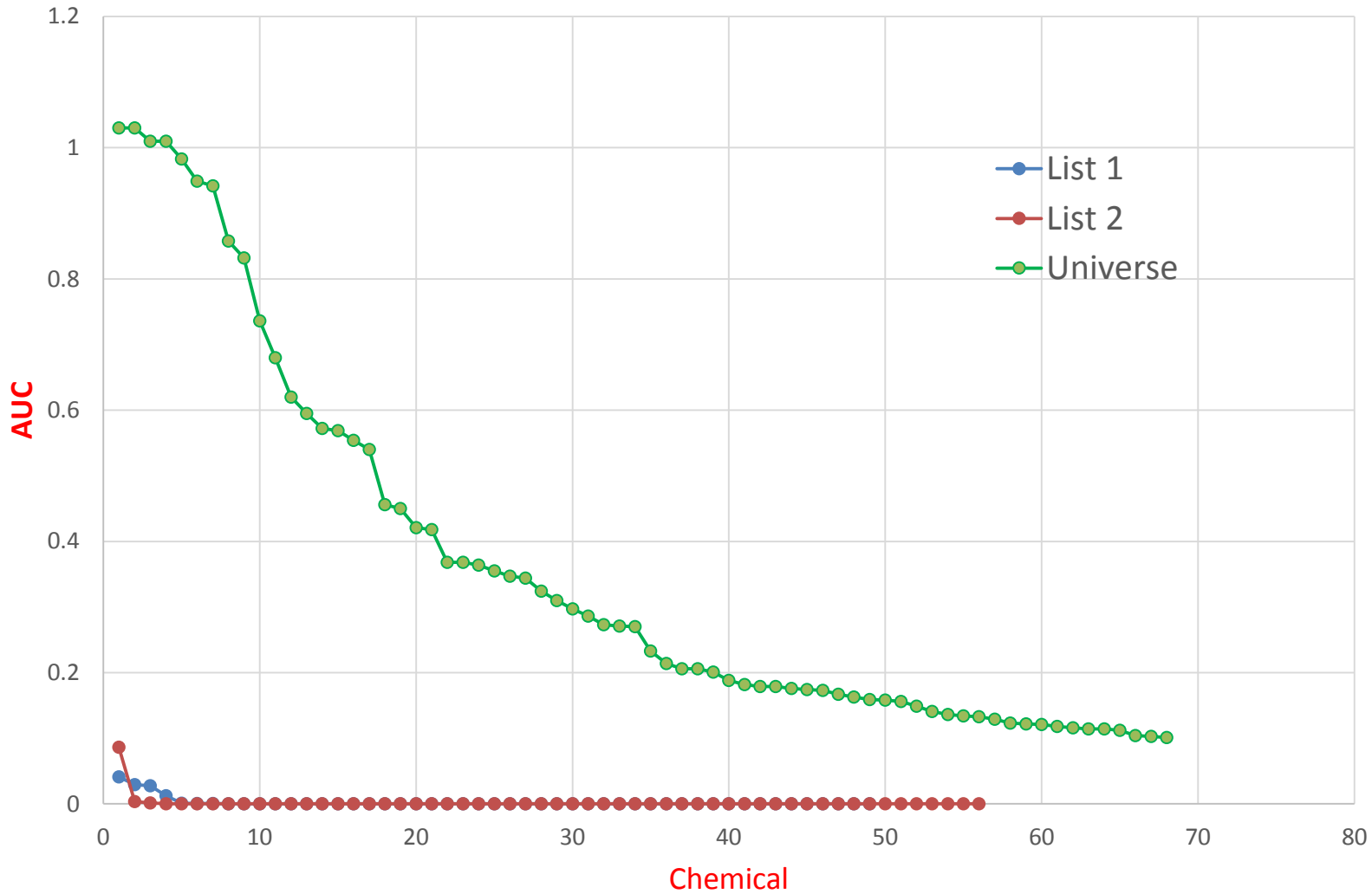


Exposure-based lists

CompTox → Prioritization

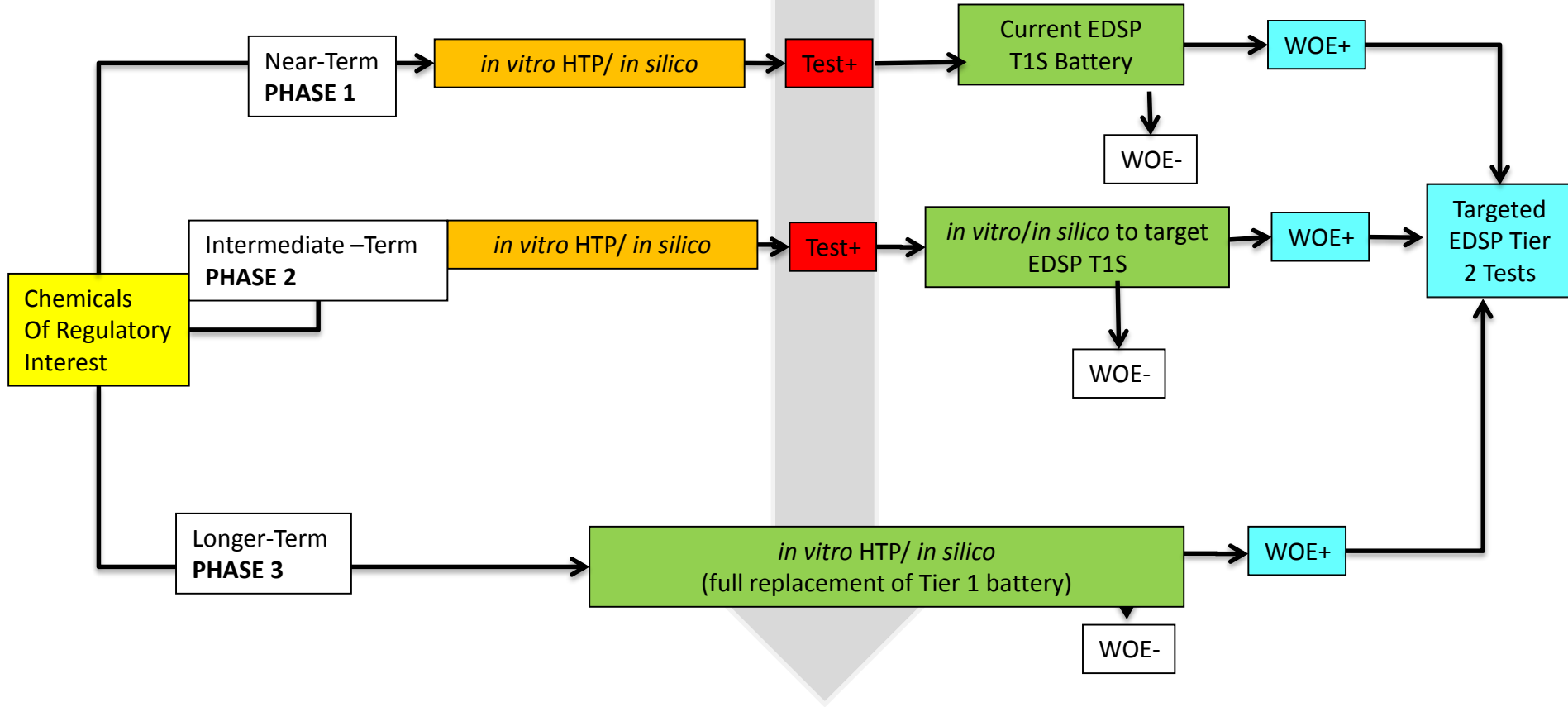


ToxCast Estrogen Activity



The universe of chemicals passes through each version of the HTP/*in silico* pipeline to evaluate chemicals in refined tests, for new pathways, to evaluate, improve, and validate methods.

EPA Research provides basis for improving the suite of assays and models to advance chemical prioritization and screening



Building Confidence: “Learn by Doing”
Phase 1: Incorporates HTP/*in silico* prioritization methods
Phase 2: Run subset of current T1S assays indicated by HTP and *in silico* predictions
Phase 3: Full replacement of EDSP T1S Battery





Current Status of EDSP Prioritization and Screening

- 52 List 1 chemicals with complete Tier 1 datasets undergoing weight-of-evidence determination of EAT endocrine activity and possible Tier 2 testing
- 109 List 2 chemicals going through OMB review for Tier 1 screening
- EDSP Universe of chemicals being prioritized for EDSP screening using computational toxicology and other tools
- Scientific Advisory Panel peer reviews being planned:
 1. Exposure Prediction Models
 2. Risk-Based Prioritization



New Science: Non-Monotonic Dose Response (NMDR) Relationships

- EPA NMDR State of Science (SOS) White Paper reviewed by NRC – released May 2014
- NRC recommendations:
 - Exploring the impact of NMDR relationships on chemical safety assessments
 - Actions:
 - Consider key recommendations and develop a plan for next steps
 - Select chemical case studies of pathways discussed in EPA NMDR SOS White Paper
 - Assess potential impact of key findings to regulatory programs