19 Years of the Endocrine Disruptor Screening Program

David J. Dix, Ph.D.
Director, Office of Science Coordination and Policy
Office of Chemical Safety and Pollution Prevention
Email: dix.david@epa.gov

NCAC SOT Meeting
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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 information to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other 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 a substantial human population may be exposed to such substance.

1998 Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC)

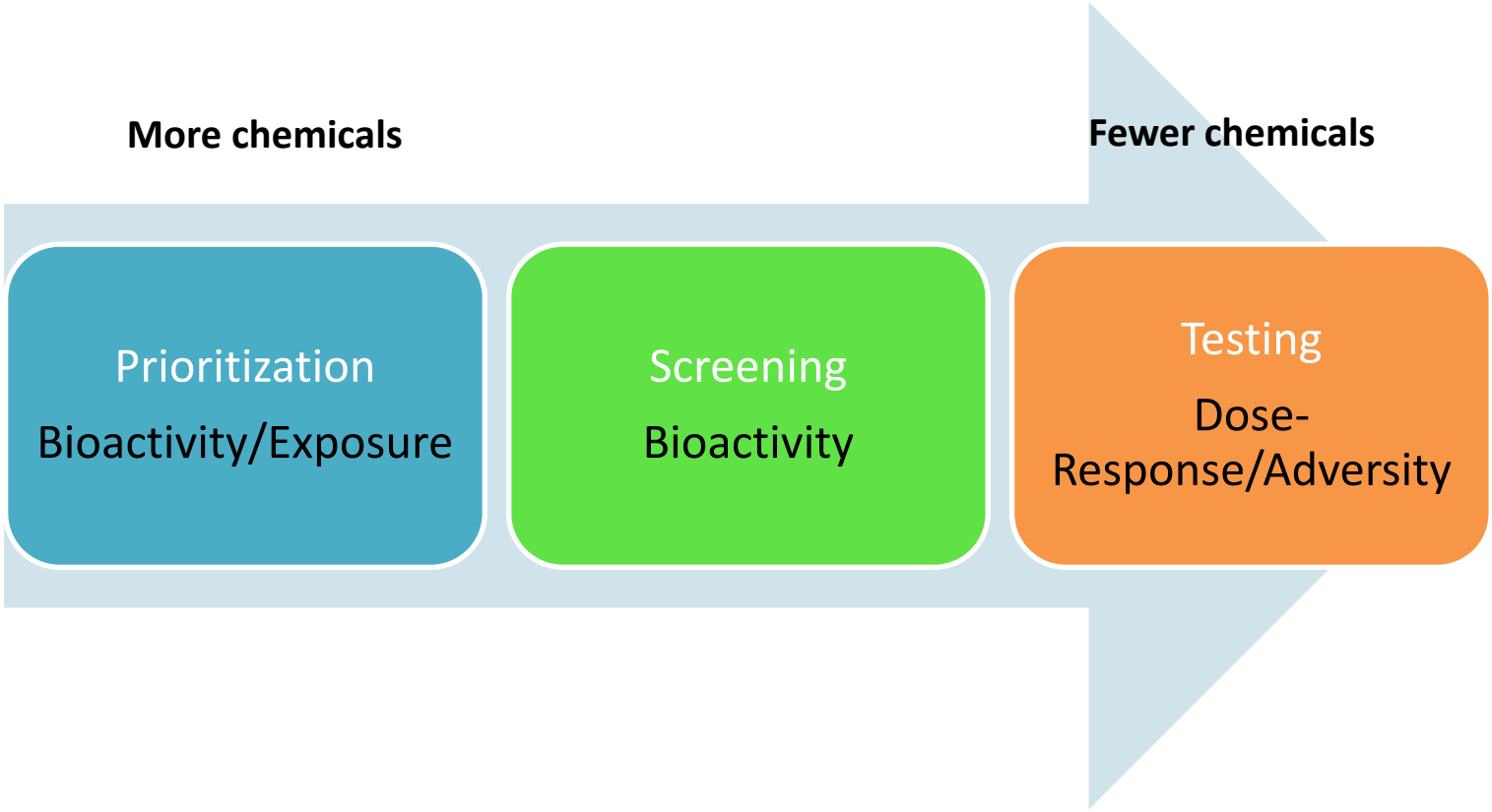
EDSTAC Key Recommendations:

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

EDSTAC Conceptual Framework:

- **Prioritization**
- **Tier 1 Screening for Endocrine Activity**
- **Tier 2 Testing to Determine Adverse Effects**

EDSP Prioritization, Screening & Testing



Prioritization and Screening for bioactivity
Testing for dose-response and adverse effects

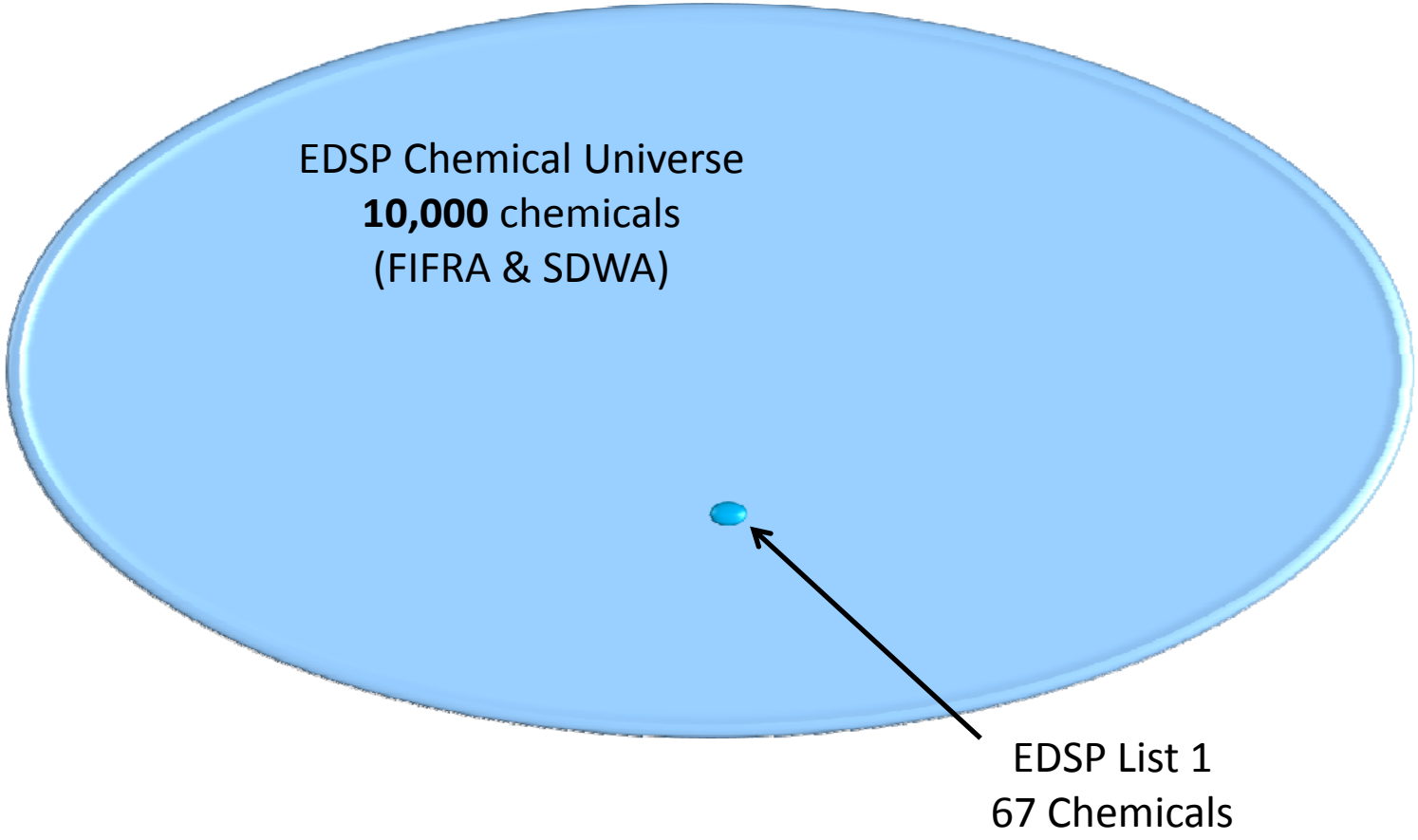
Tier 1 Screening Assays

					Steroid Synthesis			
	E	**E-**	**A**	**A-**	**T**	**E**	**HPG**	**HPT**
In vitro								
ER Binding	X	X						
ER Transcriptional Activation	X							
AR Binding			X	X				
Steroidogenesis (H295R)					X	X		
Aromatase (Recombinant)						X		
In vivo								
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

Tier 2 Tests

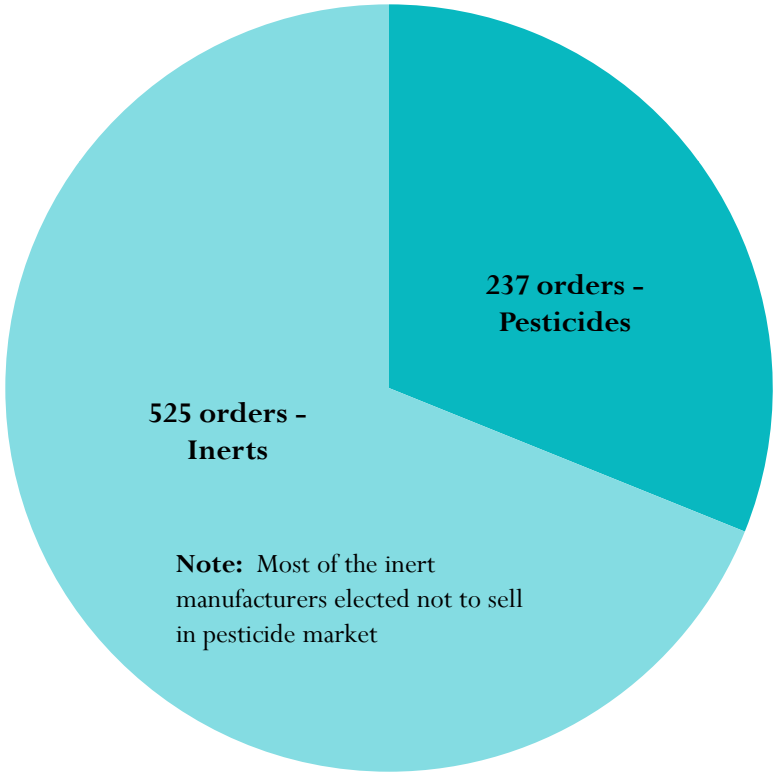
Mammalian two-generation rat (may be replaced by Extended F1-Generation)
Amphibian growth/reproduction (Xenopus)
Fish multi-generation (medaka)

EDSP Implementation To Date

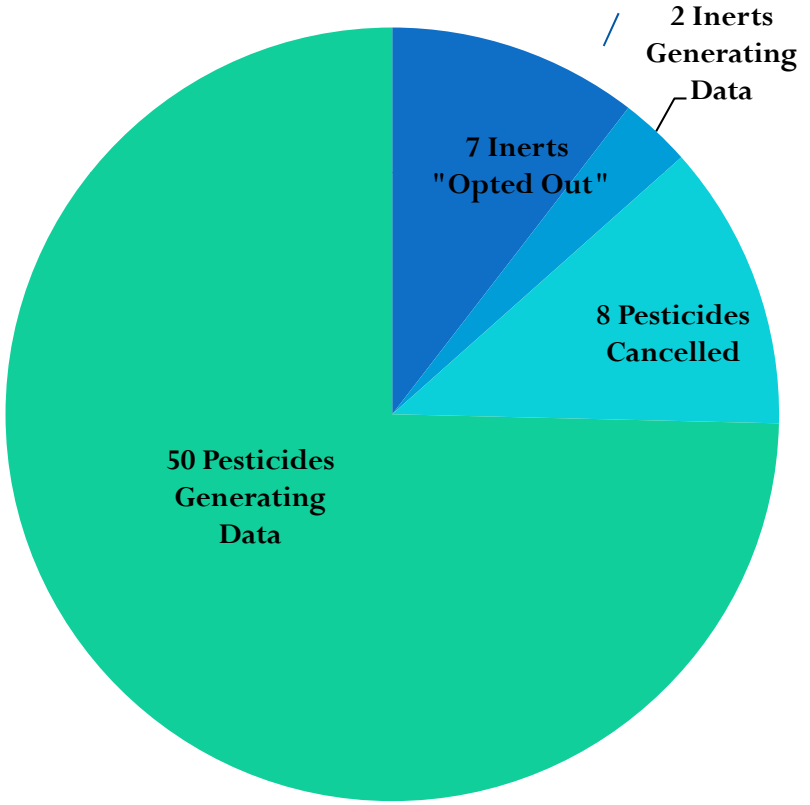


EDSP List 1 Tier 1 Test Orders

762 Orders Issued on 67 Chemicals



General Responses for the 67 Chemicals



EDSP List 1 Process History

Oct 2009-Feb 2010	Jan 2010-Dec 2010	Jan 2012-Oct 2013	Nov 2013–Dec 214	Jan 2015-June 2015
Issued 762 Test Orders for 67 Chemicals	EDRT - OSRI review	Review & Preparation of 504 DERS	Weight of Evidence Assessments 52 Chemicals	Review, Refine, Revise 52 WoEs

Data Review

HED (9 Assays/Chem)
- Aromatase
- Estrogen Receptor
- Androgen Receptor
- ERTA
- Hershberger
- Female pubertal
- Male pubertal
- Steroidogenesis
- Uterotrophic

EFED (2 Assays /Chem)
- Amphibian Metamorphosis
- Fish Short-Term Reproduction

SAP Reviews Related to List 1

May, 2013: Tier 1 Assay/Battery Performance
June, 2013: Tier 2 validation
July, 2013: WoE Approach

Tier 2 Study Recommendations

- **Human Health**
  - Opted to focused studies
    - Comparative Thyroid Assay (CTA)
    - Male reproductive toxicity
    - Studies more focused to assess specific target organ toxicity – Thyroid & Male Reproduction

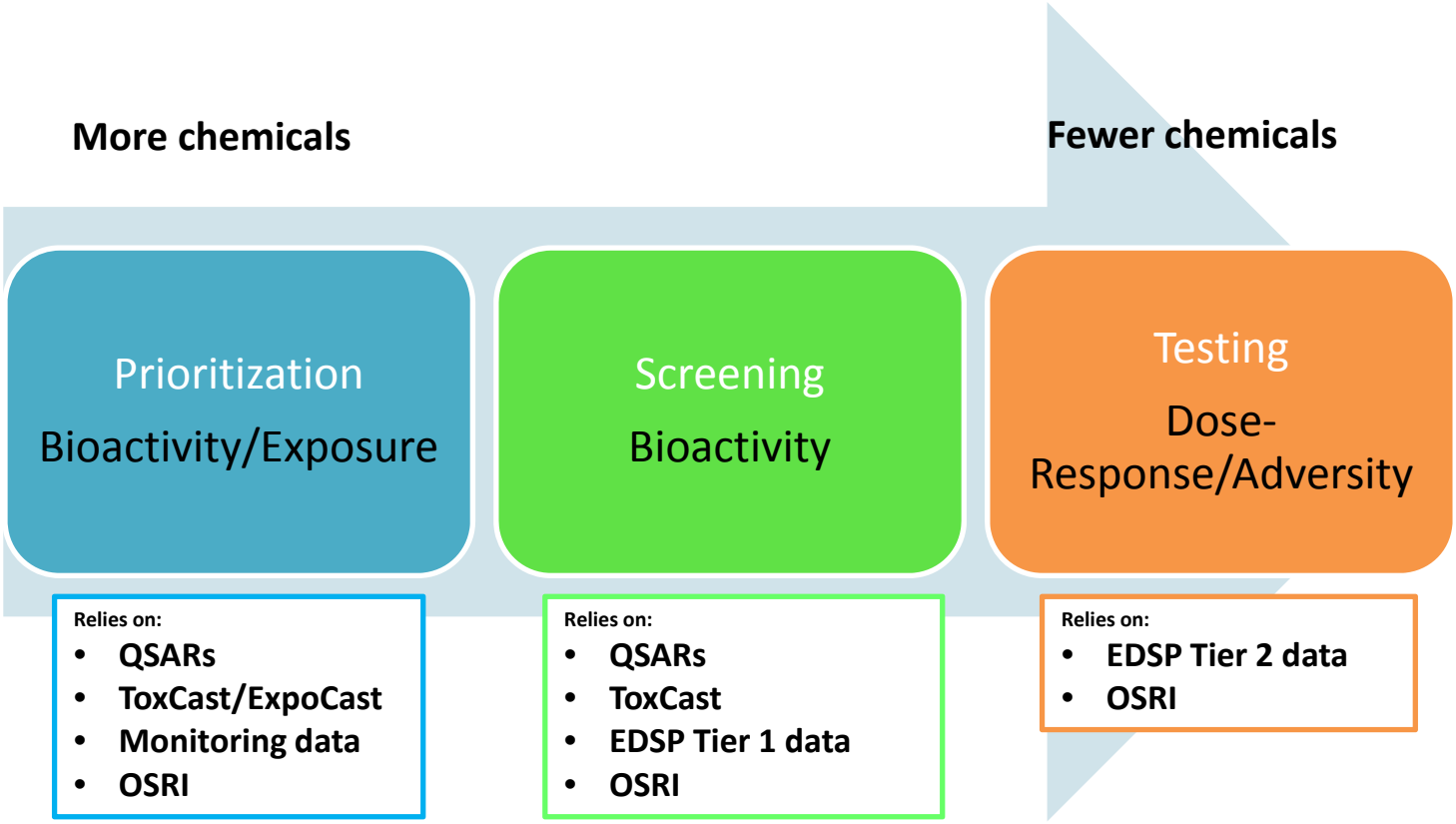
- **Wildlife**
  - T2 Medaka Extended One Generation Reproduction Test (*MEGORT*): 12 chemicals

  - T2 Larval Amphibian Growth and Development Assay (*LAGDA*): 6 chemicals

Evolution of the EDSP

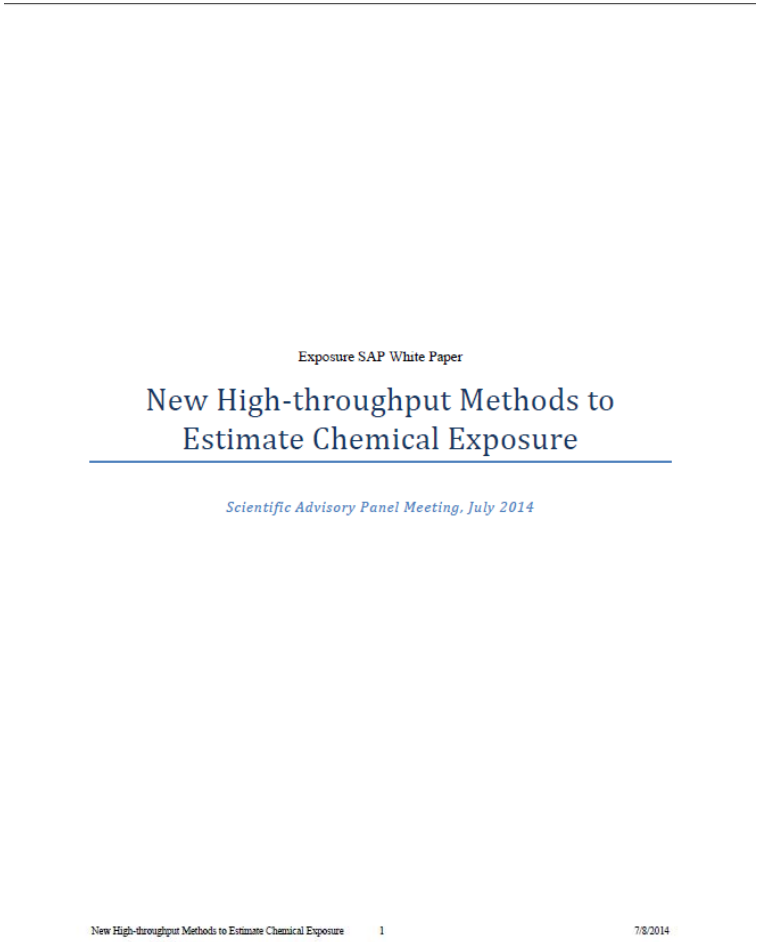
- Based on current pace it could take decades to screen all 10,000 chemicals for potential to interact with the endocrine system
- Recent advances in computational toxicology herald an important “evolutionary turning point” and an accelerated pace of screening and testing
- To address thousands of chemicals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

EDSP Prioritization, Screening & Testing



Prioritization and Screening for bioactivity
Testing for dose-response and adverse effects

Building Scientific Confidence – Peer Review

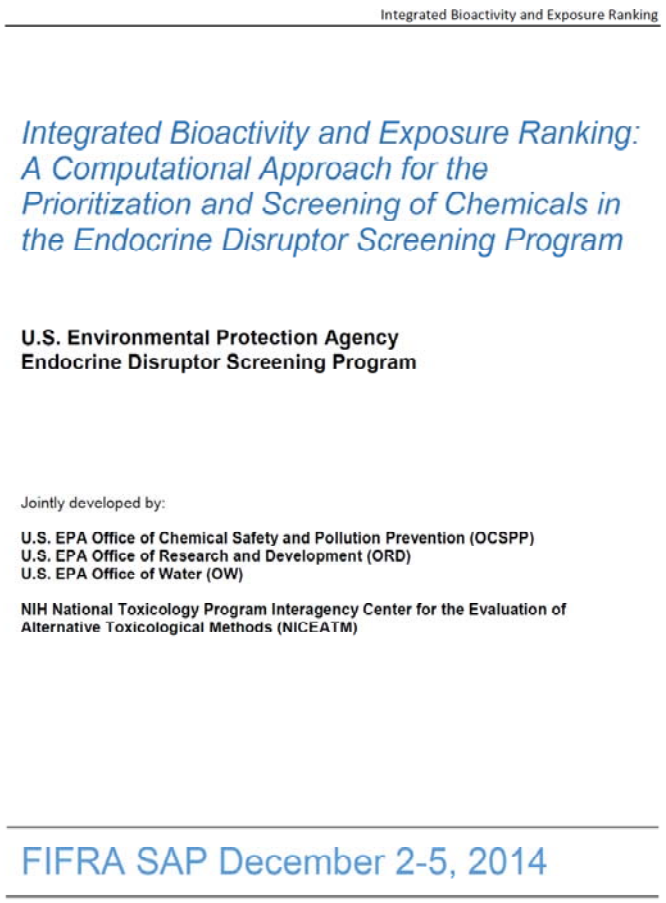


Exposure SAP White Paper

New High-throughput Methods to Estimate Chemical Exposure

Scientific Advisory Panel Meeting, July 2014

New High-throughput Methods to Estimate Chemical Exposure 1 7/8/2014



Integrated Bioactivity and Exposure Ranking

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

Jointly developed by:

U.S. EPA Office of Chemical Safety and Pollution Prevention (OCSPP)
U.S. EPA Office of Research and Development (ORD)
U.S. EPA Office of Water (OW)

NIH National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

FIFRA SAP December 2-5, 2014

http://www.epa.gov/scipoly/sap/meetings/2014/index.html

EPA Solicits Comments on Use of High-Throughput Assays and Computational Tools in Endocrine Disruptor Screening Program

- Federal Register notice describes and solicits comments on how EPA is planning to incorporate scientific advancements and new tools incorporating validated high-throughput assays and a computational model as an alternative for some of the current assays in the EDSP Tier 1 battery.

- The adoption of scientific advancements into the EDSP has been under way and part of the public dialogue about EDSP for several years, and the Agency intends to continue to incorporate in the EDSP new methods involving high-throughput assays and computational toxicology in order to accelerate the pace of screening, add efficiencies, decrease costs and reduce animal testing.

- Currently, EPA has partial screening results for over 1,800 chemicals that have been evaluated using the high-throughput assays and computational model for the estrogen receptor pathway.

- The Federal Register Notice (with information on how to provide comments) can be viewed at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2015-0305-0001.

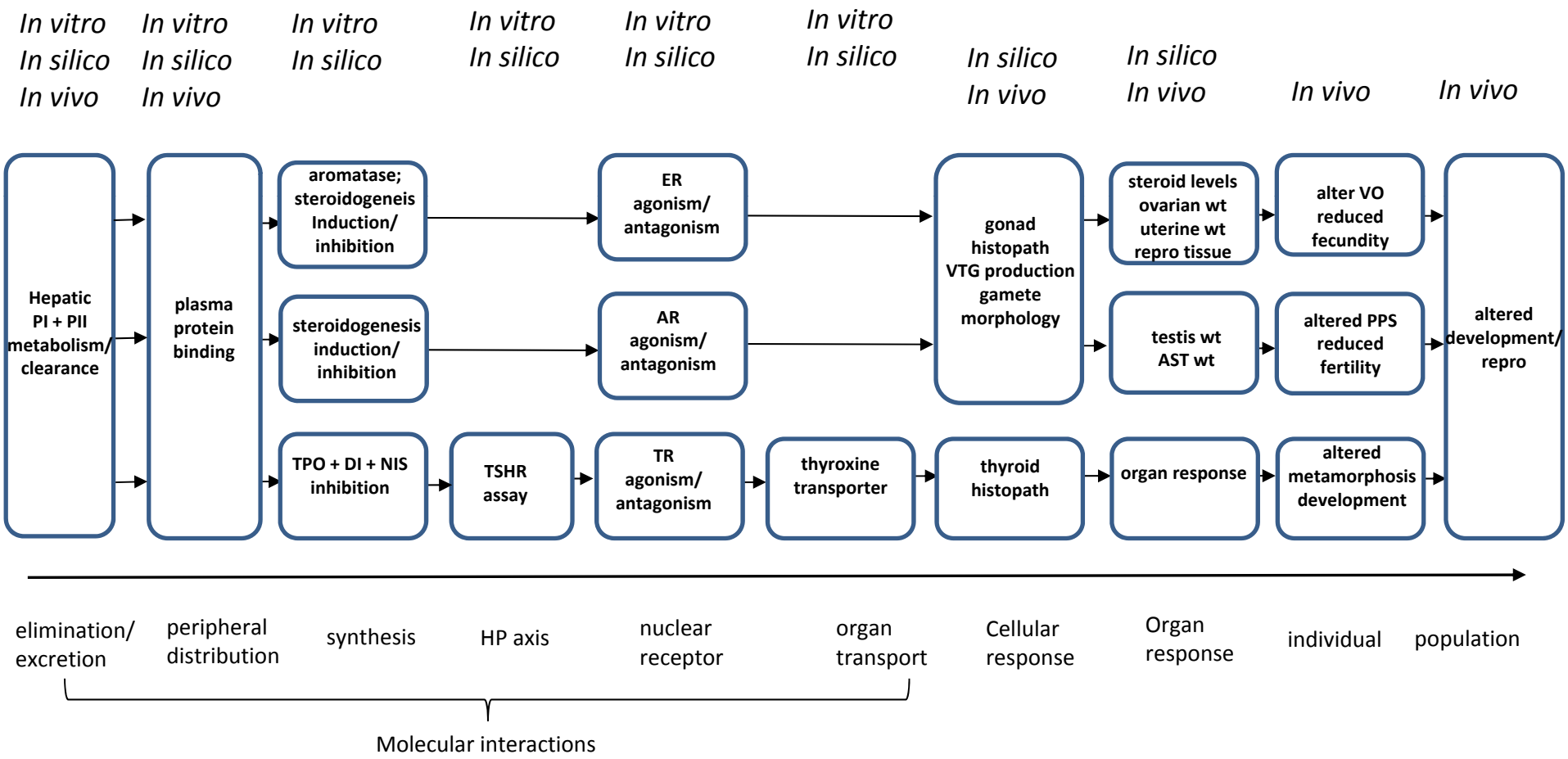
- The press release related to the publishing of this Federal Register Notice can be viewed at http://yosemite.epa.gov/opa/admpress.nsf/d0cf6618525a9efb85257359003fb69d/77377414ba7ebc5885257e68006ea110!OpenDocument.

- More detailed information on the Endocrine Disruptor Screening Program and its use of computational tools: http://www.epa.gov/endo/ or http://www.epa.gov/endo/pubs/pivot.htm.

Evolution of Screening in the EDSP

EDSP Tier 1 Battery of Assays (current)	High Throughput Assays and Computational Model Tier 1 Battery Alternatives
Estrogen Receptor (ER) Binding	ER Model (alternative)
Estrogen Receptor Transactivation (ERTA)	ER Model (alternative)
Uterotrophic	ER Model (alternative)
Female Rat Pubertal	ER, STR , and thyroid (THY) Models (Future)
Male Rat Pubertal	AR, STR , and THY Models (Future)
Androgen Receptor (AR) Binding	AR Model (Future)
Hershberger	AR Model (Future)
Aromatase	STR Model (Future)
Steroidogenesis (STR)	STR Model (Future)
Fish Short Term Reproduction	ER, AR, and STR Models (Future)
Amphibian Metamorphosis	THY Model (Future)

Endocrine Pathways



Summary

- Pivot to using high throughput and computational methods in EDSP
- Computational tools have been peer-reviewed by SAP and for publication
- Endocrine pathway models will continue to be revised and improved as more data are available (ER, AR, thyroid…)
  - Provides bioactivity predictions for thousands of chemicals
- Allows resources to be focused on chemicals more likely to have endocrine effects
  - List 1 chemicals have limited estrogen and/or androgen receptor-mediated bioactivity
  - Prioritizes chemicals based on bioactivity (and exposure)
  - Provides alternative to current Tier 1 screening
- Multi-century project becomes multi-year