PPDC Meeting: Endocrine Disruptor Screening Program Update

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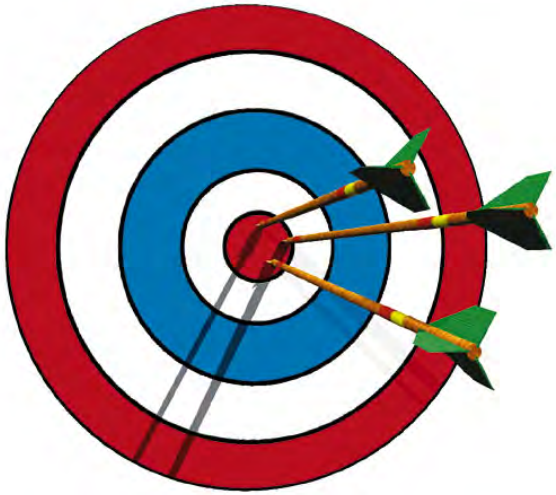
Office of Science Coordination and Policy

State of the Science Review

- Background: Mission of the Endocrine Disruptor Screening Program
  - FFDCA and SDWA 1996
- FACA process: Key recommendations of the Endocrine Disruptor Screening and Testing Advisory Committee, 1998
- External peer review of the current state of the science: 2013 FIFRA Scientific Advisory Panel Reviews
- Advancement of Science and Evolving the EDSP21 Program: Beyond the “Tipping Point”.

EDSP Mission



To protect public health and wildlife by screening and testing chemicals and taking appropriate actions for those chemicals that are found to have endocrine effects.

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.

Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), 1998

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

Tier 1 Screening Battery, 2008

In vitro
Estrogen Receptor (ER) Binding
Estrogen Receptor Transcriptional Activation Assay (ERTA)
Androgen Receptor (AR) Binding
Steroidogenesis
Aromatase
In vivo
Uterotrophic (rat)
Hershberger (rat)
Pubertal Female (rat)
Pubertal Male (rat)
Amphibian Metamorphosis Assay (frog)
Fish Short-Term Reproduction Assay (fish)

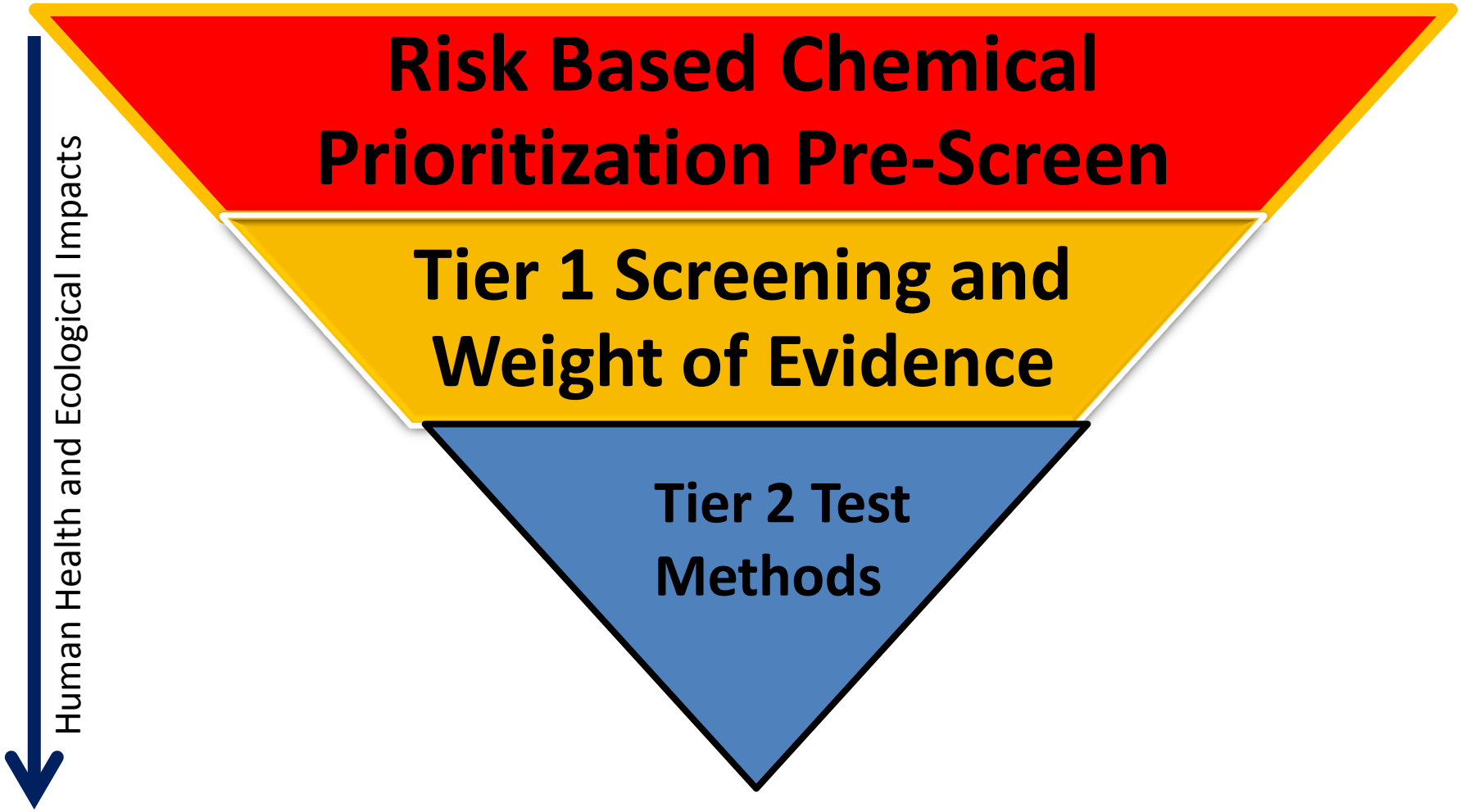
Tier 1 Screening Assays

					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

Proposed Tier 2 Test Methods

Mammalian - Validated
Mammalian Two-Generation Reproduction (Rat)
Extended One Generation Reproduction (Rat)
Ecological – Peer Reviewed
Avian Multi-Generation Reproduction (Japanese quail)
Larval Amphibian Growth and Development (Xenopus laevis)
Fish Multi-Generation Reproduction (Medaka)
Invertebrate Multi-Generation Reproduction (Mysid and Copepod)

Conceptual Framework: Strategic Testing Approach



EDSP Timeline Summary

Test Method Validation Procedures

1999 EPA established the EDSP

2008 Validated eleven Tier 1 assays

2009 Issued initial test orders for Tier 1 assays for 67 pesticide chemicals

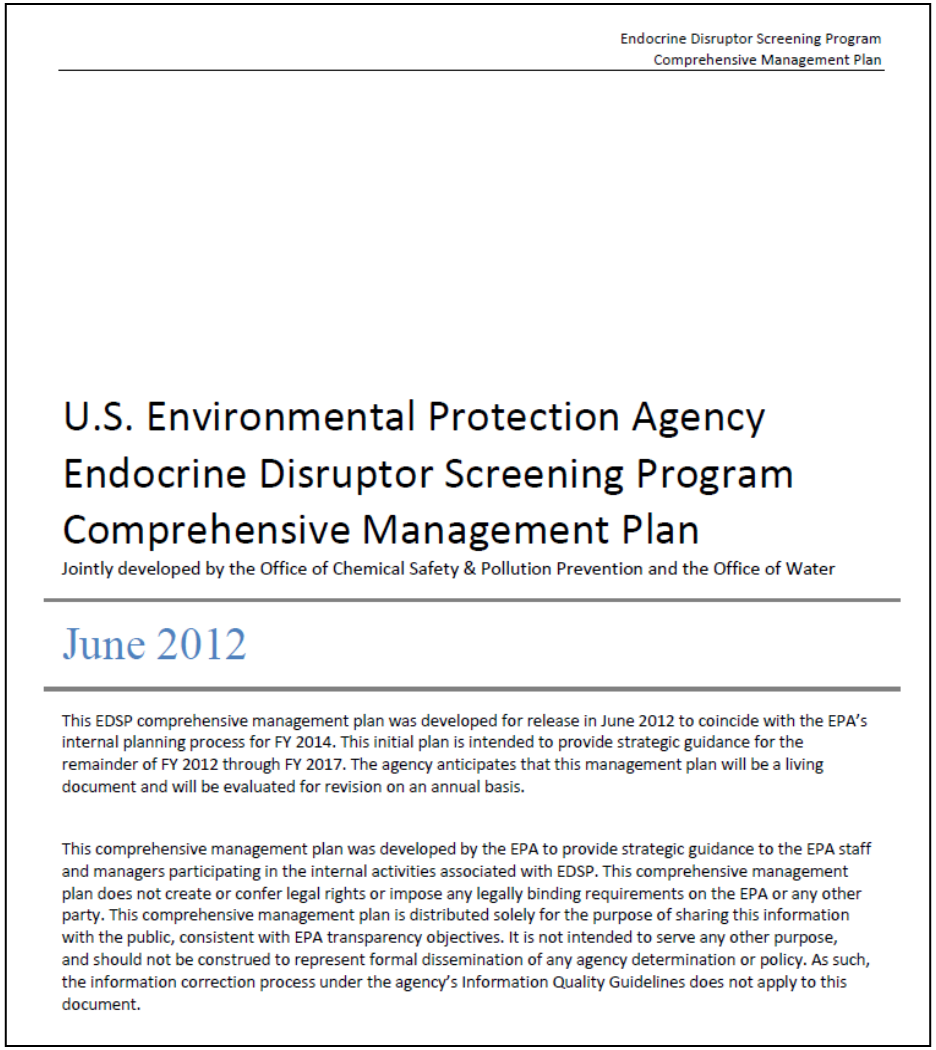
2010 Draft List 2 Chemicals for Tier 1

2011 Tier 1 Data Submitted to EPA; weight of evidence guidance document and EDSP21 Work plan

2012 **EDSP Comprehensive Management Plan**

2013 **Scientific Advisory Panels and Information Collection Requests (List 1, List 2 and Tier 2)**

Comprehensive Management Plan, 2012



U.S. Environmental Protection Agency
Endocrine Disruptor Screening Program
Comprehensive Management Plan

Jointly developed by the Office of Chemical Safety & Pollution Prevention and the Office of Water

June 2012

This EDSP comprehensive management plan was developed for release in June 2012 to coincide with the EPA's internal planning process for FY 2014. This initial plan is intended to provide strategic guidance for the remainder of FY 2012 through FY 2017. The agency anticipates that this management plan will be a living document and will be evaluated for revision on an annual basis.

This comprehensive management plan was developed by the EPA to provide strategic guidance to the EPA staff and managers participating in the internal activities associated with EDSP. This comprehensive management plan does not create or confer legal rights or impose any legally binding requirements on the EPA or any other party. This comprehensive management plan is distributed solely for the purpose of sharing this information with the public, consistent with EPA transparency objectives. It is not intended to serve any other purpose, and should not be construed to represent formal dissemination of any agency determination or policy. As such, the information correction process under the agency's Information Quality Guidelines does not apply to this document.

Comprehensive Management Plan

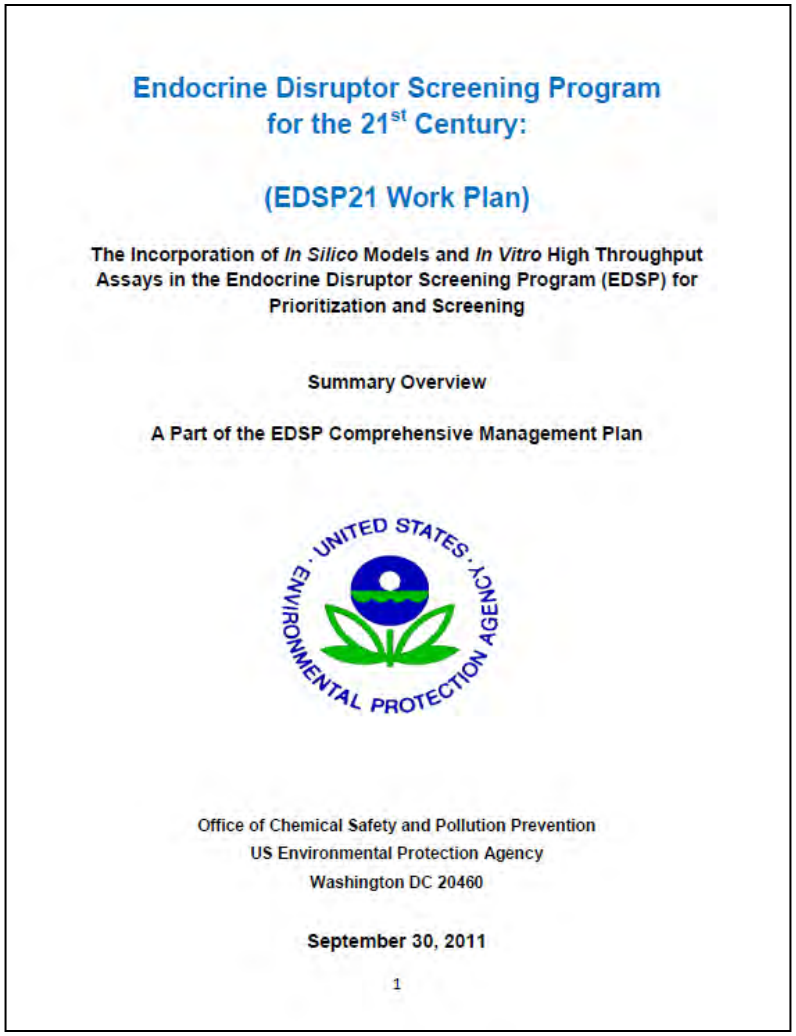
- Issued on June 28, 2012 in response to the EPA OIG recommendations in 2010/11
- Provides strategic guidance to EPA staff and managers for a 5-year time horizon
- Not intended to establish any policy or procedures or impose any requirements.
- Living document that will be evaluated for revision on an annual basis

EDSP Key Milestones in 2013

Fiscal Year	EDSP Activity	Duration of Activity
2013	Chemical prioritization using computational toxicology	2013
2013	Completion of data reviews of initial Tier 1 data and weight of evidence reviews	2014
2013	FIFRA SAP external peer review of Tier 1 assay, battery and weight of evidence determinations	2013-2014
2013	Tier 2 Inter-laboratory test methods Validation	2013-2014
2013	Issuance of List 2 chemicals, Tier 1 test orders	2013-2016*

*Note: Dependent on finalization of List 2 and associated policies and procedures

EDSP21 Work Plan, September 2011



Endocrine Disruptor Screening Program
for the 21st Century:

(EDSP21 Work Plan)

The Incorporation of *In Silico* Models and *In Vitro* High Throughput Assays in the Endocrine Disruptor Screening Program (EDSP) for Prioritization and Screening

Summary Overview

A Part of the EDSP Comprehensive Management Plan

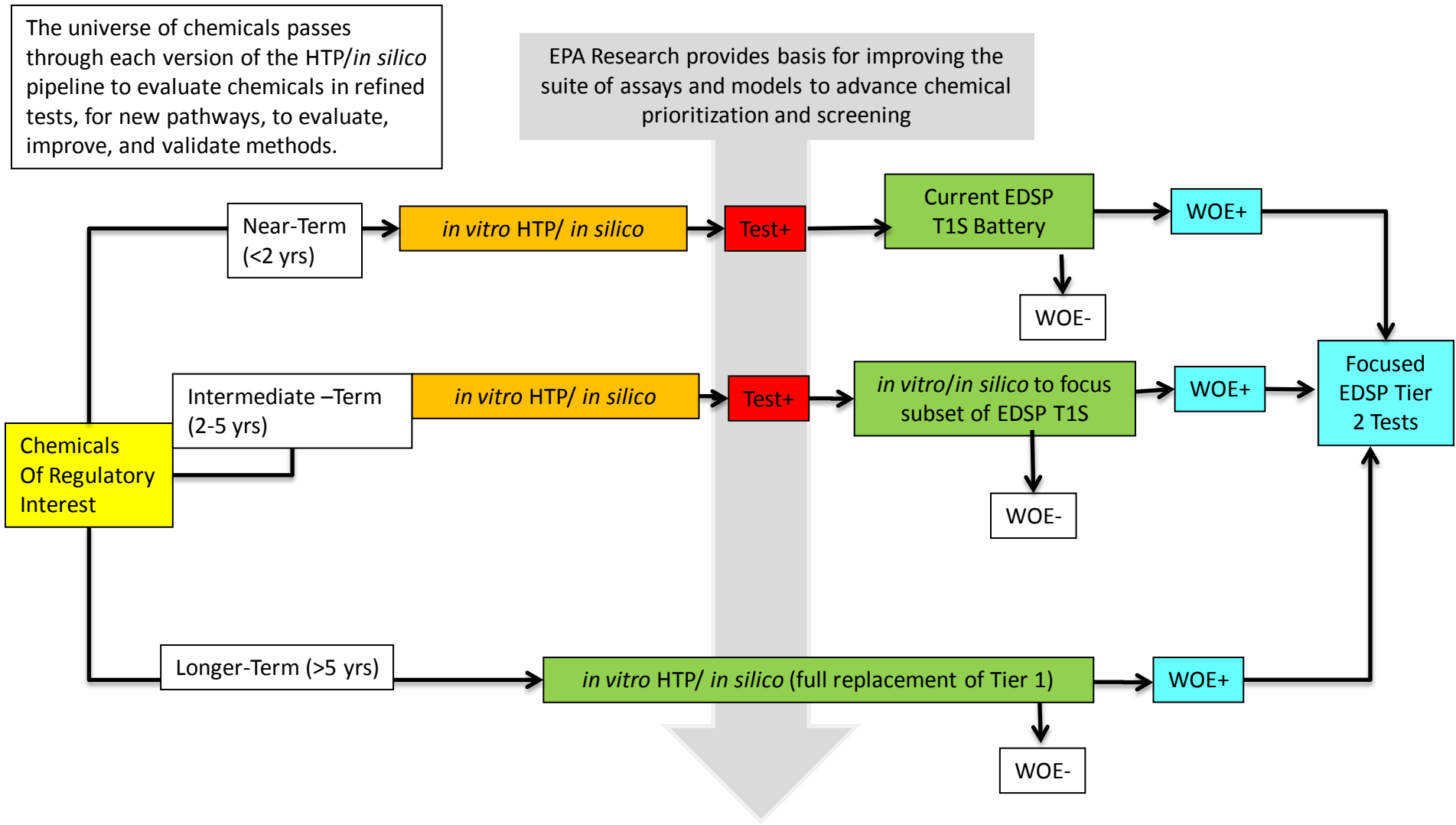
Office of Chemical Safety and Pollution Prevention
US Environmental Protection Agency
Washington DC 20460

September 30, 2011

1

" Punctuated Evolution": *Accelerated* Pace

- Based on our current pace and trajectory, it could take decades to screen all 10,000 chemicals for potential to interact with the endocrine system.
- Recent advances in computational toxicology are heralding an important "evolutionary turning point" and may ignite an accelerated pace of screening and testing.
- To address thousands of chemicals for potential to interact with the endocrine system, we must begin developing a more strategic approach to prioritize chemicals for screening.



Chemical Prioritization

Includes , registration review timeline, physico-chemical properties, exposure estimates, *in vitro* assays and computer models (QSAR, expert systems, systems biology models).

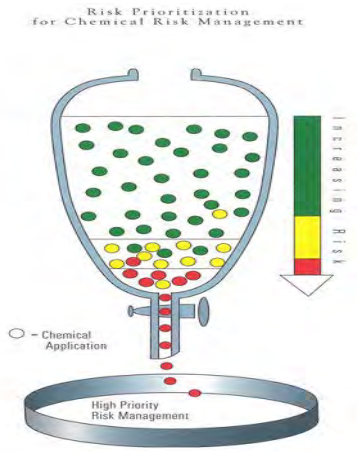
Screening Decisions

Near-Term: Incorporates HTP/*in silico* prioritization methods

Intermediate-Term: Run subset of current T1S assays indicated by HTP and *in silico* predictions

Longer-Term: Full replacement of EDSP T1S Battery

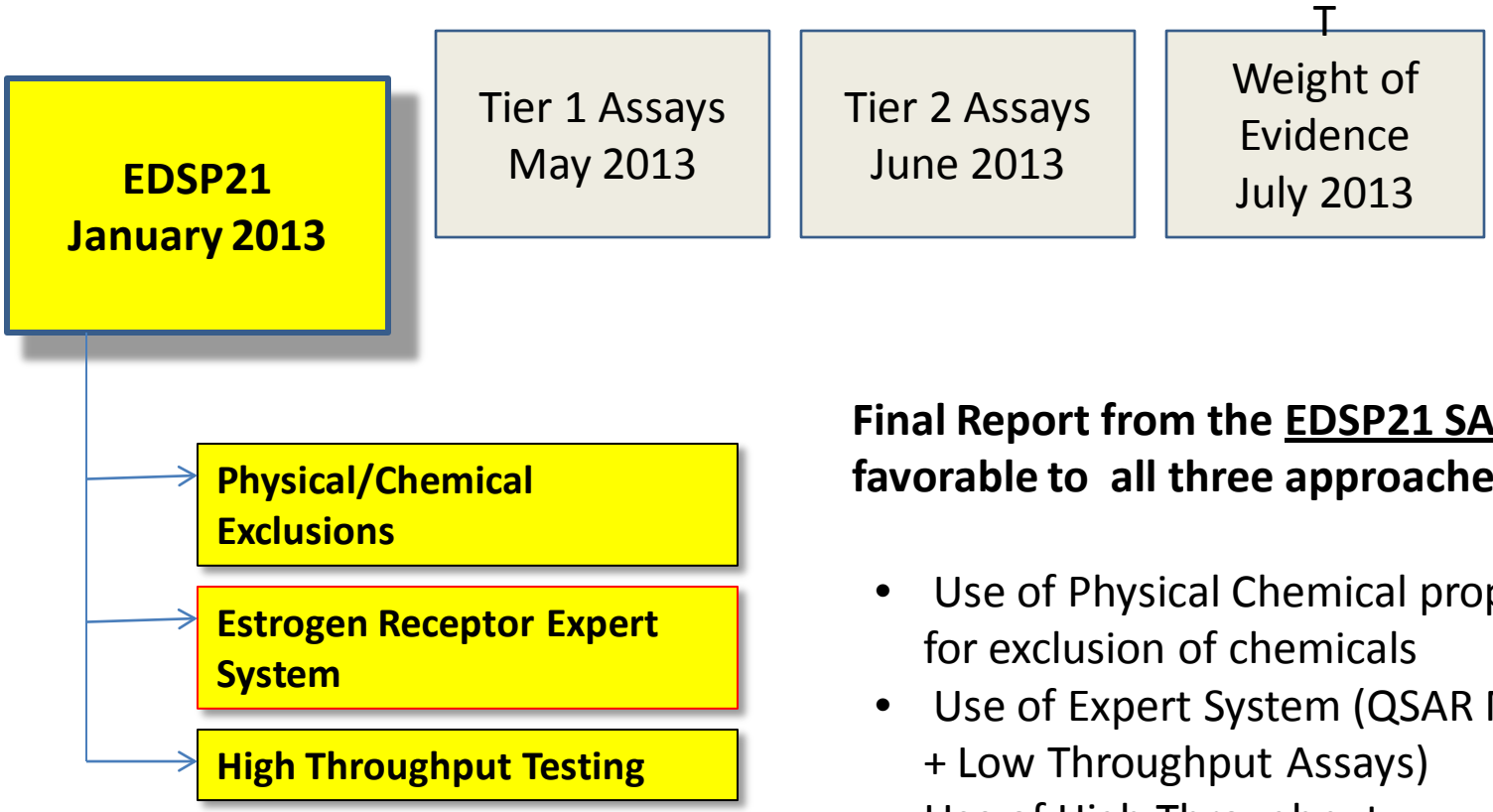
Chemical Prioritization



- Consideration of multiple data streams:
  - HTP assays for estrogen, androgen and thyroid
  - Inherent chemical properties
  - Modeling predictions (e.g., QSAR and expert systems)
  - Exposure Data considered in a risk based prioritizaion method
  - Data from structural analogs (read across)
  - Toxicity pathway based and anchored by biological mechanistically based understanding

*Figure taken from *1996, Chemical Manufacturers Association Product Risk Management Strategy Overview*

Scientific Advisory Panel Meetings 2013



Final Report from the <u>EDSP21 SAP</u> favorable to all three approaches:

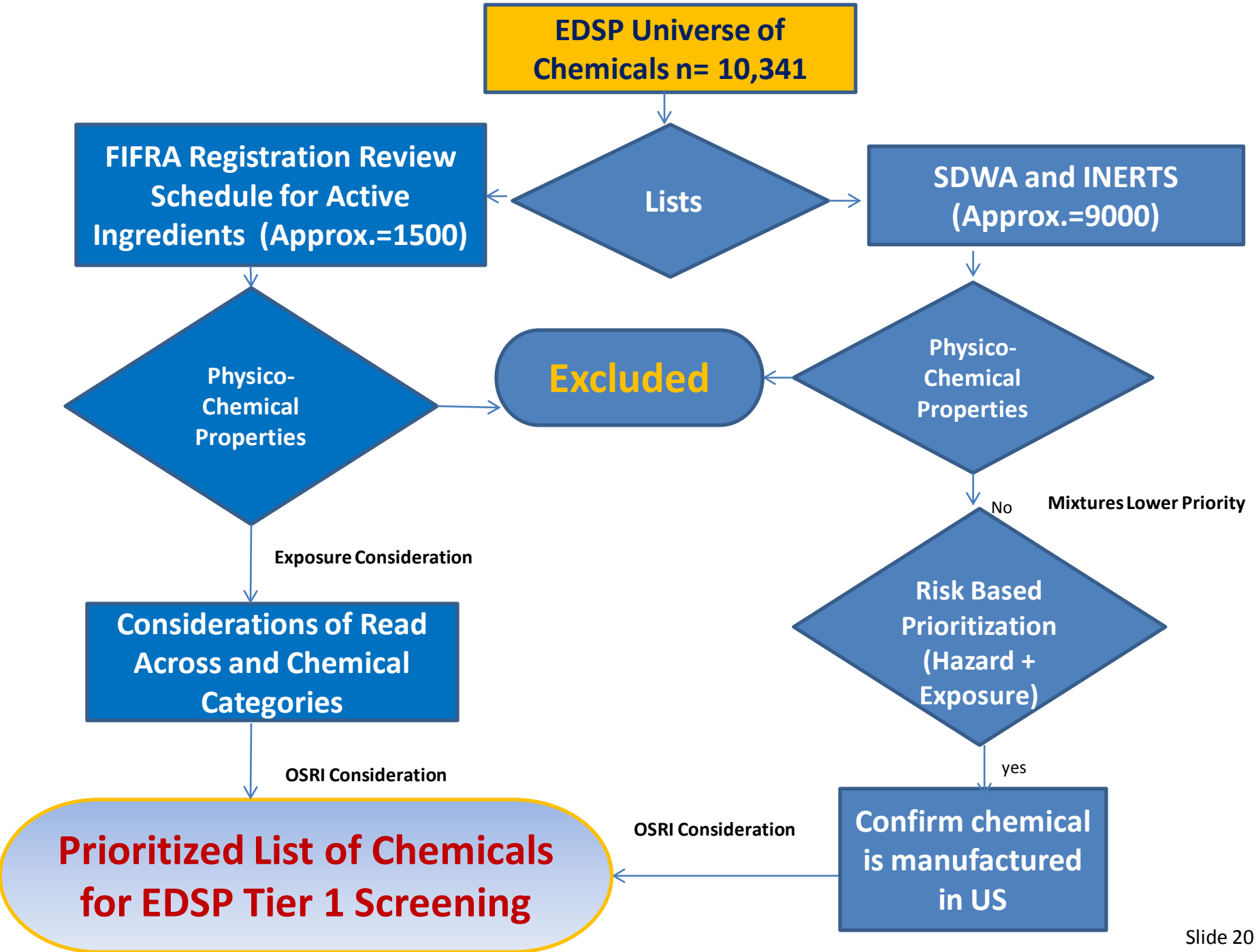
- Use of Physical Chemical properties for exclusion of chemicals
- Use of Expert System (QSAR Model + Low Throughput Assays)
- Use of High Throughput ToxCast Assays

Chemical Prioritization: FIFRA SAP January 29-31, 2013

- Focus and Objective:

  1. Prioritization of the universe of chemicals for estrogen receptor adverse outcome pathway using computational toxicology tools

  2. To obtain input and recommendations on the scientific concepts, principles and processes used to prioritize chemicals for EDSP screening.


EDSP Universe of Chemicals n= 10,341
Lists
FIFRA Registration Review Schedule for Active Ingredients (Approx.=1500)
SDWA and INERTS (Approx.=9000)
Physico-Chemical Properties
Excluded
Physico-Chemical Properties
No
Mixtures Lower Priority
Exposure Consideration
Considerations of Read Across and Chemical Categories
Risk Based Prioritization (Hazard + Exposure)
yes
OSRI Consideration
Prioritized List of Chemicals for EDSP Tier 1 Screening
OSRI Consideration
Confirm chemical is manufactured in US

SAP 2013 Key Recommendations

- Steps in the prioritization scheme were organized and clearly described, need to consider exposure earlier in the process
- Physico-chemical properties filters are founded on strong scientific principles and consistent with recommendations from 1998 EDSTAC.
- Expert System and HTP assays are potentially both useful in developing a “priority score” in combination with exposure determinations
- Other pathways: Androgen may be similar to ER pathway, but should focus on androgen antagonist. Thyroid will involve multiple modes of action that are not receptor based.

Advancing *EDSP21*

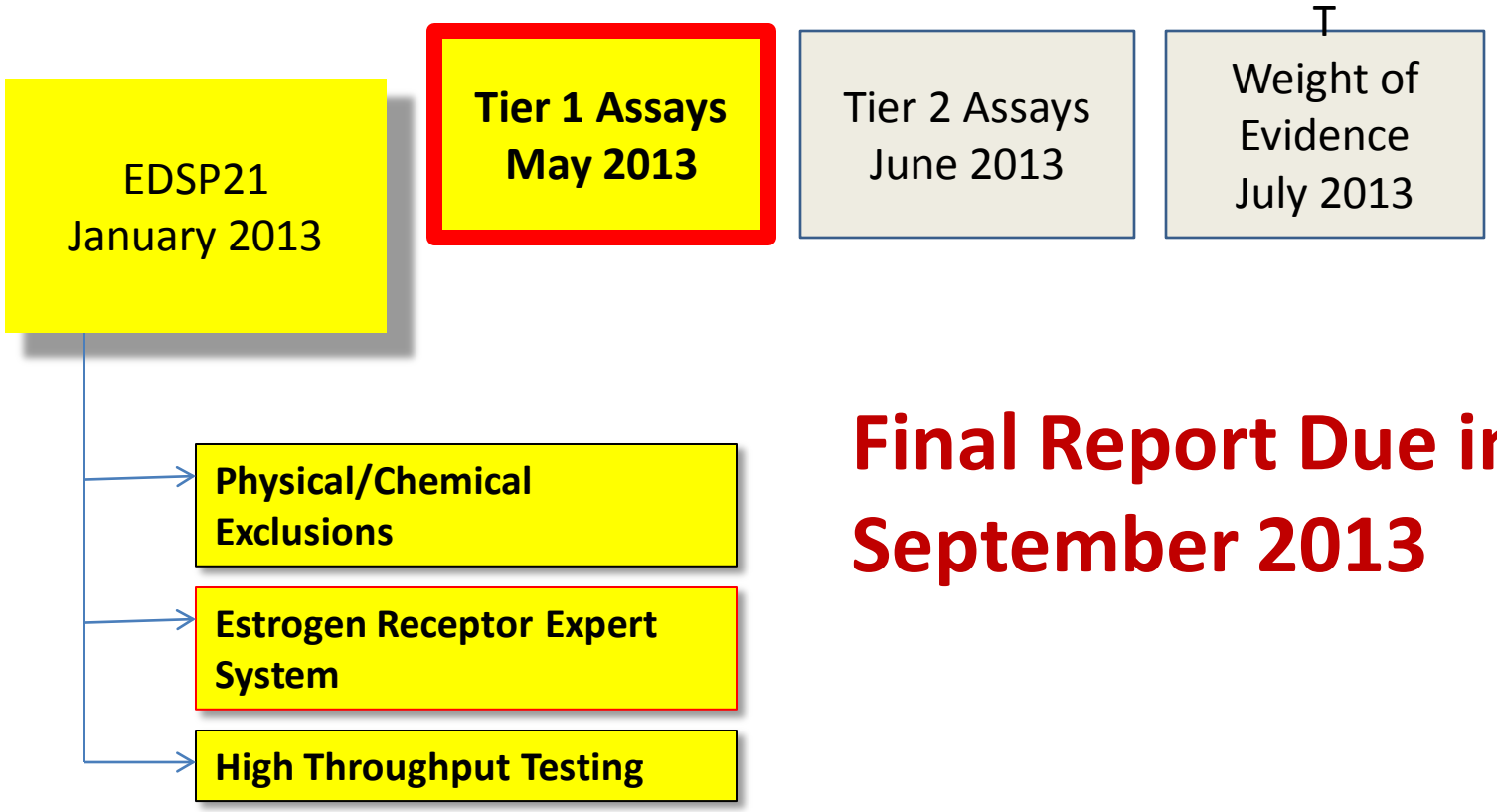
- Continue to move forward and refine approaches—Physical Chemical Properties, Expert System/High Throughput Screening based on SAP recommendations

- Update EDSP21 Workplan to reflect SAP recommendations and focus on developing a "Risk-based prioritization" approach, using both hazard and exposure data and models

-Use EDSP21 computational toxicology tools to screen chemicals across all four endocrine pathways including:

- Estrogen
- Androgen
- Thyroid
- Steroidogenesis

Scientific Advisory Panel Meetings 2013

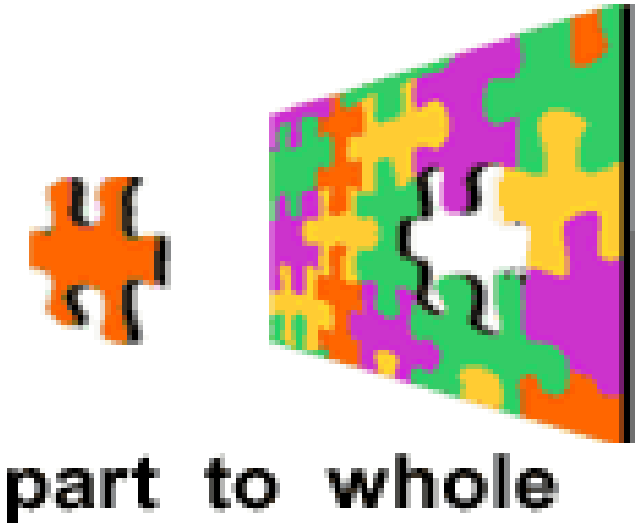


Final Report Due in September 2013

FIFRA SAP May 21-23, 2013

- Focus and Objective:
  1. Performance of EDSP Tier 1 Individual Assays
  2. Performance of the EDSP Tier 1 Battery

"Convene a panel of independent scientists to review all the screening data for 50-100 compounds, with an eye towards revising the process and eliminating those methods that don't work." (SAB/SAP panel in 1999)



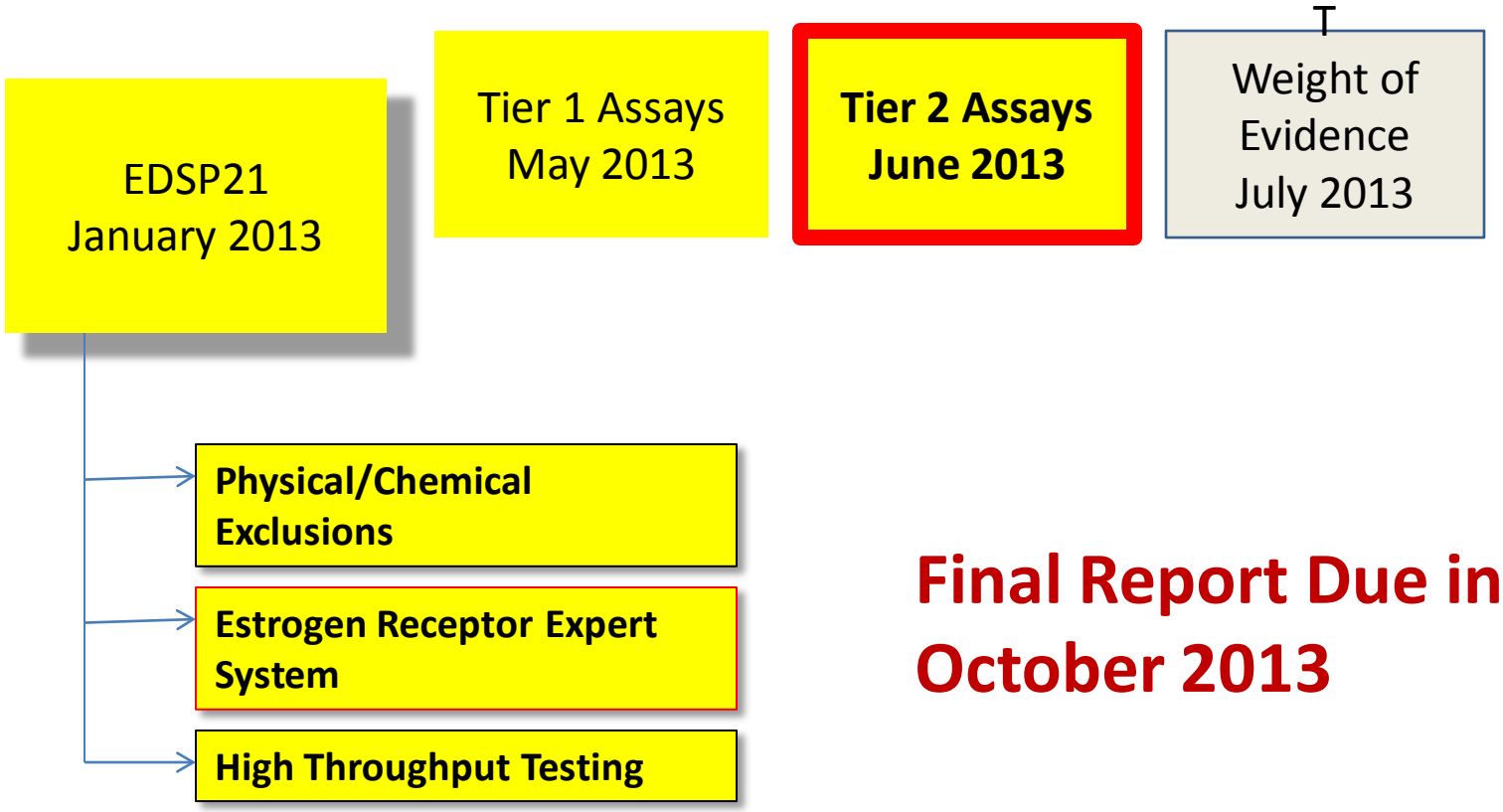
SAP 2008: Tier 1 Battery Review

- Open and transparent public process for independent, external scientific peer review
- Based on current state of the science, Tier 1 assays and battery are capable of identifying potential E, A, T endocrine activities.
- Appropriate starting point to detect potential endocrine disruptors
- Multiple taxa and mode of action endpoints provide a range of metabolism and needed corroboration

EPA 2013 Conclusions: Tier 1 Assay

- 21 chemicals selected for this evaluation: a range of physico-chemical properties and biological activity
- Tier 1 assays provide useful information to evaluate potential interactions with the E, A, and T signaling pathways.
- No major problems identified with the Tier 1 assays
- Laboratories were able to execute each assay protocol in accordance with the respective test guidelines and achieve the specified performance criteria.
- Some minor deviations from the performance criteria, but differences were not substantial

Scientific Advisory Panel Meetings 2013



Final Report Due in October 2013

Tier 2 Test Method Validation
FIFRA SAP June 2013

"Validation is a scientific process by which the reliability and relevance of an assay method are evaluated for the purpose of supporting a specific use" (ICCVAM, 1996)

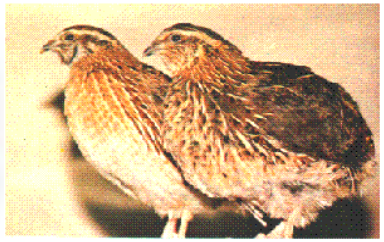
Reliability: reproducibility of results from an assay within and between laboratories
Relevance: whether a test is meaningful and useful for a particular purpose.

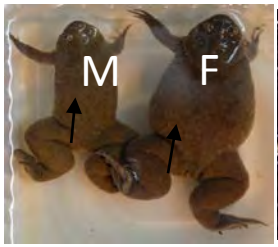
Validation Process

1. Method development and preparation of Detailed Review Paper (DRP)
2. Pre-validation
   - Demonstration of relevance
   - Development of standard optimized protocol
   - Determination of readiness for validation
3. Validation in multiple laboratories
   - Demonstrate reliability across labs
4. **Independent scientific peer review of validation effort: Integrated Summary Report (ISR)**
5. Regulatory acceptance

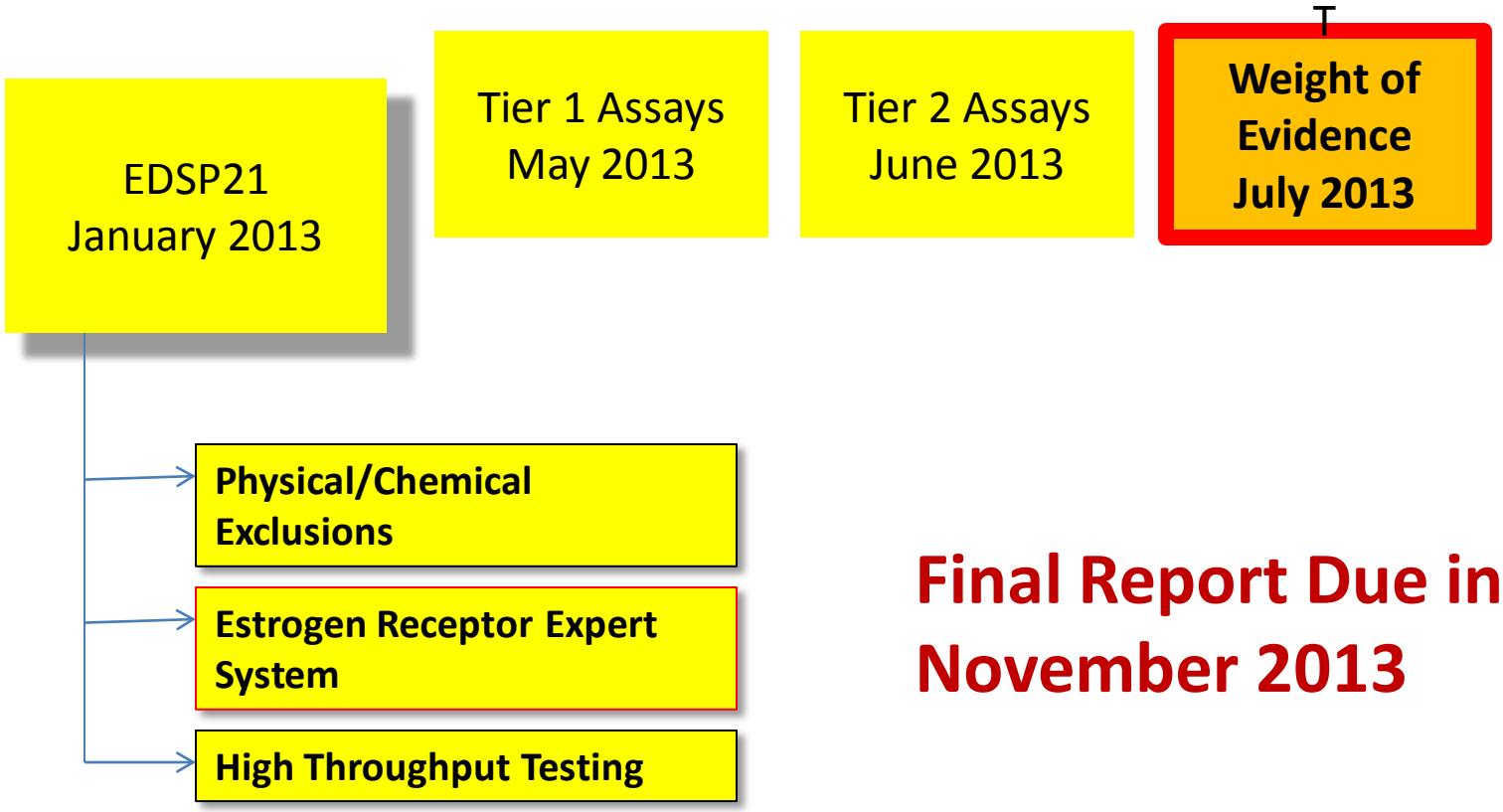
Tier 2 Test Methods

- Rat: Two-generation rat reproduction test (OECD TG 416)
  - Rat: Extended F1-Generation (OECD TG 443) - validated
- Bird: determine long-term effects of maternal transfer and *in ovo* exposure – Japanese Quail
- Fish: Medaka Multi-generation Toxicity Test (MMT) and Medaka Reproduction Test (MRT) methods
- Frog: characterize perturbations of normal development and growth – Xenopus Laevis
- Invertebrate: Mysid crustaceans have been used in regulatory testing for more than 30 years – adapted from existing 850.1350 Mysid Life Cycle Test.





EDSP Scientific Advisory Panel Meetings 2013



Final Report Due in November 2013

Weight of Evidence Analysis

- Weight of Evidence: Evaluating Results of EDSP Tier 1 Screening to Identify the Need for Tier 2 Testing, September 14, 2011.
- Selection of specific case studies to demonstrate the interpretative weight of evidence assessment with all available data, inclusive of OSRI.
- Focused Question: Whether a chemical interacts with the E, A or T endocrine pathway(s).

EDSP 2013 Significant Milestones

External Peer Reviews

- EDSP21 Chemical Prioritization: Jan. 2013
- Tier 1 assay and battery performance: May 2013
- Tier 2 test methods validation: June 2013
- Weight of Evidence Analysis: July 2013

Information Collection Requests

- Renewal ICR for List 1 Tier 1: OMB approved on July 3, 2013
- Addendum ICR for List 2 Tier 1: open for 30-day Public Comment period on 6.20.13
- ICR for List 1 Tier 2: open for 60-day Public Comment period on 6.24.13

Milestones Achieved in 2013

Fiscal Year	EDSP Activity	Milestone Achieved ✓
2013	Chemical prioritization using computational toxicology	SAP on chemical prioritization in January ✓
2013	Completion of data reviews of initial Tier 1 data and weight of evidence reviews	*Pending* final reports from SAP meetings
2013	FIFRA SAP external peer review of Tier 1 assay, battery and weight of evidence determinations	-SAP on Tier 1 assay and battery in May 2013 ✓ -SAP on WoE in July 2013
2013	Tier 2 Inter-laboratory test methods Validation	- SAP review of interlab validation in June 2013 ✓
2013	Issuance of List 2 chemicals, Tier 1 test orders	- ICR for public comment issued in June 2013 ✓, but several additional steps before test orders issued

*Note: Dependent on finalization of List 2 and associated policies and procedures

“The Tipping Point”

“If you want to bring a fundamental change in people's belief and behavior...you need to create a community around them, where those new beliefs can be practiced and expressed and nurtured.”