PESTICIDE PROGRAM DIALOGUE COMMITTEE MEETING

Arlington, VA

November 30, 2012

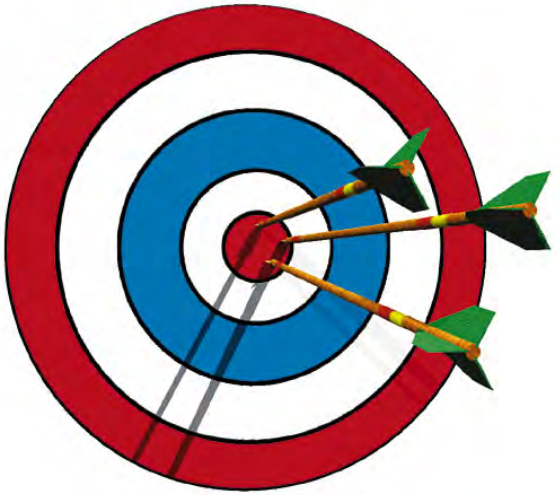
Endocrine Disruptor Screening Program: Update

Mary Manibusan, Director
Endocrine Disruptor Screening Program
Office of Science Coordination and Policy
Office of Chemical Safety and Pollution Prevention
U. S. Environmental Protection Agency
Manibusan.mary@epa.gov

Evolution of the EDSP

- Overview of EDSP: Mission and Vision
- Current Activities: Comprehensive Management Plan
  - Tier 1 Screening Data Reviews and Weight of Evidence
  - Tier 2 Test Methods Development
- Future Activities: EDSP21 Work Plan
  - Chemical prioritization involving Tox21 computational toxicology tools

EDSP Targeted 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.

Endocrine Disruptor Screening Program 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 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.

EDSP Tier 1 Screening Battery

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

Proposed EDSP Tier 2 methods

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

EDSP Current Timeline

1998/1999

EDSTAC 1998 Report and formation EDSP

2008-2010

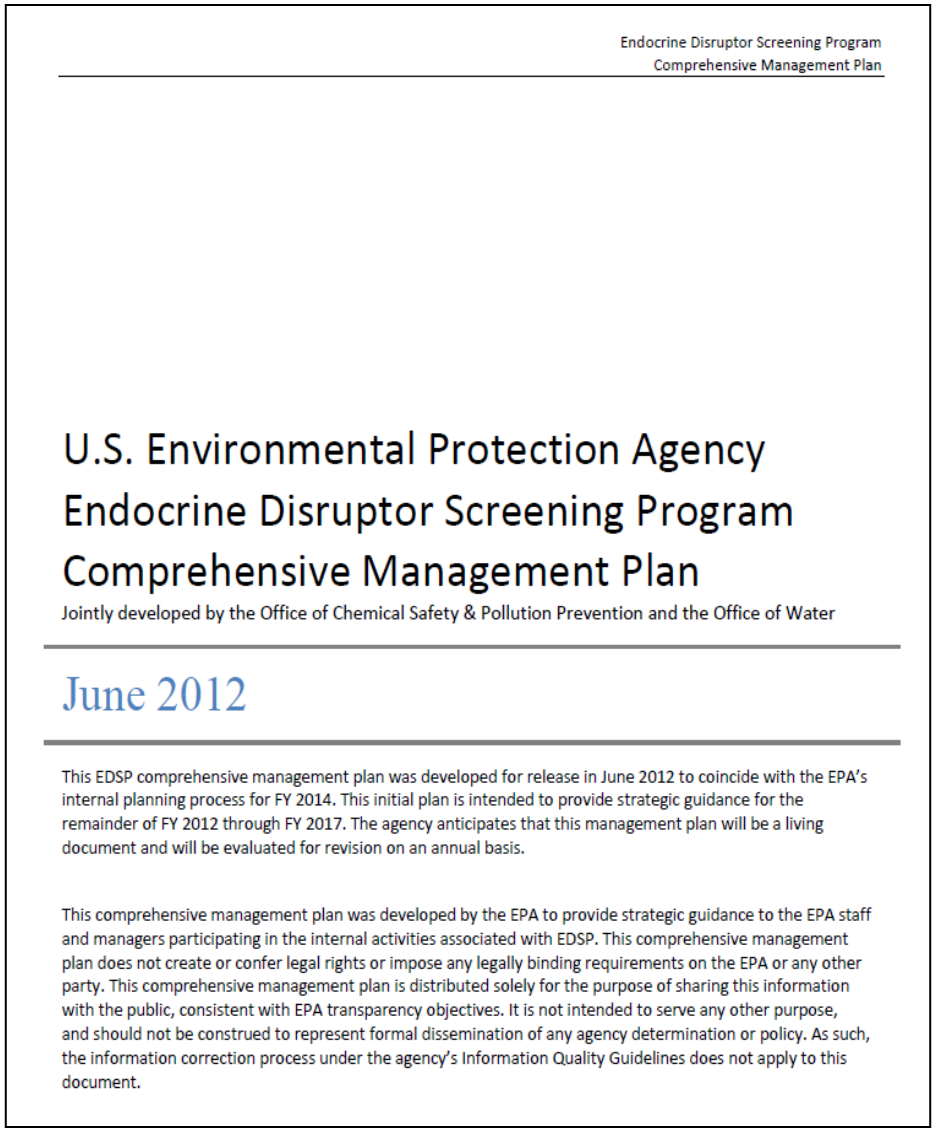
Validated Tier 1 Screening level assays, Issuance of initial test orders for List 1 and published proposed List 2

2011

EDSP21 Work Plan Summary and Weight of Evidence Document

Tier 1 Test Method Development → Tox21 Planning And Tier 2 tests → **2012 Comprehensive Management Plan**

EDSP 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

Overview of the Management Plan

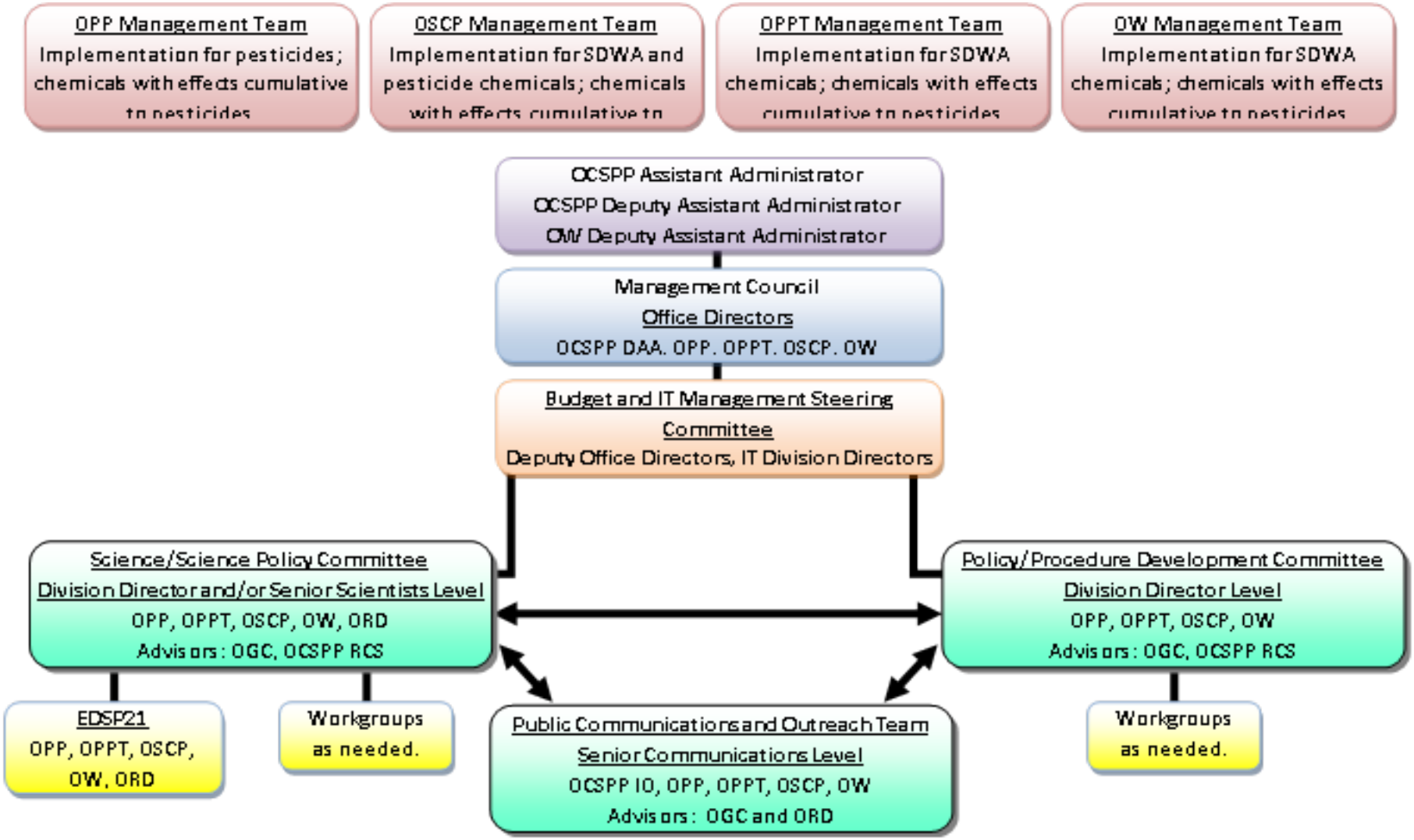
1. Management Organizational Chart – coordination across programs

2. Technical Data Reviews – ensuring uniform consistency and accuracy

3. Validation of Test methods – Tier 2 tests include multigeneration reproduction studies

4. EDSP21 Work Plan involving computational toxicology and Informational technology

EDSP Management Organizational Chart

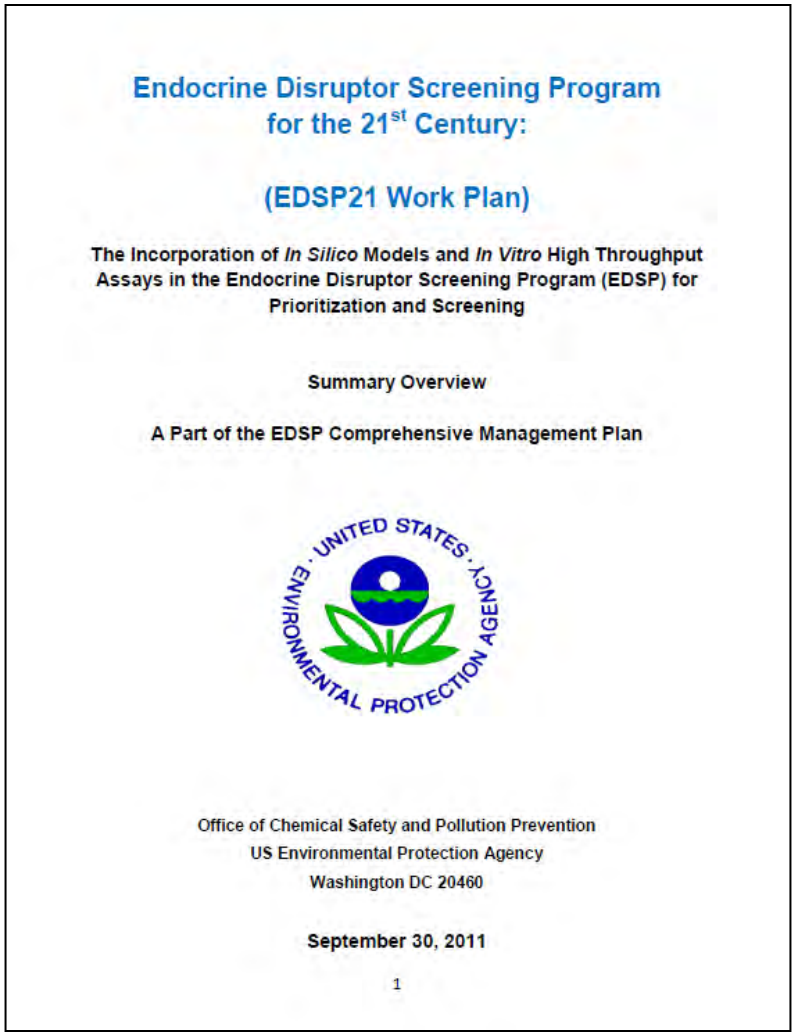


EDSP Key Milestones in 2013

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

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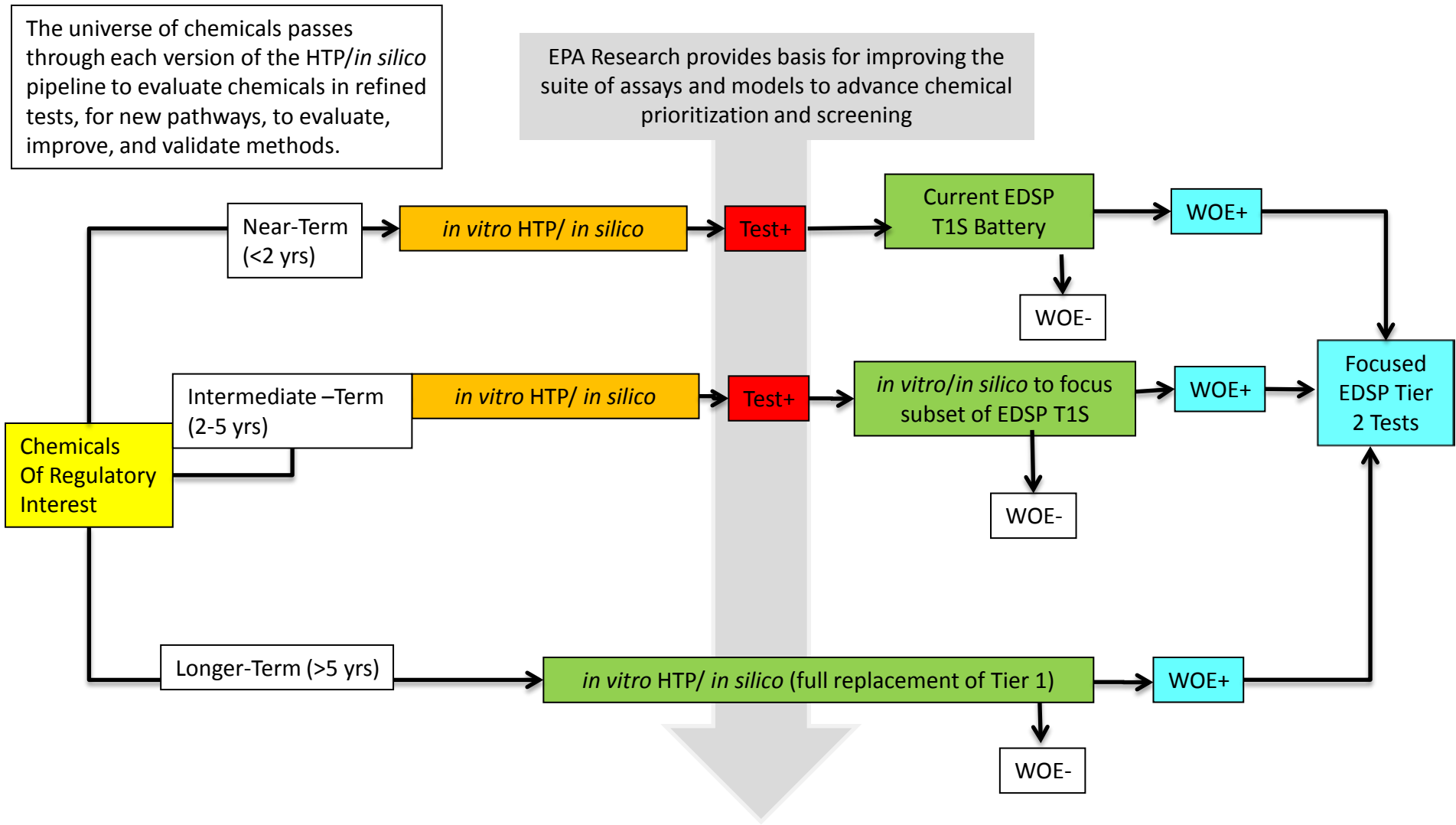
EDSP21 Objective

- Maximize use of existing data.
- Targeted *in vivo* toxicity screening.
- Use a variety of tools in a tiered testing and assessment framework.
- Systematically and *incrementally* incorporate new tools, methodologies.
- Advance understanding of key events in toxicity pathways.



Chemical Prioritization

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

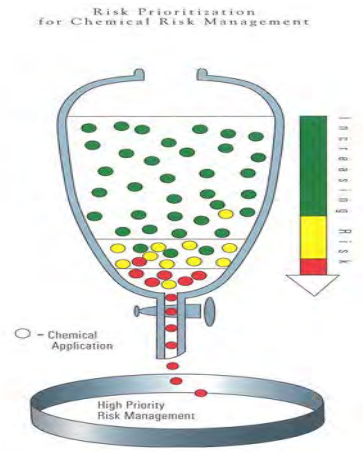
Screening Decisions

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)
  - 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*

OECD (Q)SAR Validation Principles*

- Defined Endpoint
- Unambiguous Algorithm
- Defined Domain of Applicability
- Appropriate Measures of Goodness-of-fit, Robustness and Predictivity
- Defined Biological Mechanism of Action, if possible

* The EDSP Universe of Chemicals and General Validation Principles, November 27, 2012 (www.epa.gov/endo)

Key considerations for implementation of EDSP21

- Ensure clarity of programmatic goal
- Define application and regulatory decision contexts
- Build transparent strategy with sound scientific basis
- Determine scientific validity
- Ensure public outreach

EDSP Future Timeline (2013)

January 31-Feb 1, 2013

FIFRA SAP on Chemical Prioritization

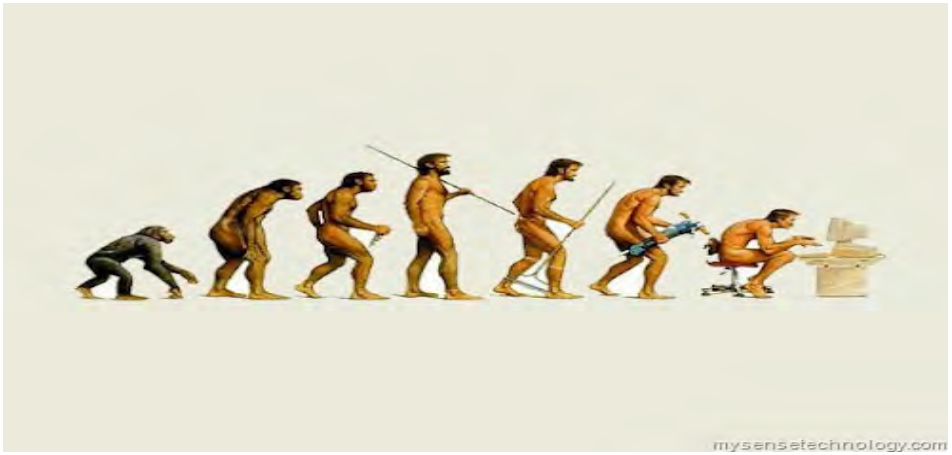
Spring-Summer

FIFRA Sap on Tier 1 data reviews, assay and battery performance and weight of evidence analyses

Spring-Summer

FIFRA SAP Review of Tier 2 assay validation efforts

Evolution of Computational Tools



"It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to change."
— Charles Darwin