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

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Introduction

The purpose of this overview is to present the rationale for and a framework of a proposed EDSP21 Work Plan. This overview describes: 1) why this work plan was developed, 2) what the agency is obligated to do, 3) how the work plan will be implemented, and 4) a proposed time line for completion. As part of the rationale, this overview presents the universe of chemicals that will be considered in the EDSP and a general description of the process for prioritizing pesticide and non-pesticide chemicals for EDSP screening.

The Need for the EDSP21 Work Plan

The USEPA developed the Endocrine Disruptor Screening Program (EDSP) in response to section 408(p) of the Federal Food, Drug, and Cosmetic Act (FFDCA) which requires 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."* 21 U.S.C. 346a(p)(1). In addition, the provision in section 1457 of the Safe Drinking Water Act (SDWA) provides that "*the Administrator may provide for testing under the screening program … any other substance that may be found in sources of drinking water if the Administrator determines that a substantial population may be exposed to such substance*." 42 U.S.C. 300j-17. Based on recommendations from the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC; 1998) and, pursuant to the Administrator's discretionary authority, EPA adopted a two-tiered screening and testing strategy known as the EDSP and expanded the program to include the androgen and thyroid hormonal pathways of the endocrine system and to address ecological effects.

The EDSP21 Work Plan describes an approach for using computational or *in silico* models and molecular-based *in vitro* high-throughput (HTP) assays to prioritize and screen chemicals to determine their potential to interact with the estrogen, androgen or thyroid (E, A, or T) hormonal systems. There are two important drivers for this work plan. First, EPA is statutorily required to complete a first round of registration review of previously registered pesticides by October 1, 2022. Each review takes about 5 to 6 years; and, currently, the agency initiates the review of approximately 70-80 active ingredients each year. So far, only a small percentage of the pesticide active ingredients under review have received test orders for screening under the EDSP. Also, Tier 1 screening has yet to begin for a large number of active ingredients. Second, the President's proposed fiscal year 2012 budget for the agency states that "In FY 2012, EPA will begin a multi-year transition from the Endocrine Disruptor Screening Program (EDSP) to validate and more efficiently use computational toxicology methods and high throughput screens that will allow the agency to more quickly and cost-effectively assess potential chemical toxicity" (President's Budget FY2012).

The Universe of Chemicals for Prioritization and Screening

In 2010 and 2011, EPA's Office of the Inspector General (OIG) evaluated the EDSP and concluded that, without a better defined universe of chemicals, the agency will not be able to estimate longer term

resource needs for completion of milestones for the program. Therefore, the OIG recommended that the agency first define and identify the universe of chemicals for EDSP screening and testing. In response, the agency has decided to incorporate a discussion of the universe of chemicals into both the EDSP21 Work Plan and the EDSP Comprehensive Management Plan. Both documents are intended to provide primary guidance regarding the strategic direction and management of the EDSP for a period of at least 5 years.

Agency Statutory Obligations

EPA believes that the scope of the EDSP is defined by the statutory requirements and discretionary authorities conveyed through passage of the FQPA amendments FFDCA and SDWA (Table 1).

Table 1. The numerical estimates of chemicals associated with each authority.

Citation	Statutory Language	Defined Universe
FFDCA §408(p)(3)(A) (21 U.S.C. 346a(p)(3)(A))	"(3) SUBSTANCES - In carrying out the screening program . . . the Administrator — (A) shall provide for the testing of all pesticide chemicals;"	Pesticide Active Ingredients = ~1,200 Chemicals Pesticide Inert Ingredients = ~2,500 Chemicals
	Discretionary Authority	
FFDCA §408(p)(3)(B) (21 U.S.C. 346a(p)(3)(B))	"(3) SUBSTANCES - In carrying out the screening program . . . the Administrator — (B) may provide for the testing of any other substance that may have an effect that is cumulative to an effect of a pesticide chemical if the Administrator determines that a substantial population may be exposed to such substance.	Anticipated to add minimally to the universe over the next 5 years. Will be dependent on case by case determinations regarding cumulative effects and exposure.
SDWA §1457 (42 U.S.C. 300j–17)	In addition to the substances referred to in section 408(p)(3)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a(p)(3)(B)) the Administrator may provide for testing . . . of any other substance that may be found in sources of drinking water if the Administrator determines that a substantial population may be exposed to such substance.	Regulated Contaminants = ~90 Chemicals Preliminary Universe ~6,000 Chemicals
	Universe of Chemicals for Prioritization and Screening	~6,000 to ~9,700

[1]See Footnote

Estimates of the universe of chemicals may change over time. The Office of Pesticide Programs (OPP) registers new pesticide active ingredients or approves new inert ingredients for incorporation into product formulations each year. OPP may also cancel registrations for certain active ingredients or discontinue approvals for inert ingredients on an annual basis. Similarly, the Office of Pollution

[1] §408(p)(3)(A) and (B) are both subject to the exemptions described at §408(p)(4) EXEMPTION.—Notwithstanding paragraph (3), the Administrator may, by order, exempt from the requirements of this section a biologic substance or other substance if the Administrator determines that the substance is anticipated not to produce any effect in humans similar to an effect produced by a naturally occurring estrogen.

Prevention and Toxics (OPPT) authorize requests from manufacturers to produce several hundred new chemicals each year. These chemicals could appear in future lists for consideration in the candidate contaminant lists (CCL) process.

How the EDSP21 Work Plan Will be Implemented

For pesticides, EPA's strategy is to coordinate the timing of issuance of EDSP Tier 1 test orders with the timing of the registration review program. By issuing test orders for an active ingredient before the start of the registration review process for the active ingredient, the results of any EDSP Tier 2 tests that might be needed for the active ingredient should be available for OPP scientists to review when they are also examining the toxicology database to develop updated and more expeditious risk assessments. Reviewing both sets of data concurrently will reduce duplication of effort and lead to decisions more expediently. However, the time needed to fulfill test order requirements using the current validated Tier 1 assays can make it challenging to integrate data from the current EDSP Tier 1 assays into the reregistration review of some pesticides. This would mean that the data for some active ingredients may not be available early enough to be easily integrated into their registration review. It is envisioned that the EDSP21 program, along with a combination of existing data, and *in silico* and *in vitro* methodologies, will enable the agency to prioritize and identify EDSP Tier 1 information needs for pesticide active ingredient cases entering the registration review program over the next several (1-3) years.

In addition to the above chronology-based approach and prioritization for pesticide active ingredients, the EDSP21 Work Plan proposes a method to prioritize non-pesticide active ingredient chemicals for EDSP Tier 1 screening. The approach is based on advances in computational modeling and molecular biology, understanding of endocrine-specific initiating events and adverse outcome pathways, as well as robotics for conducting rapid *in vitro* assays on hundreds of chemicals simultaneously. The work plan is a collaborative effort involving several offices within EPA including the Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Water (OW), and Office of Research and Development (ORD).

This proposed approach can serve as a prototype to implement the type of computational and molecular-based chemical screening recommended by the National Research Council (NRC) in their report, ''Toxicity Testing in the 21st Century: A Vision and a Strategy'' (NRC, 2007). This report, sponsored by the EPA, recommends that the Agency develop a strategy to use existing information, *in silico* models, and *in vitro* HTP assays to prioritize information needs and screen environmental chemicals as a more efficient and effective approach to evaluate potential hazard and risk. The report also highlights how advanced use of these contemporary tools could reduce and ultimately replace reliance on whole-animal toxicity testing.

Timeline for Completion

The proposed EDSP21 Work Plan involves a multi-level and integrated approach to determine whether a chemical has the potential to interact with E, A, or T. The Work Plan describes three main objectives:

1. ***Prioritization*** **-** The near-term goal (<2 years) is to use existing data, *in silico* models, and individual or suites of *in vitro* HTP assays to determine the relative order in which non-pesticide chemicals and pesticide active ingredients going through registration review should be screened.

2. ***Screening* (Tier 1)-** The intermediate-term goal (2-5 years) is to replace current validated *in vitro* screening assays with validated *in vitro* HTP assays; use the results to inform and target current *in vivo* estrogen- or androgen-specific screening assays; and, where possible, reduce the use of animals for screening purposes.

3. ***Replacement*** – The long-term goal (>5 years) is to consider full replacement of the *in vivo* screening assays with validated *in vitro* HTP assays and eliminate the use of animals for screening purposes.

The following figures illustrate the timing and approach described in the Work Plan.

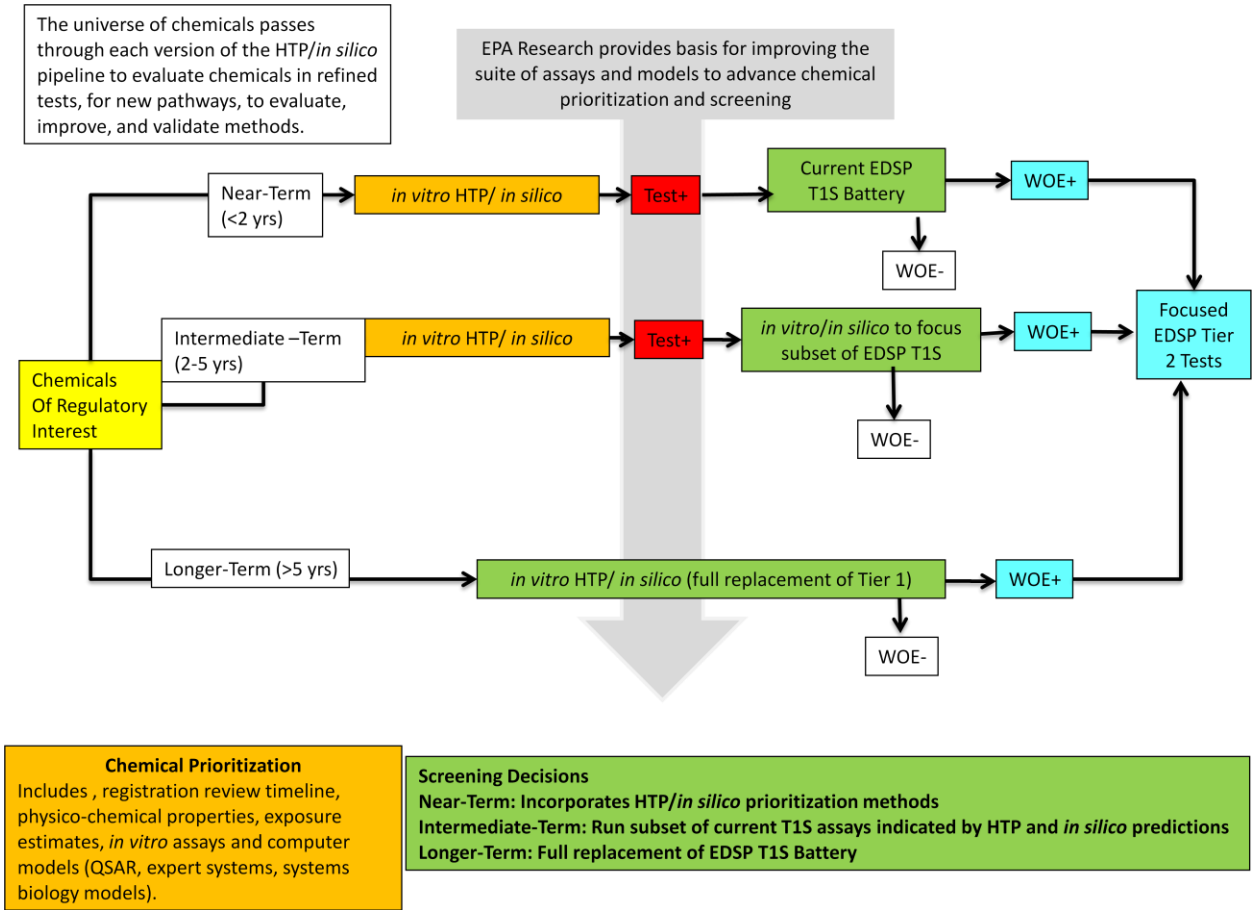

Figure 1: **Illustration of the evolution of the EDSP Tier 1**.
The chemical library could be analyzed using a battery of HTP assays. Computer models can be used as a prescreen method as appropriate. Chemicals that have been identified during this initial phase will be prioritized for the issuance of test orders under the current Tier 1 Screening (T1S) Battery. In the intermediate-term, chemicals would only be queued for T1S assays that are indicated based on the biological activity identified by HTP assays *in vitro and in silico* models. In addition, where appropriate, certain *in vivo* T1S assays would be replaced by one or a combination of validated *in vitro/in silico* models. The long term goal is to use information derived from *in vitro*, *in silico* and existing data to fully replace the current EDSP T1S Battery so that animal-based assays for screening are eliminated.
WOE - weight of evidence evaluation for determining which chemicals need EDSP Tier 2 testing.

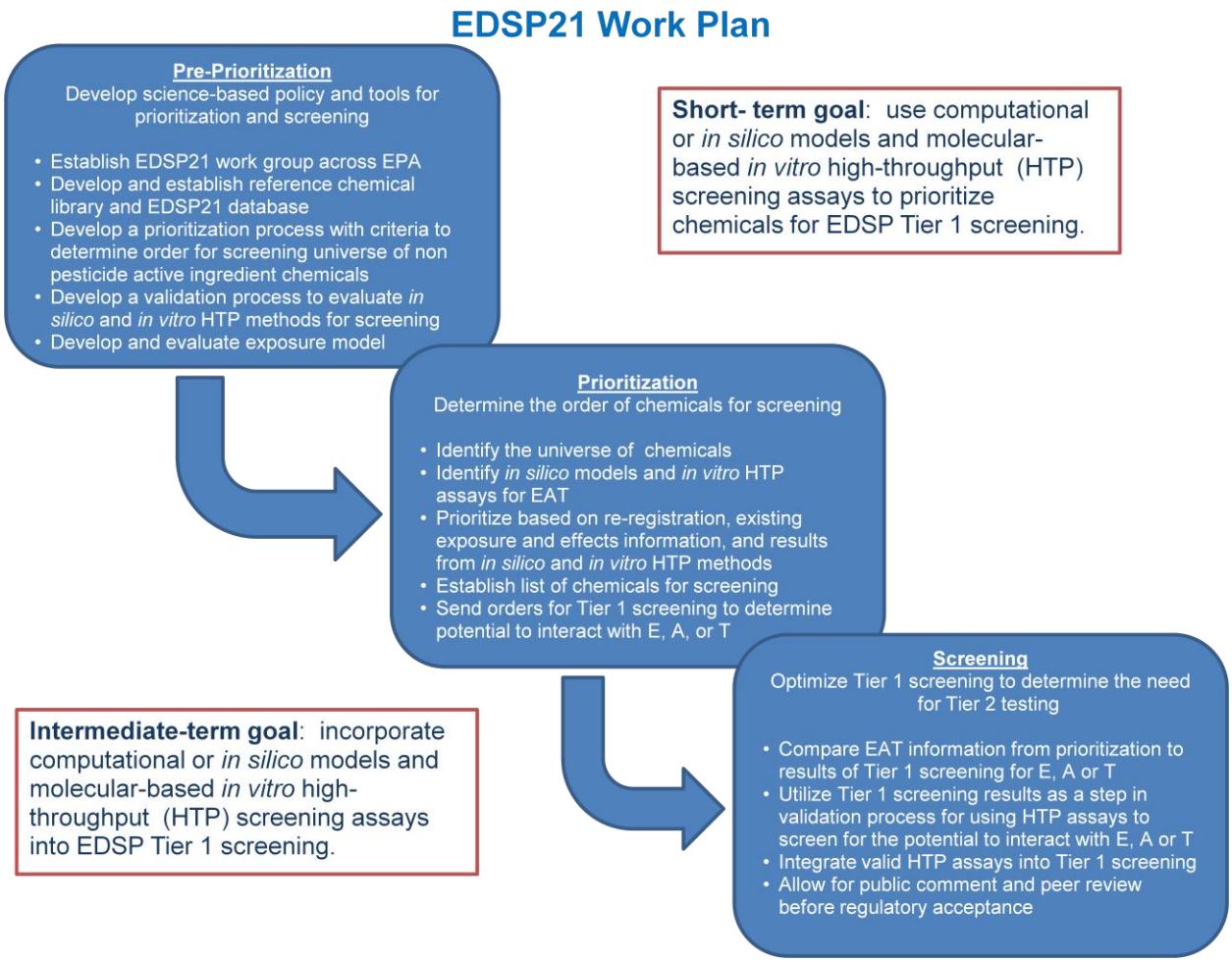

Figure 2: Work Plan activities that will enable reaching the Near-term and Intermediate-term goals.

References for Universe of Chemicals

Antimicrobials: http://www.epa.gov/oppsrrd1/registration_review/2011-14-antimicrobial.pdf,
Biochemicals: http://www.epa.gov/oppsrrd1/registration_review/2011-14-biochemical.pdf,
Conventionals: http://www.epa.gov/oppsrrd1/registration_review/2011-14-conventional.pdf,
Microbials: http://www.epa.gov/oppsrrd1/registration_review/2011-14-microbial.pdf
CCL Universe: http://water.epa.gov/scitech/drinkingwater/dws/ccl/upload/CCL3_Chemicals_Universe_08-31-09_508_v3.pdf
Registration Review Program: http://www.epa.gov/oppsrrd1/registration_review.

General References

EDSTAC (1998) Endocrine Disruptor Screening and Testing Advisory Committee, Final Report, Volume I-II. http://www.epa.gov/scipoly/oscpendo/pubs/edspoverview/finalrpt.htm
FQPA, 1996: http://www.epa.gov/pesticides/regulating/laws/fqpa/
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NRC (2007) Toxicity Testing in the 21st Century: A Vision and a Strategy. National Academy of Sciences, Washington, D.C. http://www.nap.edu/catalog.php?record_id=11970#toc
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