Endocrine Disruptor Screening Program (EDSP)

ICCVAM Public Forum Update

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EDSP Goals for Using Computational Toxicology Data

Use computational tools and models in the EDSP framework to:

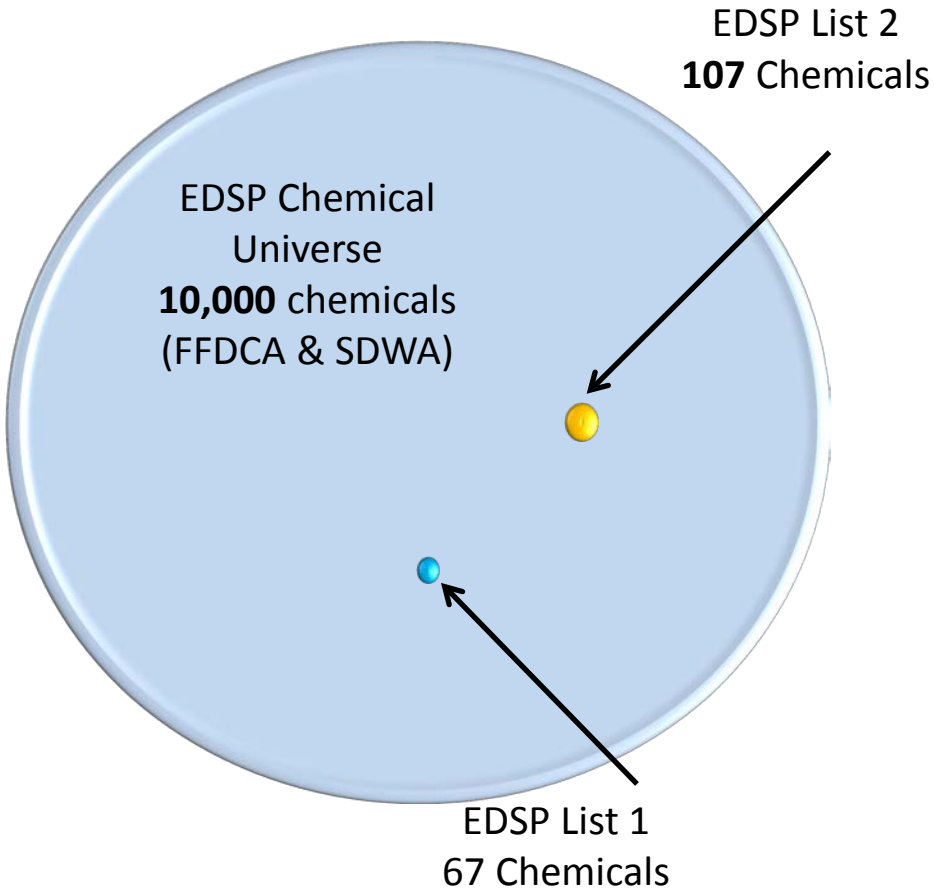
- Rapidly **screen** chemicals for endocrine bioactivity
- **Contribute** to the weight of evidence screening level determination of a chemical's potential bioactivity
- Provide **alternative** data for specific endpoints in the EDSP Tier 1 battery

Ultimately, goals are common to estrogen, androgen and thyroid pathways, however, estrogen agonist bioactivity is the most mature model and is used to demonstrate the proposed approach.

EDSP Universe of Chemicals

Chemical List	Number of Compounds
Conventional Active Ingredients	838
Antimicrobial Active Ingredients	324
Biological Pesticide Active Ingredients	287
Non Food Use Inert Ingredients	2,211
Food Use Inert Ingredients	1,536
Fragrances used as Inert Ingredients	1,529
Safe Drinking Water Act Chemicals	3,616
TOTAL	**10,341**

Evolution of EDSP- the "Pivot"



- Based on current pace it could take decades to screen all 10,000 chemicals in EDSP Universe
- Employ high throughput assays and predictive models to rapidly screen chemicals for potential bioactivity and exposure

EDSP "Pivot" Announcement

FEDERAL REGISTER
The Daily Journal of the United States Government

June 19, 2015
FRL-9928-69

"Use of High Throughput Assays and Computational Tools; Endocrine Disruptor Screening Program; Notice of Availability and Opportunity for Comment"

https://www.federalregister.gov/articles/2015/06/19/2015-15182/use-of-high-throughput-assays-and-computational-tools-endocrine-disruptor-screening-program-notice

35350 Federal Register / Vol. 80, No. 118 / Friday, June 19, 2015 / Notices

may claim all or part of a response confidential. EPA will disclose information that is covered by a claim of confidentiality only to the extent permitted by, and in accordance with, the procedures in TSCA section 14 and 40 CFR part 2.

Burden statement: The annual public reporting and recordkeeping burden for this collection of information is estimated to average 31.5 hours per response. Burden is defined in 5 CFR 1320.3(b).

The ICR, which is available in the docket along with other related materials, provides a detailed explanation of the collection activities and the burden estimate that is only briefly summarized here:

Respondents/Affected Entities: Entities potentially affected by this ICR are companies that manufacture, process or import chemical substances, mixtures or categories.

Estimated total number of potential respondents: 1.

Frequency of response: On occasion.

Estimated total average number of responses for each respondent: 1.

Estimated total annual burden hours: 31.5 hours.

Estimated total annual costs: $2,388. This includes an estimated burden cost of $2,388 and an estimated cost of $0 for capital investment or maintenance and operational costs.

III. Are There Changes in the Estimates from the Last Approval?

There is a decrease of 916 hours in the total estimated respondent burden compared with that identified in the ICR currently approved by OMB. This decrease reflects additional both adjustment changes from a reduction in the assumed number of PAIR reports filed annually, and program changes resulting from mandatory electronic submissions of PAIR reports. In recent years (FY 2011–FY 2014), EPA has received no PAIR submissions and, for the purposes of this analysis, EPA assumes an annual rate of one submission per year. At the time OMB last renewed this ICR, EPA estimated an average of 33 reports from 14.8 submitters based on fiscal year 2006–2010 data. The ICR supporting statement provides a detailed analysis of the change in burden estimate. This change is both an adjustment and a program change.

IV. What is the Next Step in the Process for this ICR?

EPA will consider the comments received and amend the ICR as appropriate. The final ICR package will then be submitted to OMB for review and approval pursuant to 5 CFR 1320.12. EPA will issue another **Federal Register** document pursuant to 5 CFR 1320.5(a)(1)(iv) to announce the submission of the ICR to OMB and the opportunity to submit additional comments to OMB. If you have any questions about this ICR or the approval process, please contact the technical person listed under **FOR FURTHER INFORMATION CONTACT.**

Authority: 44 U.S.C. 3501 *et seq.*

Dated: June 10, 2015.

James Jones,

Assistant Administrator, Office of Chemical Safety and Pollution Prevention.

[FR Doc. 2015–14946 Filed 6–18–15; 8:45 am]

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ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–OPPT–2015–0305; FRL–9928–69]

Use of High Throughput Assays and Computational Tools; Endocrine Disruptor Screening Program; Notice of Availability and Opportunity for Comment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: This document describes how EPA is planning to incorporate an alternative scientific approach to screen chemicals for their ability to interact with the endocrine system. This will improve the Agency's ability to fulfill its statutory mandate to screen pesticide chemicals and other substances for their ability to cause adverse effects by their interaction with the endocrine system. The approach incorporates validated high throughput assays and a computational model and, based on current research, can serve as an alternative for some of the current assays in the Endocrine Disruptor Screening Program (EDSP) Tier 1 battery. EPA has partial screening results for over 1800 chemicals that have been evaluated using high throughput assays and a computational model for the estrogen receptor pathway. In the future, EPA anticipates that additional alternative methods will be available for EDSP chemical screening based on further advancements of high throughput assays and computational models for other endocrine pathways. Use of these alternative methods will accelerate the pace of screening, decrease costs, and reduce animal testing. In addition, this approach advances the goal of providing sensitive, specific, quantitative, and efficient screening using alternative test methods to some assays in the Tier 1 battery to protect human health and the environment.

DATES: Comments must be received on or before August 18, 2015.

ADDRESSES: Submit your comments, identified by docket identification (ID) number EPA–HQ–OPPT–2015–0305, by one of the following methods:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute.
- *Mail:* Document Control Office (7407M), Office of Pollution Prevention and Toxics (OPPT), Environmental Protection Agency, 1200 Pennsylvania Ave. NW., Washington, DC 20460–0001.
- *Hand Delivery:* To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at *http://www.epa.gov/dockets/contacts.html.*

Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at *http://www.epa.gov/dockets.*

FOR FURTHER INFORMATION CONTACT: *For technical information contact:* Jane Robbins, Office of Science Coordination and Policy (OSCP), Office of Chemical Safety and Pollution Prevention, Environmental Protection Agency, 1200 Pennsylvania Ave. NW., Washington, DC 20460–0001; telephone number: (202) 564–6625; email address: robbins.jane@epa.gov.

For general information contact: The TSCA-Hotline, ABVI-Goodwill, 422 South Clinton Ave., Rochester, NY 14620; telephone number: (202) 554–1404; email address: *TSCA-Hotline@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this action apply to me?

This action is directed to the public in general, and may be of interest to a wide range of stakeholders including those interested in endocrine testing of chemicals (including pesticides), and the EDSP in general. Since others also may be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action.

B. What is the agency authority for taking this action?

The EDSP is established under section 408(p) of the Federal Food, Drug and

Estrogen Receptor Bioactivity Model

- 18 high throughput screening assays in ToxCast
- Detects receptor interaction at various points along signaling pathway
- Mathematical predictive model
- Integrates the area under the curve (18 assays) to give a single bioactivity value
- Uses a variety of technologies
  - Capable of distinguishing “true” activity from cytotoxicity
- Values range from 0 to 1
  - ER agonists/antagonists

Note: The conceptual framework above is applicable to future endocrine models such as androgen receptor

Developing Alternative EDSP Assays

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)
Androgen Receptor (AR) Binding	AR Model (Near Future)
Hershberger	AR Model (Near Future)
Aromatase	STR Model (Future)
Steroidogenesis (STR)	STR Model (Future)
Female Rat Pubertal	ER, STR , THY Models (Future)
Male Rat Pubertal	AR, STR , THY Models (Future)
Fish Short Term Reproduction	ER, AR, STR Models (Future)
Amphibian Metamorphosis	THY Model (Future)
EDSP Tier 2 Tests	**High Throughput Assays and Computational Model Tier 2 Battery Alternatives**
Rat 2-gen/EOGRT	ER, AR, STR, THY(Future)
Medaka Extended 1-Gen Reproduction	ER, AR, STR (Future)
Larval Amphibian Growth & Development	THY (Future)
Avian Multi-Generation Reproduction	ER, AR, STR, THY (Future)

ER = estrogen receptor; AR = androgen receptor; STR = steroidogenesis; THY = thyroid

How Are Models Being Evaluated/Validated?

- Comparison to existing literature studies that reflect EDSP Tier 1 data
- Comparison to EDSP Tier 1 List 1 data
  - 52 chemicals
- Data on Reference chemicals
- Peer-reviewed publications
- FIFRA Scientific Advisory Panel (SAP)

Judson et al. 2015, Tox Sci: "Integrated Model of Chemical Perturbations of a Biological Pathway Using 18 In Vitro High Throughput Screening Assays for the Estrogen Receptor"

Kleinstreuer et al. 2015, EHP: "A Curated Database of Rodent Uterotrophic Bioactivity"

Browne et al. 2015, ES&T: "Screening Chemicals for Estrogen Receptor Bioactivity Using a Computational Model"

Projected Development of Alternative EDSP Assays

EDSP Tier 1 Battery of Assays	Model Alternative Development
Estrogen Receptor (ER) Binding	**ER Model FY 2015**
Estrogen Receptor Transactivation (ERTA)	**ER Model FY 2015**
Uterotrophic	**ER Model FY 2015**
Androgen Receptor (AR) Binding	AR Model FY 2016
Hershberger	AR Model FY 2016
Aromatase	STR Model FY 2016
Steroidogenesis (STR)	STR Model 2016
Female Rat Pubertal	**ER**, STR & THY Models FY 2017
Male Rat Pubertal	AR, STR & THY Models FY 2017
Fish Short Term Reproduction	**ER**, AR & STR Models FY 2017
Amphibian Metamorphosis	THY Model FY 2017

ER = estrogen receptor; AR = androgen receptor; STR = steroidogenesis; THY = thyroid

Timeline

- FR Notice expanding use of ER model, and establishing use of AR model
- Refine/Develop ER, AR, STR & THY models
- Establish AR, STR & THY models

Path Forward

- Toxicity pathways for evaluating alternative data for Tier 1 endpoints
  - HTS assays and predictive model(s) for Tier 1 assay
- Requires high quality, robust reference chemicals for each assay/endpoint
- Performance-based approach to validating alternatives (HTS and predictive models)
- Toxicity pathways for evaluating alternative data for Weight of Evidence determination of estrogen, androgen, and thyroid activity
  - Integrate more assays
  - Integrate more key events
  - Network multiple models