Update
Endocrine Disruptor Screening Program (EDSP)

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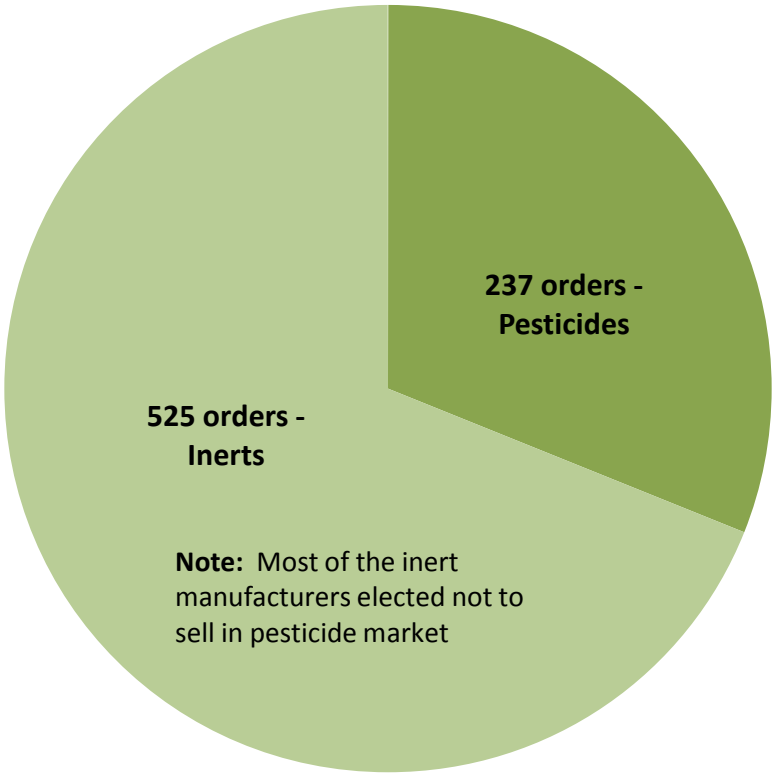
Pesticide Program Dialogue Committee
October 22, 2015

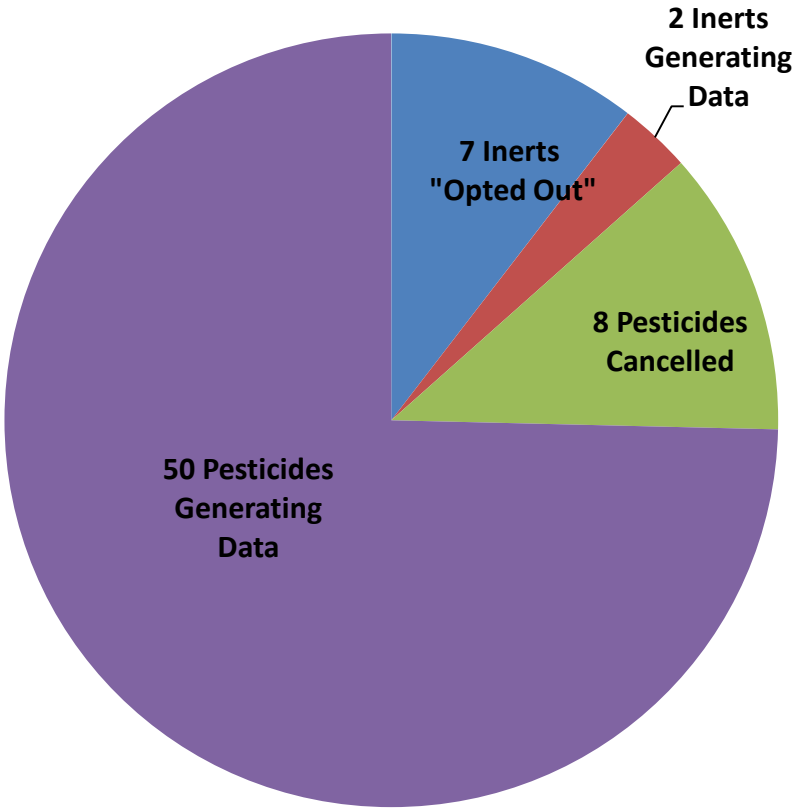
EDSP List 1:
Tier 1 Orders & Tier 1 WoE Determinations

EDSP List 1 Orders Overview

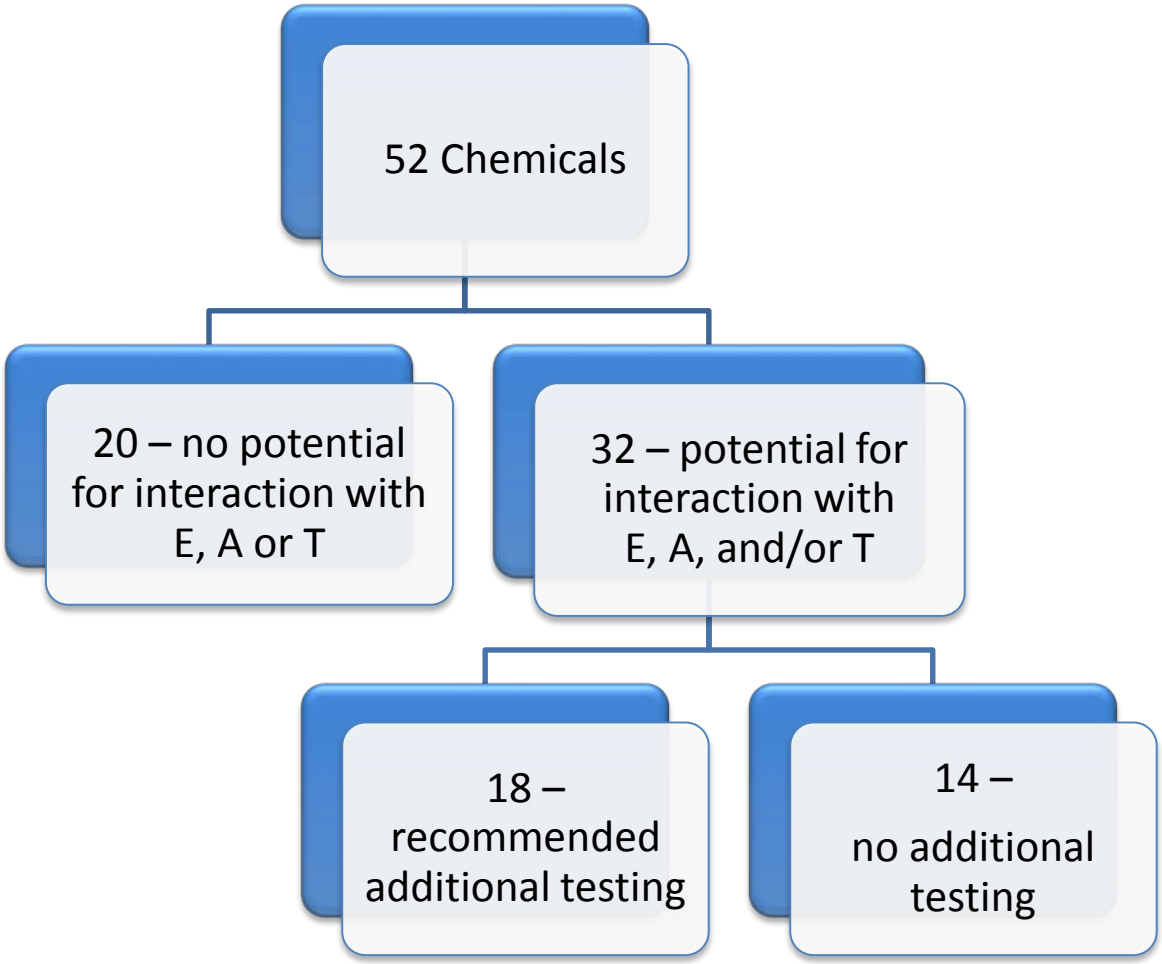
762 Orders Issued on 67 Chemicals



General Responses for the 67 Chemicals



Tier 1 WoE Results



Additional Testing for Chemicals with E, A and/or T Bioactivity

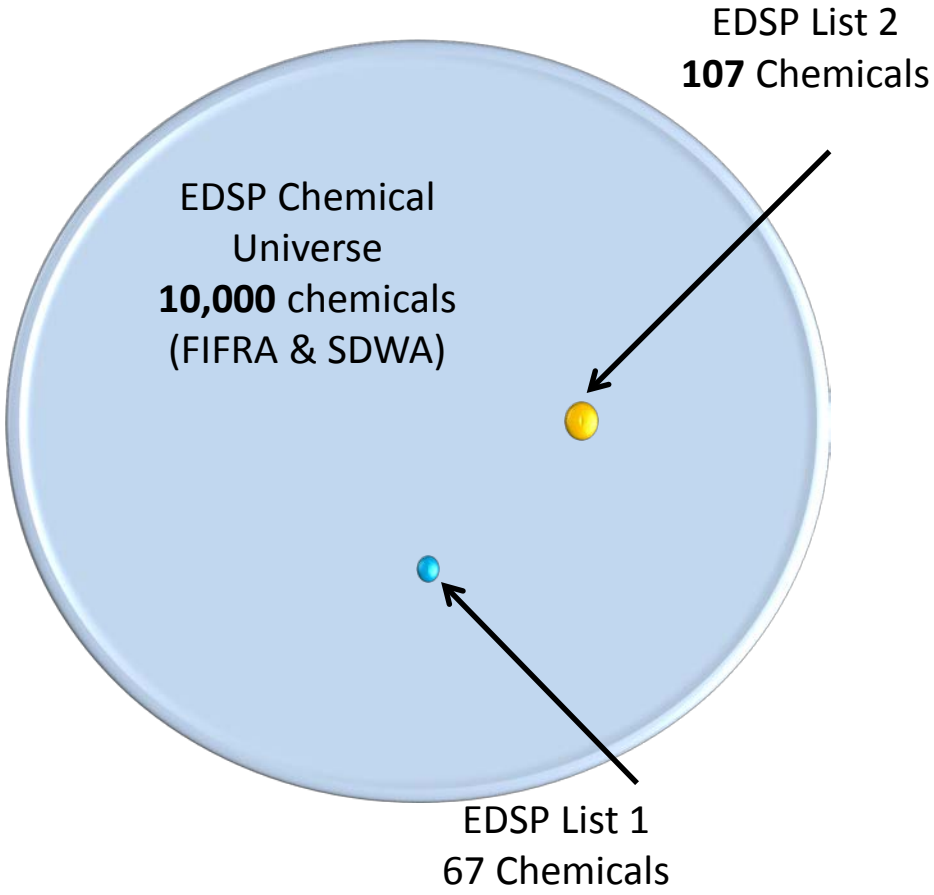
	Chemical	Human Health	Wildlife
1	Carbaryl	None	MEOGRT
2	Chlorothalonil	None	LAGDA
3	Cypermethrin	Special study: Assess androgen-related effects in adult males	MEOGRT
4	DCPA	CTA (comparative thyroid assay)	LAGDA
5	Dichlobenil	None	MEORGT
6	Dimethoate	CTA	None
7	Flutolanil	None	MEOGRT
8	Folpet	None	MEOGRT
9	Iprodione	None	MEOGRT
10	Linuron	CTA	MEOGRT, LAGDA
11	Metalaxyl	None	MEOGRT
12	Metribuzin	CTA	LAGDA
13	Myclobutanil	None	MEOGRT
14	O-phenylphenol	None	MEOGRT
15	PCNB	None	MEOGRT
16	Propargite	None	LAGDA
17	Propiconazole	None	MEOGRT
18	Tebuconazole	None	MEOGRT

EDSP List 1 Tier 2 Study Recommendations

- **Human Health**
  - Studies more focused to assess specific target organ toxicity
    - Thyroid & Male Reproduction
- **Wildlife**
  - T2 Medaka Extended One Generation Reproduction Test (*MEGORT*)
    - 13 chemicals
  - T2 Larval Amphibian Growth and Development Assay (*LAGDA*)
    - 5 chemicals

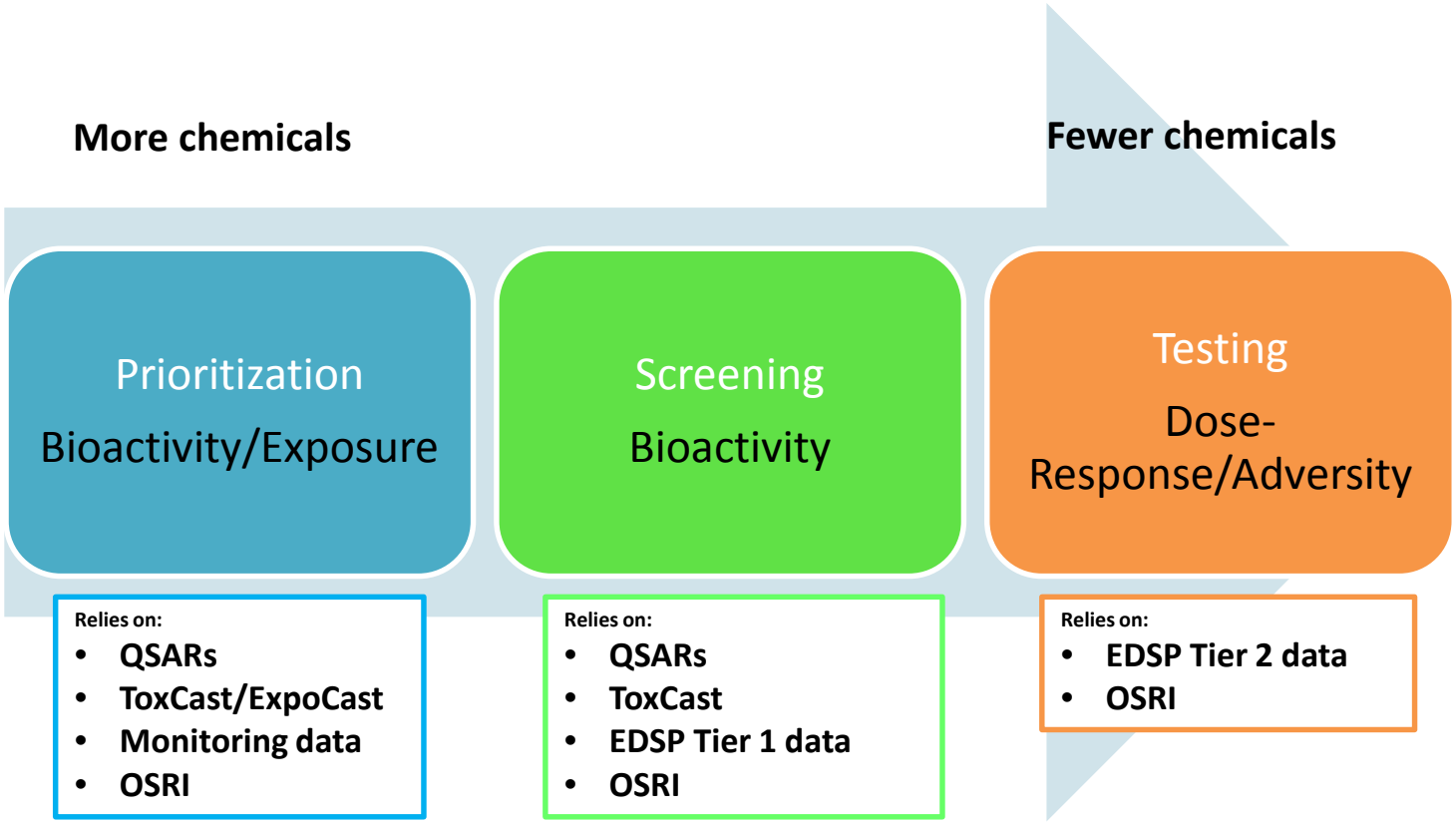
EDSP:
Status of High Throughput Assays & Computational Models

Evolution of EDSP- the "Pivot"



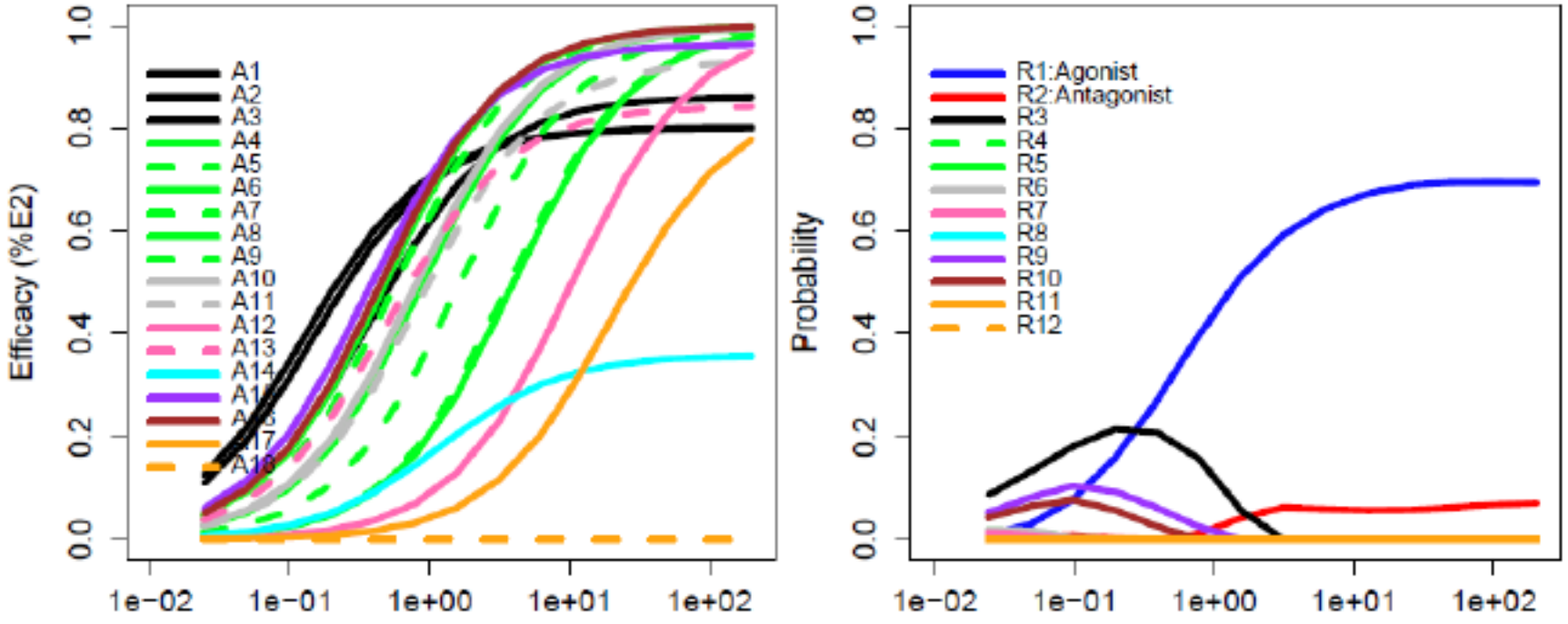
- Based on current pace it could take decades to screen all 10,000 chemicals in EDSP Universe
- Pivot: use high throughput assays and computational models to rapidly screen chemicals for potential bioactivity and exposure

EDSP Prioritization, Screening & Testing



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

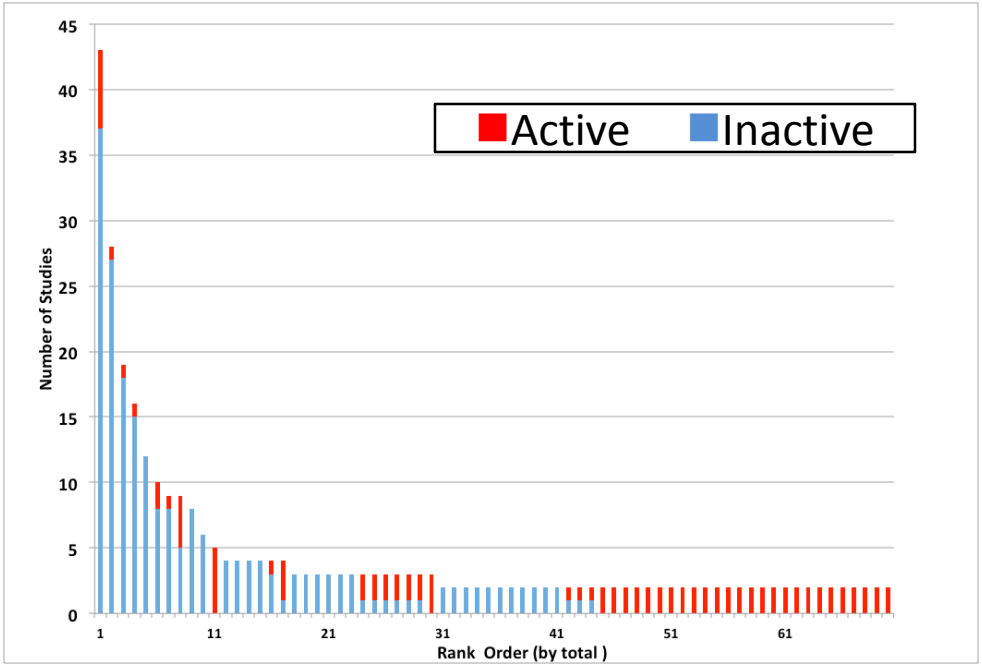
High Throughput Assays Integrated Into Pathway Bioactivity Models



[Judson *et al.* 2015 Tox Sci]

ER Bioactivity Model Versus Tier 1

- ER model performs as well or better than existing methods
- Model evaluated with 45 reference chemicals
  - T1 ER binding: 23 (35% were not were not consistent with expected outcome)
  - T1 ERTA: 12
  - T1 UT: 7
- ER model in 100% agreement with Tier 1 ER, ERTA, and Uterotrophic results for List 1 chemicals (very low or no ER activity)
- ER model may be more sensitive than Tier 1 assays due to redundancy



Results from uterotrophic studies for chemicals that had at least two independent GL studies. Blue bars represent the number of active reports; red bars represent the number of inactive reports. Data from chemicals commonly used as positive controls (i.e., ethinyl estradiol and estradiol) were excluded from this plot.

[Kleinstreuer *et al.* 2015 Environmental Health Perspectives]

Browne *et al.* 2015
Environmental Science & Technology

Subscriber access provided by the EPA Library | US Environmental Protection Agency

Article

SCREENING CHEMICALS FOR ESTROGEN RECEPTOR BIOACTIVITY USING A COMPUTATIONAL MODEL

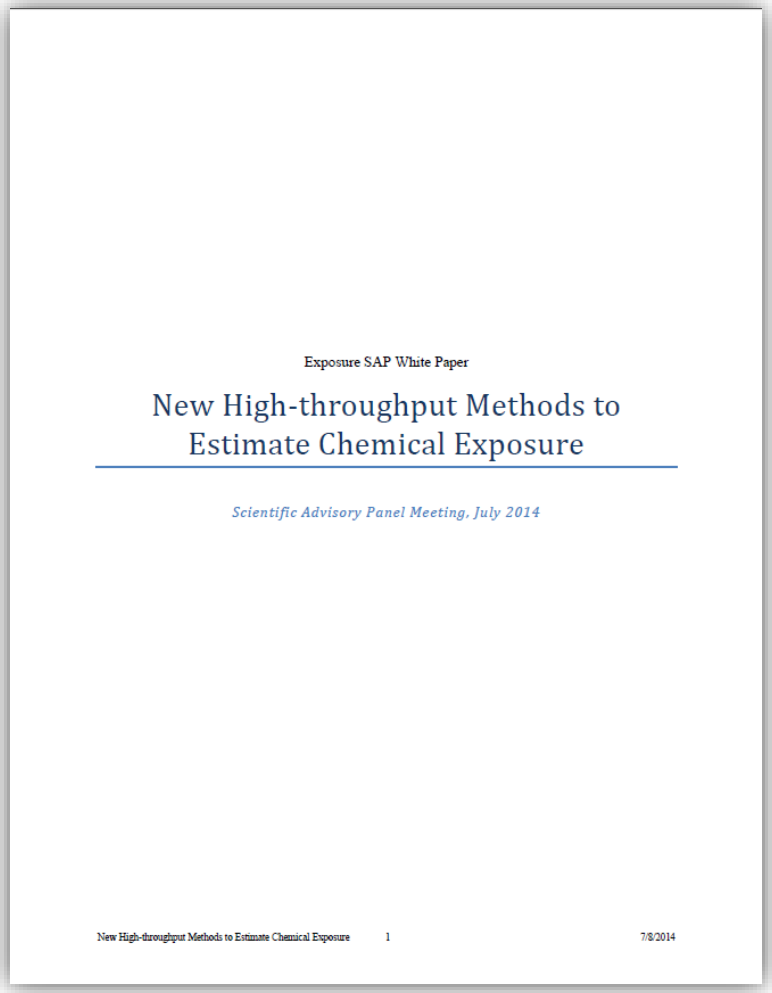
Patience Browne, Richard S. Judson, Warren Casey, Nicole Kleinstreuer, and Russell S. Thomas

Environ. Sci. Technol., **Just Accepted Manuscript** • DOI: 10.1021/acs.est.5b02641 • Publication Date (Web): 12 Jun 2015

Downloaded from http://pubs.acs.org on June 15, 2015

http://pubs.acs.org/doi/abs/10.1021/acs.est.5b02641

Building Scientific Confidence – Peer Review

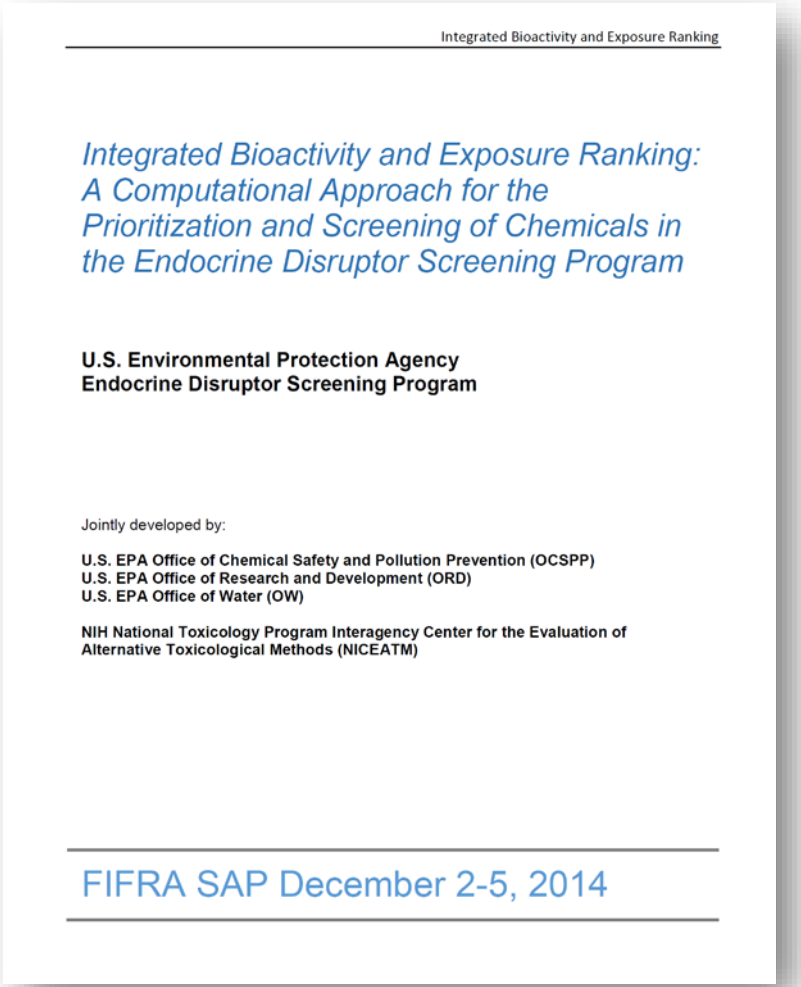


Exposure SAP White Paper

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

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

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]

BILLING CODE 6560–50–P

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

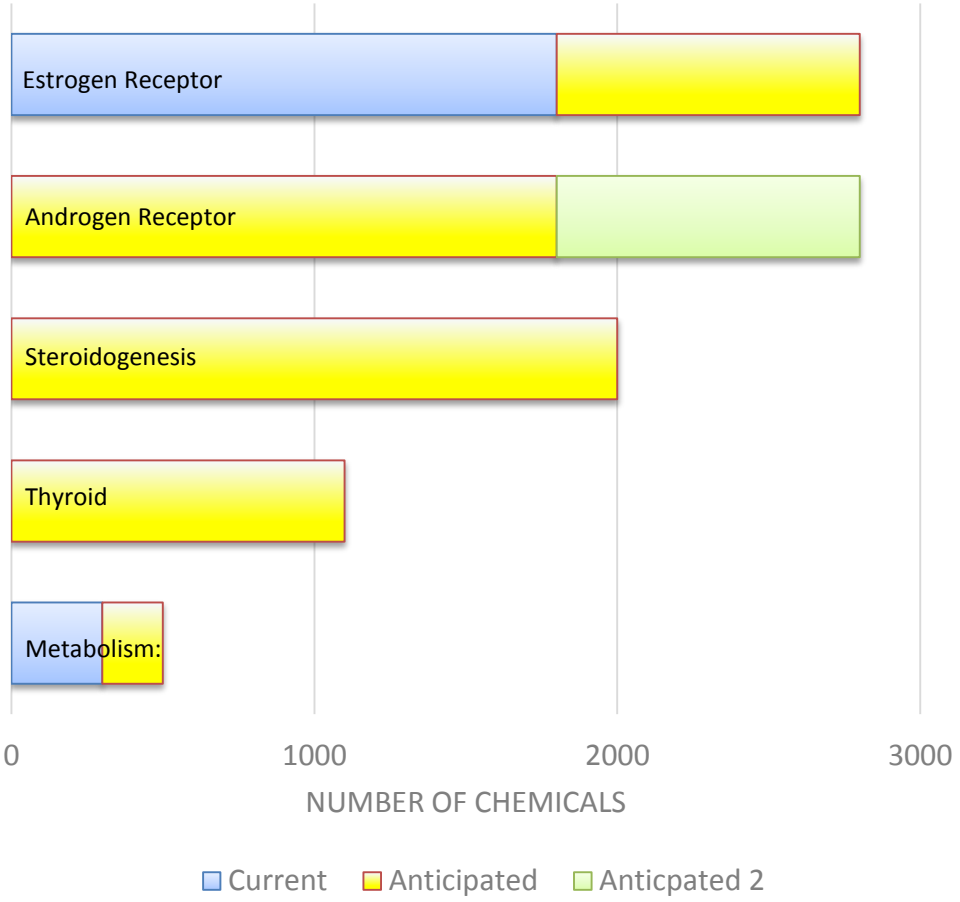
Evolution of Screening and Testing in the EDSP

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)
Androgen Receptor (AR) Binding	AR Model (Future)
Hershberger	AR Model (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)

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

High Throughput Screening in the EDSP

High Throughput Assays and Computational Model Tier 1 Battery Alternatives
ER Model
ER Model
ER Model
ER, STR, THY, MTB Models
AR, STR, THY, MTB Models
AR Model
AR Model
STR Model
STR Model
ER, AR, STR, MTB Models
THY, MTB Models



Summary

- EDSP "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