# US Regulatory Perspective on Developmental Neurotoxicity Testing with Special Focus on Endocrine Disrupting and Industrial Chemicals

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# What is the problem and how big is it?

- Broad chemical space and broad biological space required for testing of potential neurotoxicants and especially developmental neurotoxicants.
- Huge number(~10K) of substances which excludes pesticides and drugs with known mode of action and target sites.
- Approaches Needed for Prioritization, Screening, Testing and Assessment.

# TSCA Major Improvements in 2016

- Mandatory duty on EPA to evaluate existing chemicals with clear and enforceable deadlines
  - *Old TSCA – no duty to review; no deadlines for action*
- Chemicals assessed against a risk-based safety standard
  - *Old TSCA – risk-benefit balancing standard*
- Unreasonable risks identified in the risk evaluation must be eliminated
  - *Old TSCA – Signficant risks might not be addressed due to cost/benefit balancing and no mandate to act*
- Expanded authority to more quickly require development of chemical information when needed
  - *Old TSCA – Required lengthy rulemaking*

# TSCA New Chemicals

- TSCA 21 requires EPA to make affirmative finding on new chemicals or significant new uses of existing chemicals
- Before the chemical can enter the market, EPA must find that the chemical:
  - "presents an unreasonable risk" and issue a 5(f) order to address such risk;
  - "information…is insufficient to permit a reasoned evaluation…" and issue a 5(e) order;
  - "may present an unreasonable risk" and issue a 5(e) order; or
  - is "not likely to present an unreasonable risk"

# TSCA Specific Requirements Existing Chemicals

- Prioritizing Chemicals for Assessment
  - Establish a risk-based process to identify “high” and “low” priority substances
  - High priority – the chemical may present an unreasonable risk of injury to health or the environment due to potential hazard and route of exposure, *including to susceptible subpopulations*
  - Low priority – the chemical use does not meet the standard for high-priority

# TSCA Alternative Testing

*Section 4*

**When requiring the development of new information** relating to a chemical substance or mixture under paragraph (2), the Administrator shall identify the need for the new information, describe how information reasonably available to the Administrator was used to inform the decision to require new information, **explain the basis for any decision that requires the use of vertebrate animals**, and, as applicable, explain why issuance of an order is warranted instead of promulgating a rule or entering into a consent agreement.

# TSCA Tiered Testing

*Section 4*

**When requiring the development of new information** under this subsection, the Administrator **shall employ a tiered screening and testing process**, under which the results of screening-level tests or assessments of available information inform the decision as to whether 1 or more additional tests are necessary, unless information available to the Administrator justifies more advanced testing of potential health or environmental effects or potential exposure without first conducting screening-level testing.

# What is the scope of the problem?

- Can we estimate how many chemicals in commerce are neurotoxic (NTX)?
- Best estimates-

  OTA estimates (1990) that the number chemicals (> 65,000) in commerce with NTX potential ranged from 3-28% (2,000- 20,000).

  Majority of over 500 registered pesticides have NTX mechanism/mode of action

# Endocrine Disruptor Screening Program

- **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.

- Based on two legislative mandates:
  - 1996 Federal Food, Drug and Cosmetic Act, Section 408(p)
  - 1996 Safe Drinking Water Act Amendments, Section 1457

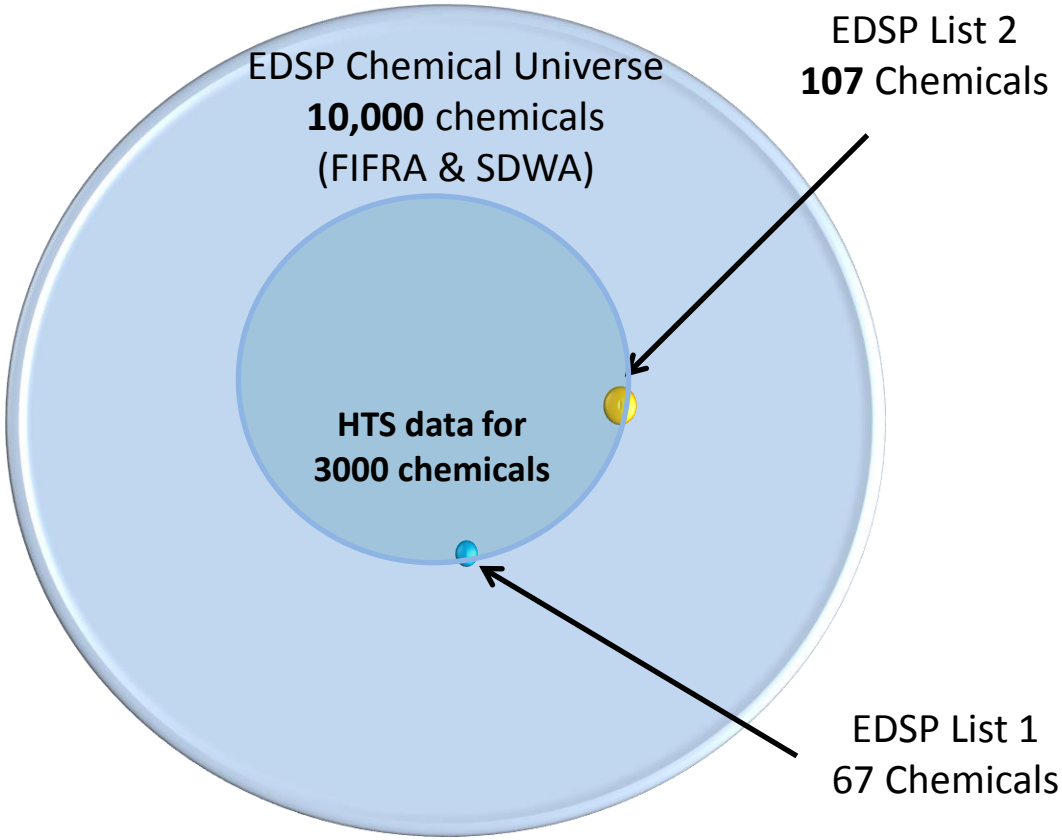
- Focus on Estrogen, Androgen, Steroidogenesis and Thyroid Pathways

- Program based on a Tiered Approach:
  - Tier 1: Screening to identify chemicals that have potential to interact with the endocrine system using a battery of assays
  - Tier 2: If found to have potential, then Tier 2 testing may be required to identify and establish doses at which adverse effects may occur

# 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

# Is Assessment of Developmental Neurotoxicity Necessary?

- Do we assess the structural and/or functional integrity of the nervous system following developmental exposure in Multigen/Extended 1 Gen or Developmental Guideline studies.

- If you don't look you don't see (Goldey *et al*., 1995; Ulbrich and Palmer, 1996, Makris *et al.*, 1999, DNT Retrospective study).

# NTX related testing

- EDSP Tiered screening recommendations for CTA (comparative thyroid assay) 4 pesticides from EDSP list 1
- Pesticide actives -101 DNT data evaluation records (DERs) with 24 DNT endpoints serving as regulatory endpoints
- Requests for TSCA new chemicals NTX testing since 1979-2016---1,010 consent orders covering 1,666 PMNs out roughly 22,000 PMNs- ---testing triggered
- 5 out of 55 New chemical categories identify NTX as CE possible NTX testing; 2/5 developmental NTX
- NTX for existing chemicals not required but one of screening criteria in OPPT work plan was NTX potential

# Summary of NTX in IRIS data base of Existing Chemicals (Tilson, 2000)

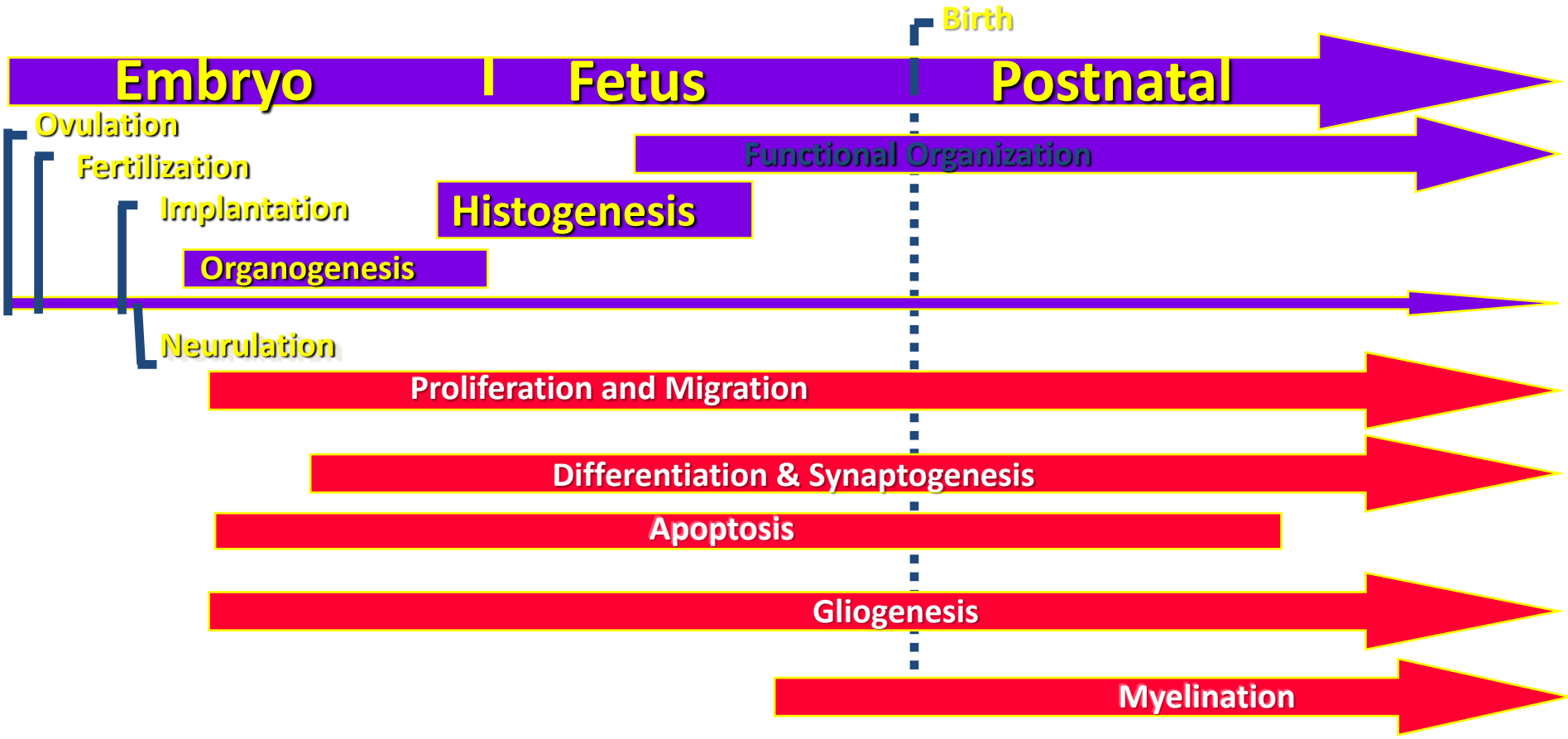
| | |
|---|---|
| **Sufficient data base for NTX** | **392** |
| • Critical effect (CE) was NTX | 74 |
| – DNT endpoint critical effect | 2 out of 74 |
| • NTX reported but not CE | 46 |
| • Non NTX | 272 |
| **Insufficient data base for NTX** | **145** |
| • Cancer assessments | 57 |
| • Noncancer assessments | 1 |
| • No values listed | 87 |
| **TOTAL** | **537** |

# Challenges in Developmental Neurotoxicology

- **Complexity of Nervous System.**
  - **number of cells.**
  - **number of cell phenotypes.**
  - **number of connections.**
- **Baseline may change rapidly with Time.**

  **each region has different time scale.**
- **Patency of blood-brain barrier limited during early development**
- **Potential for Compensation and Recovery.**
- **“Silent damage”**
  - **Not expressed till later in life or**
  - **Not revealed until challenged**

# *Development is Temporally and Regionally Determined by Multiple Processes.*



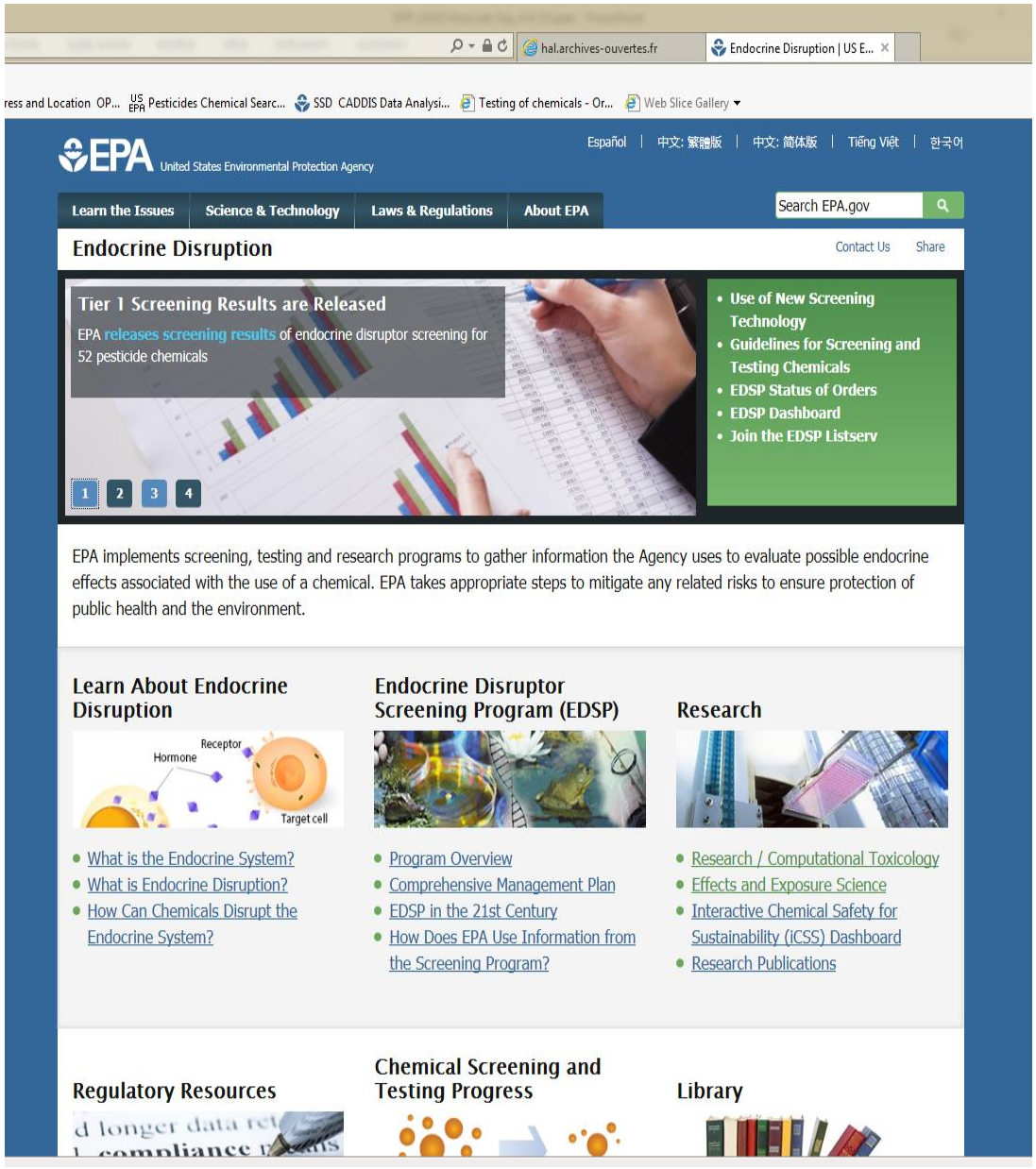

Barone, S. Jr. *et al.*, 2000; *NeuroToxicology*. 21:(1-2) 15-36.

# DNT Testing Battery Needs

- Screening of high volume of chemicals
- Coverage of a broad number of biological processes and targets
- Well characterized performance based criteria for test of battery
- Reference list of chemicals for tests
- Predictive of adverse outcomes
- Informative of chemical categories, SAR and QSAR for prioritizing further testing

# Summary of Use of NTX and Developmental NTX in Decision Context

- Screening and prioritization of thousands of chemicals
- Testing of chemicals based upon insight of AOPs- potential to reduce number of animals used in testing
- Setting up biological context for read across approaches using AOP's and HTS
- Informing weight of evidence analysis
- Inform risk decision using SAR, QSAR, read across approaches in New Chemicals context




# Acknowledgements

- EPA OSCP/OPP
- EPA ORD

https://www.epa.gov/endocrine-disruption

# References


- USEPA Neurotoxicity Risk assessment guidelines 1998
  - https://www.epa.gov/sites/production/files/2014-11/documents/neuro_tox.pdf
- OTA, 1990, *Neurotoxicity: Identifying and Controlling Poisons of the Nervous System*
  - http://www.wws.princeton.edu/~ota/ns20/year_f.html
- OTA, 1995: *Screening and Testing Chemicals in Commerce* (Chapter 4)
  - http://www.wws.princeton.edu/~ota/ns20/year_f.html

# Recommended Additional Testing including TIER 2 for Chemicals that Showed Potential Interaction with E, A and/or T

| | 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 "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]

**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