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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 [*insert date 60 days after date of publication in the Federal Register*].

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 Cosmetic Act (FFDCA), 21 U.S.C. 346a(p). Section 408(p)(1) 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 such other effects as [EPA] may designate.” [21 U.S.C. 346a(p)(1)]. Section 408(p)(2) requires that the screening program be implemented “after obtaining public comment and review...by the scientific advisory panel established under section 25(d) of the Federal Insecticide, Fungicide, and Rodenticide Act...” [21 U.S.C. 346a(p)(2)].

This document describes the new scientific methods that are available as alternatives to some of the current EDSP Tier 1 screening assays and solicits public comment on EPA’s plan to use these alternative approaches to screen chemicals for their ability to interact with the endocrine system. The approach described in this document is not binding on either EPA or any outside

parties, and EPA may depart from the approach presented in this document where circumstances warrant and without prior notice.

C. What Action is the Agency Taking?

This document describes and solicits comments on how EPA is planning to incorporate scientific advancements and tools into the EDSP. The adoption of scientific advancements into the EDSP has been underway and part of the public dialogue about EDSP for several years. As EPA has consistently indicated, the Agency intends to continue to incorporate in the EDSP new methods involving high throughput assays and computational toxicology. Also, EPA has identified a universe of approximately 10,000 chemicals as potential candidates for screening and testing under the EDSP (Ref. 1). This approach is expected to accelerate the pace of screening, add efficiencies, decrease costs, and reduce animal testing.

EPA is planning to incorporate the partial screening results from validated high throughput assays and computational models as an alternative to data from some of the current assays in the EDSP Tier 1 screening battery. Currently, EPA has partial screening results for over 1800 chemicals that have been evaluated using the high throughput assays and computational model for the estrogen receptor pathway.

The use of high-throughput assays and computational models for EDSP screening is an initial step in EPA's integration of 21st-century integrated assessment and testing approaches broadly, beyond EDSP, across a wide range of chemicals related to regulatory and non-regulatory decisions made in programs under the Agency's purview (Ref. 2). Much of the knowledge gained in using these approaches for EDSP screening will be useful in applying high throughput assays and computational models to thousands of chemicals across many toxicological endpoints and exposure scenarios.

D. What Should I Consider as I Prepare My Comments for EPA?

1. *Submitting CBI.* Do not submit this information to EPA through [regulations.gov](http://www.epa.gov/regulations) or email. Clearly mark the part or all of the information that you claim to be CBI. For CBI information in a disk or CD-ROM that you mail to EPA, mark the outside of the disk or CD-ROM as CBI and then identify electronically within the disk or CD-ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that includes information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

2. *Tips for preparing your comments.* When preparing and submitting your comments, see the commenting tips at <http://www.epa.gov/dockets/comments.html>.

II. Background

A. What is the Endocrine Disruptor Screening Program (EDSP)?

The Food Quality Protection Act (FQPA) of 1996 amended FFDCFA to require 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 such other effects as [EPA] may designate” (21 U.S.C. 346a(p)(1)). Also in 1996, the Agency chartered the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), under the provisions of the Federal Advisory Committee Act (FACA) (5 U.S.C. App. 2, section 9(c)), to provide advice on developing an endocrine disruptor screening program (Ref. 3). The EDSTAC was comprised of members representing the commercial chemical and pesticides industries, Federal and State agencies, worker protection and labor organizations, environmental and public health groups, and research scientists. EDSTAC recommended that EPA’s program address both potential human and wildlife effects; examine effects on estrogen, androgen, and thyroid hormone-related processes; and include non-pesticide chemicals, contaminants, and mixtures in addition to pesticide chemicals (Ref. 2).

In 1998, based on the EDSTAC recommendations, EPA established the EDSP using a two-tiered approach (Ref. 4). The purpose of Tier 1 (referred to as “screening”) is to identify substances that have potential biological activity (“bioactivity”) in the estrogen, androgen, or thyroid hormone pathways using a battery of assays. The purpose of Tier 2 (referred to as “testing”) is to identify and establish a dose-response relationship for any adverse effects that might result from the endocrine bioactivity identified through the Tier 1 assays. The ultimate purpose of the EDSP is to provide information to the Agency that will allow the Agency to evaluate any possible endocrine effects associated with the use of a chemical and take appropriate steps to mitigate any related risks to ensure protection of public health.

In 2009, the Agency issued test orders requiring Tier 1 screening for 67 chemicals (“List 1”) (Ref. 5). Between the time needed to review the substantial volume of “other scientifically relevant information” submitted by test order recipients to satisfy selected screening assays, the time and resources of industry spent generating data, the time spent by the Agency reviewing the information, and the delays resulting from the limited laboratory capacity for conducting many of the Tier 1 assays and corresponding time extension requests, the review of the initial List 1 chemicals has taken over four years and has imposed significant burdens on test order recipients and the agency. The Agency is still finalizing the data evaluation records and determinations concerning which of the List 1 chemicals need further Tier 2 testing. More information on the EDSP history and the status of current activities is available at <http://www.epa.gov/endo>.

B. What is Meant by “High Throughput Assays and Computational Model”?

High throughput assays are automated methods that allow for a large number of chemicals to be rapidly evaluated for a specific type of bioactivity at the molecular or cellular level. This approach, which can help identify compounds that may modulate specific biological pathways, was initially developed by pharmaceutical companies for drug discovery. The results of these methods provide an initial understanding of a biochemical interaction or possible role of a chemical in a given biological process. *In vitro* high throughput assays are usually conducted using a microtiter plate: a plate containing a grid with a large number of small divots called “wells.” The wells contain chemical and/or biological substrate (e.g., living cells or proteins). Depending on the nature of the experiment, changes can be detected (e.g., color, fluorescence, etc.) when the chemical is added to indicate whether there is bioactivity. High throughput microtiter plates typically come in multiples of 96 wells (96, 384, or 1536), so that through the use of robotics, data processing and control software, liquid handling devices, and sensitive detection methods, an extremely large number of chemicals can be evaluated very efficiently.

High throughput assays can be run for a range of test chemical concentrations and produce concentration-response information representing the relationship between chemical concentration and bioactivity. The concentration-response data from multiple assays can be mathematically integrated in a computational model of a biological pathway, providing values representative of a chemical’s bioactivity in that pathway (e.g., estrogen receptor pathway). To reduce non-specific results, the computational model can use results from multiple assays and technologies to predict whether a chemical is truly bioactive in the pathway being evaluated. The most prominent cause of non-specific results (activity in an assay that is likely not due to bioactivity of the chemical in the pathways) is cytotoxicity in cell-based assays. In other cases, chemicals influence the assays through a manner dependent on the physics and chemistry of the technology platform (i.e., “assay interference”).

C. What is ToxCast™?

To improve efficiencies in screening and testing chemicals, EPA scientists are harnessing advances in molecular and systems biology, chemistry, toxicology, mathematics, and computer technology. In doing this, they are helping to revolutionize chemical screening and safety testing based on advances in computational toxicology. A major part of this effort is the Agency's Toxicity Forecaster, or ToxCast™, which uses automated, robotics-assisted high throughput assays to expose living cells or proteins to chemicals and measure the results. The high throughput assays produce concentration-response information representing the relationship between chemical concentration and bioactivity. These innovative methods have the potential to quickly and efficiently screen large numbers of chemicals and other substances. ToxCast™ is part of EPA's contribution to a federal research collaboration called “Toxicity Testing in the 21st Century”, or “Tox21,” pooling resources and expertise from EPA, the National Institutes of Health and the U.S. Food and Drug Administration to use robotics for screening thousands of chemicals for potential bioactivity (Ref. 6).

As part of EPA's commitment to gather and share its chemical data openly and clearly, all ToxCast™ chemical data are publicly available through user-friendly web applications called the interactive Chemical Safety for Sustainability (iCSS) and EDSP21 dashboards (Refs. 7 and 8). The EDSP21 and iCSS dashboards provide accessible portals for users to search and query the ToxCast™ chemical data. Users can review chemicals and data of interest, as well as export the information. Making ToxCast™ data available through the dashboards creates an environment that encourages external stakeholder interactions identifying potential issues, concerns, and suggesting improvements.

D. What is Meant by the ToxCast™ ER Model for Bioactivity?

The ToxCast™ ER Model for bioactivity ("ER Model") includes data from 18 estrogen receptor (ER) high throughput assays from ToxCast™ that detect multiple events in the receptor pathway. The ER Model also includes a computational module that integrates the assay data to produce a value for ER agonist and antagonist bioactivity for each chemical (Ref. 9). An ER agonist binds and activates the receptor, and an antagonist binds and blocks activation. These 18 high throughput assays measure bioactivity at different sites along the ER pathway including receptor binding, receptor dimerization, chromatin binding of the mature transcription factor, gene transcription and changes in estrogen-receptor growth kinetics. Bioactivity (i.e., response) is measured using various detection methods (e.g., fluorescence, etc.) across a range of concentrations to examine potential concentration-response relationships, including no change across concentrations indicating no bioactivity. Concentration-response relationships for each assay are mathematically integrated in the "ER Model" to quantify bioactivity from multiple assays. The computational model integrates the results of each of the 18 ER assays as an area under the curve (AUC) for ER agonist or antagonist bioactivity for each chemical. The bioactivity values generally range from 0 to 1 for each chemical, with 0 indicating no bioactivity and 1 approximating the positive reference chemical (e.g., estradiol for ER agonism).

In order to validate the ER Model, ToxCast™ data have been collected and reviewed on over 1800 chemicals, including ER reference agonists and antagonists (Ref. 10). ER agonist and antagonist bioactivity scores from the "ER Model" compare very well with reported bioactivity of reference chemicals across a range of structures and potencies. Of the over 1800 chemicals tested, over 1700 chemicals had very low or no detectable ER bioactivity (Ref. 10). The "ER Model" bioactivity scores were validated by comparing the scores to 45 reference chemicals, equivalent to a performance-based approach to validation. EPA also compared "ER Model" results to a database of curated uterotrophic studies published in peer-reviewed literature. ER agonist bioactivity scores accurately predicted *in vivo* ER agonist activity for a large set (~150) of chemicals with uterotrophic data (Refs. 9 and 11). The validation of the "ER Model" as an alternative screening method for three current Tier 1 assays (ER binding, ER transcriptional activation (ERTA), and uterotrophic) was peer reviewed by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) in December 2014 (Refs. 9 and 11). The FIFRA SAP fully endorsed the use of these alternatives for the ER binding and ERTA assays;

however, there was not consensus among panel members on the use of the “ER Model” as an alternative for the uterotrophic assay (Ref. 11). In response to the concerns raised by the FIFRA SAP, EPA has published a paper clarifying the relationship between “ER Model” bioactivity and uterotrophic results, and illustrating that a uterotrophic assay would provide no added value if “ER Model” data are available (Ref. 12). Based on these findings, EPA concludes that “ER Model” data are sufficient to satisfy the Tier 1 ER binding, ERTA and uterotrophic assay requirements. The Agency intends to build on the performance-based validation approach presented at the December 2014 FIFRA SAP expanding this approach to include other key events in the estrogen pathway.

III. Using High Throughput Assays and Computational Models for Screening

A. How Will ToxCast™ Data be Used for Screening in the EDSP?

The ability to screen chemicals rapidly for bioactivity in several endocrine pathways, and reducing the use of animals in testing, have been EDSP goals since 1998, when the program was first adopted (Ref. 4). As previously noted, when the first Tier 1 orders (for List 1 chemicals) were issued in 2009, EPA had not confirmed the reliability and relevance of the ToxCast™ results so that they could be cited as “other scientifically relevant information” to satisfy the Tier 1 ER binding, ERTA, and uterotrophic assays (Ref. 13). However, since that time, EPA has reached a critical juncture, determining that the science has progressed such that reevaluation of EPA’s earlier position is warranted. Based on scientific advances, EPA intends to implement the use of high throughput assays and computational models to evaluate, and to a significant extent, screen chemicals. The *in vitro* high throughput and computational model alternatives provide an accurate quantitative measure of specific endocrine pathway bioactivity and mechanisms. The current Tier 1 battery includes animal-based assays that do not clearly identify or differentiate pathways and mechanisms. Specifically, the current Tier 1 ER binding, ERTA and uterotrophic assays do not provide both estrogen agonist and antagonist activity and animals are required to conduct the ER binding and uterotrophic assays.

EPA is planning to adopt *in vitro* high throughput assays and computational models for detecting and measuring ER agonist and antagonist bioactivity as an alternative for three current Tier 1 assays: 1) ER binding *in vitro* assay (Ref. 14); 2) ER transcriptional activation *in vitro* assay (ERTA) (Ref. 15); and 3) *in vivo* uterotrophic assay (Refs. 16 and 17). EPA is also planning to accept existing results for chemicals that have been evaluated using the ToxCast™ “ER Model” for bioactivity. The accompanying database contains the ER agonist bioactivity and ER antagonist bioactivity for over 1800 chemicals and identifies those chemicals that are pesticide active ingredients, pesticide inert ingredients, and on EDSP Lists 1 or 2 (Ref. 10). This is a “living” database that will continue to incorporate bioactivity results for chemicals as they become available. This database is available at <http://www.epa.gov/endo> and in the docket identified for this document in a format that can be easily reviewed and manipulated electronically (Ref. 10). It is important, however, not to equate a determination of a chemical’s

bioactivity from the “ER Model” with a determination that a chemical causes endocrine disruption. The World Health Organization (WHO)/International Programme on Chemical Safety (IPCS) defines endocrine disruption as being caused by “an exogenous substance or mixture that alters function(s) of the endocrine system...and ...consequently causes adverse health effects in an intact organism or its progeny, or (sub)populations” (Ref. 18). Bioactivity is an indicator that a chemical has the potential to alter endocrine function, but (1) whether the chemical actually alters endocrine function and (2) whether that altered function produces an adverse outcome in an intact animal cannot be determined without further testing (i.e., Tier 2 testing).

The EDSP has been developed over the past 19 years, and has demonstrated that the current screening process may take upwards of 5 years before a Tier 1 decision is available or Tier 2 test orders are issued. In light of recent advances in high throughput assays and computational models, and advances likely to come in the next two years, it is prudent for the Agency to consider new, rapid screening methods. The availability of additional alternative high throughput assays and computational models in the near term will allow EPA to screen more chemicals in less time, involve fewer animals, and cost less for everyone. Furthermore, reconsideration of the EDSP List 2 chemicals may be appropriate since “ER Model” data are available for many List 2 and other chemicals (Refs. 10 and 19). Ongoing use of high throughput assays and computational models will address thousands of chemicals in the future.

These advancements in the EDSP screening program will not affect the overall framework-- i.e., the Tier 1 screening battery and Tier 2 testing approach focused on estrogen, androgen and thyroid pathways in humans and wildlife remains unaffected. Instead, as discussed above, EPA is planning to adopt sensitive, specific, quantitative, and efficient screening methods that will rapidly screen many chemicals and substantially decrease costs and animal use and may be used as an alternative to some EDSP Tier 1 screening assays. Accordingly, EPA intends a future recipient of an EDSP test order to be able to satisfy the screening requirement for ER, ERTA, and uterotrophic in one of three ways: 1) cite existing ToxCast™ “ER Model” for bioactivity data as “other scientifically relevant information” (where available); 2) generate new data relying on the 18 ER high throughput assays and the ToxCast™ “ER Model” for bioactivity; or 3) generate their own data using the current Tier 1 ER binding, ERTA, and uterotrophic assays.

B. How Does EPA Intend to Use High Throughput Assays and Computational Models for the EDSP in the Future?

EPA believes that ongoing adoption of alternative methods and technologies will continue to advance EDSP screening of chemicals for bioactivity in the estrogen, androgen, and thyroid pathways. EPA is continuing research on the “ER Model” to determine if ToxCast™ assays can provide comparable information as that of the Female Rat Pubertal and the Fish Short Term Reproduction assays. In addition, research continues on the ToxCast™ “AR Model” for bioactivity which, if fully validated, may be considered as an alternative (alone or with the

“ER Model”) for the following current Tier 1 assays: AR binding, Male Rat Pubertal, Hershberger, and Fish Short Term Reproduction. Research is also underway to develop steroidogenesis ToxCast™ (STR) and thyroid (THY) bioactivity models. Over time, the Agency’s goal is to develop a set of “non-animal” high throughput assays and computational bioactivity models as an alternative to all of the assays in the current Tier 1 screening battery. The following table is intended to illustrate the evolution of screening in the EDSP:

Current EDSP Tier 1 Battery of Assays	Alternative High Throughput Assays and Computational Model for EDSP Tier 1 Battery
Estrogen Receptor (ER) Binding	ER Model (alternative)
Estrogen Receptor Transactivation (ERTA)	ER Model (alternative)
Uterotrophic	ER Model (alternative)
Female Rat Pubertal	ER, STR , and thyroid (THY) Models (<i>Future</i>)
Male Rat Pubertal	AR, STR , and THY Models (<i>Future</i>)
Androgen Receptor (AR) Binding	AR Model (<i>Future</i>)
Hershberger	AR Model (<i>Future</i>)
Aromatase	STR Model (<i>Future</i>)
Steroidogenesis (STR)	STR Model (<i>Future</i>)
Fish Short Term Reproduction	ER, AR, and STR Models (<i>Future</i>)
Amphibian Metamorphosis	THY Model (<i>Future</i>)

The table indicates combinations of various alternative assays and models that might overlap for evaluating potential endocrine bioactivity of chemicals. The *in vitro* high throughput and computational model alternatives provide a focused evaluation of the mechanistic aspects of endocrine pathways, thereby providing specific and quantitative measures of bioactivity. Several assays in the Tier 1 battery rely on intact animals and identify bioactivity in the multiple biological pathways present. For this reason, the specificity of the *in vitro* high throughput and computational model alternatives may be more informative of specific endocrine pathway bioactivity.

The annual EDSP Comprehensive Management Plan and future FIFRA SAP meetings are opportunities for staying informed on EPA’s scientific progress on the evolution of Tier 1 screening in the EDSP. For information, visit EPA’s Website (<http://www.epa.gov/endo>) or sign-up to receive announcements go to (<http://www.epa.gov/endo/pubs/assayvalidation/listserv.htm>).

IV. Issues for Comment

In connection with EPA's stated intention to use the scientific tools discussed in this Notice as alternatives to some of the current EDSP Tier 1 screening assays, EPA is specifically seeking public comment on the following:

1. The use of the ToxCast™ "ER Model" for bioactivity as an alternative method for the current ER binding and ERTA Tier 1 screening assays.
2. The use of the ToxCast™ "ER Model" for bioactivity as an alternative method for the current uterotrophic Tier 1 screening assay.
3. The use of results from the ToxCast™ "ER Model" for bioactivity on over 1800 chemicals as partial screening for the estrogen receptor pathway.

V. References

The following is a listing of the documents that are specifically referenced in this document. The docket includes these documents and other information considered by EPA, including documents that are referenced within the documents that are included in the docket, even if the referenced document is not physically located in the docket. For assistance in locating these other documents, please consult the technical person listed under FOR FURTHER INFORMATION CONTACT.

1. U.S. EPA. Endocrine Disruptor Screening Program; Universe of Chemicals and General Validation Principles. November 2012. Available at http://www.epa.gov/endo/pubs/edsp_chemical_universe_and_general_validations_white_paper_11_12.pdf.
2. U.S. EPA. 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. September 30, 2011. Available at http://www.epa.gov/endo/pubs/edsp21_work_plan_summary%20overview_final.pdf.
3. U.S. EPA. Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC); Final Report. August 1998. Available at <http://www.epa.gov/endo/pubs/edspoverview/finalrpt.htm>.
4. U.S. EPA. Endocrine Disruptor Screening Program; Proposed Statement of Policy; Notice. **Federal Register** (63 FR 71542, December 28, 1998) (FRL-6052-9).
5. U.S. EPA. Endocrine Disruptor Screening Program; Tier 1 Screening Order Issuance Announcement; Notice. **Federal Register** (74 FR 54422, October 21, 2009) (FRL-8434-8).

6. U.S. EPA. Office of Research and Development (ORD); Description of Computational Toxicology Research Program. Available at <http://epa.gov/ncct>.
7. U.S. EPA. Interactive Chemical Safety for Sustainability (iCSS) Dashboard, Version 0.5. Available at <http://actor.epa.gov/dashboard>.
8. U.S. EPA. EDSP21 Dashboard. Available at <http://actor.epa.gov/edsp21>.
9. U.S. EPA. Integrated Bioactivity and Exposure Ranking: A Computational Approach for the Prioritization and Screening of Chemicals in the Endocrine Disruptor Screening Program. December 2014. Docket ID No. EPA-HQ-OPP-2014-0614-0003. Available at <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2014-0614-0003>.
10. U.S. EPA. Endocrine Disruptor Screening Program (EDSP); Estrogen Receptor Bioactivity Based on ToxCast™ “ER Model.” June 1, 2015. Available at <http://www.epa.gov/endo>.
11. U.S. EPA. FIFRA SAP Minutes No. 2015-01. FIFRA SAP Meeting on the Integrated Bioactivity and Exposure – Based Prioritization and Screening, held December 2-4, 2014. Docket ID No. EPA-HQ-OPP-2014-0614-0029. March 2, 2015. Available at <http://www.epa.gov/scipoly/sap/meetings/2014/december/120214minutes.pdf>.
12. Browne, P., Judson, R.S., Casey, W., Kleinstreuer, N., Thomas, R.S. Screening Chemicals For Estrogen Receptor Bioactivity Using A Computational Model. Manuscript accepted for publication. *Environ. Sci. Technol.* June 12, 2015. Available in the docket and electronically at <http://pubs.acs.org/journal/esthag>.
13. U.S. EPA. Endocrine Disruptor Screening Program; Policies and Procedures for Initial Screening; Notice. **Federal Register** (74 FR 17560, April 15, 2009) (FRL-8399-9). Note: the status and progress of all List 1 Tier 1 orders are available at <http://www.epa.gov/endo/pubs/toresources/index.htm>.
14. U.S. EPA. Endocrine Disruptor Screening Program Test Guidelines; OPPTS 890.1250: Estrogen Receptor Binding Assay Using Rat Uterine Cytosol (ER-RUC). October 2009. EPA 740-C-09-005. Available at http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series890.htm.
15. U.S. EPA. Endocrine Disruptor Screening Program Test Guidelines; OPPTS 890.1300: Estrogen Receptor Transcriptional Activation (Human Cell Line (HeLa-9903)). October 2009. EPA 740-C-09-006. Available at http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series890.htm.

16. U.S. EPA. Endocrine Disruptor Screening Program Test Guidelines; OPPTS 890.1600: Uterotrophic Assay. October 2009. EPA 740-C-09-0010. Available at http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series890.htm.

17. Organization of Economic Co-operation and Development (OECD). Test Guideline No. 440: Uterotrophic Bioassay in Rodents: A short-term screening test for oestrogenic properties. OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris. DOI: <http://dx.doi.org/10.1787/9789264067417-en>.

18. World Health Organization (WHO)/International Programme on Chemical Safety (IPCS). Global Assessment of the State-of-the-Science of Endocrine Disruptors. WHO/IPCS/EDC/02.2. 2002. Available at http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en.

19. U.S. EPA. Endocrine Disruptor Screening Program; Final Second List of Chemicals and Substances for Tier 1 Screening; Notice. **Federal Register** (78 FR 35922, June 14, 2013) (FRL-9375-8). Available at <http://www.gpo.gov/fdsys/pkg/FR-2013-06-14/pdf/2013-14232.pdf>.

Authority: 21 U.S.C. 346a(p).

Dated: June 11, 2015.

James J. Jones,

Assistant Administrator, Office of Chemical Safety and Pollution Prevention.

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