ENVIRONMENTAL PROTECTION AGENCY

[EPA-HQ-OPP-2021-0756; FRL-10116-01-OCSPP]

Availability of New Approach Methodologies in the Endocrine Disruptor Screening Program; Notice of Availability and Opportunity for Comment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of availability.

SUMMARY: The Environmental Protection Agency (EPA) is announcing the availability of and soliciting public comment on a draft White Paper entitled "Availability of New Approach Methodologies (NAMs) in the Endocrine Disruptor Screening Program (EDSP)." This draft White Paper was developed pursuant to the Federal, Food, Drug and Cosmetic Act (FFDCA), which requires EPA to develop a screening program, 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 endocrine effects. This draft White Paper announces that certain NAMs have been validated and may now be accepted by the EPA as alternatives for certain EDSP Tier 1 assays while others are useful for prioritization purposes and for use as other scientifically relevant information, where appropriate, in weight of evidence evaluations.

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-OPP-2021-0756, through the Federal eRulemaking Portal at *https://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. Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at *https://www.epa.gov/dockets*.

FOR FURTHER INFORMATION CONTACT: Natalie Bray, Pesticide Reregistration Division (7508M), Office of Pesticide Programs, Environmental Protection Agency; telephone number: (202) 566-2222; email address: *bray.natalie@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 environmental, human health, farm worker, and agricultural advocates; the chemical industry; pesticide users; and members of the public interested in the sale, distribution, or use of pesticides. Since others also may be interested, the agency has not attempted to describe all the specific entities that may be affected by this action. If you have any questions regarding the applicability of this action to a particular entity, contact the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. What should I consider as I prepare my comments for EPA?

1. *Submitting CBI*. Do not submit CBI information to EPA through regulations.gov or email. Clearly mark the part or all of the information that you claim to be 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. *Multimedia submissions*. Multimedia submissions (audio, video, etc.) must be accompanied by a written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. The EPA will generally not consider comments or comment contents located outside of the primary submission (*i.e.*, on the web, cloud, or other file sharing system).

3. *Tips for preparing your comments*. When preparing and submitting your comments,

see the commenting tips at https://www.epa.gov/dockets/comments.html. Please note that once submitted, comments cannot be edited or removed from the docket. The EPA may publish any comment received to its public docket.

II. Executive Summary

A. *What is the Agency's authority for taking this action?*

Section 408(p)(1) of the Federal, Food, Drug and Cosmetic Act (FFDCA), 21 U.S.C. 408, 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 endocrine effects as [EPA] may designate."

B. What action is the Agency taking?

The Agency is releasing the draft document entitled "Availability of New Approach Methodologies (NAMs) in the Endocrine Disruptor Screening Program (EDSP)" [herein called the draft "White Paper"]. This draft White Paper announces that certain NAMs have been validated and may now be accepted by the EPA as alternatives for certain EDSP Tier 1 assays while others are useful for prioritization purposes and for use as other scientifically relevant information, where appropriate, in weight of evidence evaluations. The draft White Paper provides further details concerning when specified NAMs may be used.

In 1998, pursuant to FFDCA section 408(p)(1), EPA introduced the EDSP including the use of a two-tiered screening framework consisting of a battery of *in vitro* and *in vivo* assays (63 FR 42852, August 11, 1998 (FRL-6021-3) and 63 FR 71542, December 28, 1998 (FRL-6052-9)). The purpose of Tier 1 screening is to identify chemicals that have potential biological activity ("bioactivity") in the estrogen, androgen or thyroid hormone pathways using a battery of assays. For more than a decade at the EPA, research efforts have focused on the development and evaluation of high-throughput *in vitro* assays and *in silico* methods as NAMs, including databases and computational models, for use as alternatives to the current suite of assays in the

EDSP Tier 1 battery to accelerate the pace of screening, add efficiencies, decrease costs, and reduce animal testing.

EPA has determined that the Estrogen Receptor (ER) pathway model based on the full 18-assay ToxCast/Tox21 battery may be used as an alternative to performing certain EDSP Tier 1 screening assays: ER binding *in vitro* assay (OCSPP 890.1250), ER transcriptional activation *in vitro* assay (ERTA; OCSPP 890.1300), and the *in vivo* Uterotrophic assay (rat) (OCSPP 890.1600). EPA has further determined that the Androgen Receptor (AR) pathway model based on the full 11-assay ToxCast/Tox21 battery may be used as an alternative for the AR binding *in vitro* assay (OCSPP 890.1150). The data from these NAMs will be evaluated on a chemical-by-chemical basis (each assay evaluated independently).

The following models and assays are not yet accepted by the EDSP as alternatives *per se* for Tier 1 screening assays, but may be used for priority setting for EDSP Tier 1 screening or for consideration for use as other scientifically relevant information, where appropriate in weight of evidence evaluations:

(1) ER and AR pathway models using assay subsets (also referred to as reduced or minimal assay data sets); (2) *In Silico* Qualitative Structure Activity Relationship Consensus Models for ER and AR (*https://ntp.niehs.nih.gov/whatwestudy/niceatm/comptox/ct-opera/opera.html*); (3) Integration of Bioactivity and Exposure (Integrated Bioactivity Exposure Ratio), which compares an estimated external dose threshold for a biological effect, based on an internal dose (*i.e.*, plasma concentration) derived from bioactivity data (*e.g.*, ER and AR pathway model outputs), with estimates of exposure; and, (4) The Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) tool for interspecies extrapolation.

EPA requests the public provide comment on the clarity and completeness of the draft document. Given the strengths and uncertainties of these methods, EPA also requests the public provide comment on the draft conclusions that certain NAMs have been validated and may now be accepted by the EPA as alternatives for certain EDSP Tier 1 assays while others are useful for

prioritization purposes and for consideration for use as other scientifically relevant information.

Included in the docket for this action are two documents that respond to comments on related subject matter. One document responds to comments received in response to a notice issued in the *Federal Register* of June 19, 2015 (80 FR 35350 (FRL-9928-69), see also docket ID No. EPA-HQ-OPPT-2015-0305) requesting comment on EPA's document titled "Endocrine Disruptor Screening Program: Use of High Throughput Assays and Computational Tools." The other document contains EPA's responses to comments regarding the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) Meeting from November 28-30, 2017 (82 FR 26097, June 6, 2017 (FRL-9962-79) and 82 FR 36137, August 3, 2017 (FRL-9965-61), see also docket ID No. EPA-HQ-OPP-2017-0214). EPA is including these documents in the docket for this action because they provide useful context on past public input on the EDSP which EPA considered when developing the draft White Paper. EPA is not requesting public comment on these response to comments documents.

III. Do guidance documents contain binding requirements?

As guidance, the draft White Paper is not binding on the Agency or any outside parties, and the Agency may depart from it where circumstances warrant and without prior notice. While EPA has made every effort to ensure the accuracy of the discussion in the guidance, the obligations of EPA and the regulated community are determined by statutes, regulations, or other legally binding documents. In the event of a conflict between the discussion in the guidance documents and any statute, regulation, or other legally binding document, the guidance documents will not be controlling.

Authority: 21 U.S.C. 408.

Dated: January 13, 2023.

Michal Freedhoff,

Assistant Administrator, Office of Chemical Safety and Pollution Prevention.

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