

AGENDA
U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA)
FIFRA SCIENTIFIC ADVISORY PANEL (SAP)
OPEN MEETING
December 2-4, 2014
FIFRA SAP WEB SITE <http://www.epa.gov/scipoly/sap/>
DOCKET NUMBER: EPA-HQ-OPP-2014-0614
U.S. ENVIRONMENTAL PROTECTION AGENCY
CONFERENCE CENTER LOBBY LEVEL
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2777 S. CRYSTAL DRIVE, ARLINGTON, VA 22202

**Scientific Issues Associated with Integrated Endocrine Bioactivity and Exposure-Based
Prioritization and Screening**

Please note that all times are approximate (see note at the end of the Agenda).

Day 1 Tuesday, December 2, 2014
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- 9:00 A.M. Opening of Meeting and Administrative Procedures** – Fred Jenkins, Ph.D., Designated Federal Official, Office of Science Coordination and Policy, EPA

- 9:05 A.M. Introduction and Identification of Panel Members** – James McManaman, Ph.D., FIFRA Scientific Advisory Panel (SAP) Session Chair

- 9:10 A.M. Welcome and Opening Remarks** – David Dix, Ph.D., Director, Office of Science Coordination and Policy (OSCP), EPA

- 9:20 A.M. Introduction** – Steven Knott, Director, Exposure Assessment Coordination and Policy Division (EACPD), OSCP, EPA

- 9:40 A.M. Estrogen Pathway Data and Models** – Richard Judson, Ph.D., Office of Research and Development (ORD), National Center for Computational Toxicology (NCCT), EPA

- 10:40 A.M. Break**

- 10:55 A.M. Curated Review of Uterotrophic Literature and Comparison to ToxCast Estrogen Receptor (ER) Agonist Area Under the Curve (AUC) Data** – Warren Casey, Ph.D., Director, US National Toxicology Program's Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

- 11:25 A.M. Comparison of ToxCast Data and List 1/Tier 1 ER Assays and ER Agonist Bioactivity of Endocrine Disruptor Screening Program (EDSP) Universe Chemicals** – Patience Browne, Ph.D., EACPD, OSCP, EPA
- 12:00 P.M. Lunch**
- 1:15 P.M. Androgen Pathway Data and Models** – Nicole Kleinstreuer, Ph.D., ORD, NCCT, EPA
- 1:45 P.M. Androgen Receptor (AR) Interpretation and Application** – Patience Browne, Ph.D., EACPD, OSCP, EPA
- 2:05 P.M. Break**
- 2:20 P.M. High Throughput Exposure; Toxicokinetics/Dosimetry** – John Wambaugh, Ph.D., ORD, NCCT, EPA
- 3:00 P.M. Integrated (RTK) Bioactivity Exposure Ranking (IBER), Modeling Uncertainty** – Richard Judson, Ph.D., ORD, NCCT, EPA
- 3:20 P.M. IBER Interpretation and Application** – Patience Browne, Ph.D., EACPD, OSCP, EPA
- 3:30 P.M. Adjourn**

Day 2
Wednesday December 3, 2014

- 9:00 A.M. Opening of Meeting and Administrative Procedures** – Fred Jenkins, Ph.D., Designated Federal Official, Office of Science Coordination and Policy, EPA
- 9:05 A.M. Introduction and Identification of Panel Members** – James McManaman, Ph.D., FIFRA Scientific Advisory Panel Session Chair
- 9:10 A.M. Future Directions** – Steven Knott, Director, Exposure Assessment Coordination and Policy Division (EACPD), OSCP, EPA
- 9:30 A.M. Public Comments**
- 10:30 A.M. Break**
- 10:40 A.M. Public Comments (Cont'd)**
- 12:00 P.M. Lunch**
- 1:15 P.M. Charge to Panel**

1. EPA's proposed approach for quantifying a chemical's potential estrogen bioactivity is based on a computational model integrating data from 18 high throughput ToxCast assays measuring several endpoints along the estrogen receptor (ER) signaling pathway. The computational model outputs are expressed as area under the curve (AUC) scores for ER agonist (R1) and antagonist (R2) bioactivity. Before routinely using the ER computational model in the Endocrine Disruptor Screening Program (EDSP) framework, EPA is reviewing the scientific strengths and limitations of the ER model described in the white paper to: i) prioritize chemicals for further EDSP screening and testing based on estimated bioactivity, ii) contribute to the weight of evidence evaluation of a chemical's potential bioactivity, and iii) substitute for specific endpoints in the EDSP Tier 1 battery. Please address the following charge questions relevant to Section 2 of the white paper and estrogen bioactivity:

Charge Question 1a. How clearly has EPA described the computational tools in Section 2.1 (*i.e.*, high throughput assays and models) used to estimate ER agonist and antagonist bioactivity?

- 2:15 P.M. Charge to Panel**

Charge Question 1b. What are strengths and limitations of the ER AUC model's ability to identify reference chemicals that include a variety of structures and have a wide range of *in vitro* ER bioactivities?

3:15 P.M. Break

3:30 P.M. Charge to Panel

Charge Question 1c. EPA used data from published *in vivo* studies that are methodologically consistent with EDSP Tier 1 guidelines to evaluate concordance between ER AUC model scores of *in vitro* bioactivity, and the *in vivo* uterotrophic response studies (Section 2.2.1). What are strengths and limitations of the curation methods and quality standards used for evaluating published *in vivo* studies?

4:30 P.M. Charge to Panel

Charge Question 1d. Based on all the data presented in Section 2 on ER AUC model performance including characterization of reference chemicals, and concordance with *in vivo* uterotrophic results, what are strengths and limitations of using the ER AUC
Page 2 of 3 model to distinguish and prioritize chemicals based on potential estrogen bioactivity?

5:30 P.M. Adjourn

<p>Day 3 Thursday December 4, 2014</p>
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9:00 A.M. Opening of Meeting and Administrative Procedures – Fred Jenkins, Ph.D.
Designated Federal Official, Office of Science Coordination and Policy, EPA

9:05 A.M. Introduction and Identification of Panel Members – James McManaman,
Ph.D., FIFRA SAP Advisory Panel Session Chair

9:10 A.M. Charge to Panel (Cont'd)

Charge Question 1e. Based on all the data presented in Section 2 on ER AUC model performance including characterization of reference chemicals, concordance with *in vivo* uterotrophic results, and comparison with Tier 1 assay endpoints, what are strengths and limitations of the ER AUC model to contribute to the weight of evidence determination of a chemical's potential estrogen bioactivity?

9:55 A.M. Charge to Panel

Charge Question 1f. Based on all the data presented in Section 2 on ER AUC model performance including characterization of reference chemicals, concordance with *in vivo* uterotrophic results, and comparison with Tier 1 assay endpoints, what are strengths and limitations of using the ER AUC model to substitute for EDSP Tier 1 ER binding, ER transactivation, or Uterotrophic assays for the purpose of characterizing a chemical's potential estrogen bioactivity?

10:45 A.M. Break

11:00 A.M. Charge to Panel

2. EPA's proposed approach for quantifying a chemical's potential androgen bioactivity is based on a computational model integrating data from nine high throughput ToxCast assays measuring several endpoints along the androgen receptor (AR) signaling pathway. The computational model outputs are expressed as area under the curve (AUC) scores for AR agonist (R1) and antagonist (R2) bioactivity. Before routinely using the AR computational models in the EDSP framework, EPA is reviewing the scientific strengths and limitations of the AR AUC model described in this white paper to: i) prioritize chemicals for further EDSP screening and testing based on estimated bioactivity, and ii) contribute to the weight of evidence evaluation of a chemical's potential bioactivity. Please address the following charge questions relevant to Section 3 of the white paper and androgen bioactivity:

Charge Question 2a. How clearly has EPA described the computational tools in Section 3.1 (*i.e.*, high throughput assays and models) used to estimate AR agonist and antagonist bioactivity?

11:30 A.M. Charge to Panel

Charge Question 2b. What are strengths and limitations of the AR AUC model's ability to identify reference chemicals that include a variety of structures and have a wide range of *in vitro* AR bioactivities?

12:00 P.M. Lunch

1:15 P.M. Charge to Panel (Cont'd)

Charge Question 2c. EPA plans to use data from published *in vivo* studies that are methodologically consistent with EDSP Tier 1 guidelines to evaluate concordance between AR Page 3 of 3 AUC model scores of *in vitro* bioactivity, and the *in vivo* androgenic and antiandrogenic responses (Section 3.2.1). What are strengths and limitations of the planned curation methods and quality standards for evaluating published *in vivo* studies?

2:15 P.M. Charge to Panel

Charge Question 2d. Based on the data presented in Section 3 on AR AUC model's performance, what are strengths and limitations of using the AR AUC model to distinguish and prioritize chemicals based on potential androgen bioactivity?

3:15 P.M. Break

3:30 P.M. Charge to Panel

3. For Endocrine Disruptor Screening Program (EDSP) chemicals with ToxCast estrogen receptor (ER) and androgen receptor (AR) bioactivity scores (Section 2 and 3), and ExpoCast high throughput toxicokinetics and exposure estimates (Sections 4 and 5), the IBER approach was used to rank chemicals based on the ratio between the bioactivity dose range, and the expected exposure range (Section 6). The IBER approach extends point estimates of bioactivity, toxicokinetics, and exposure for a chemical, to distribution ranges based on uncertainty and population variability. Chemical rankings are based on the ratio of the lower range of the bioactive dose, to the upper range of the exposure estimate. Please address the following charge questions relevant to Section 6 of the white paper and the IBER approach:

Charge Question 3a. How clearly has EPA described the computational tools in Section 6 to develop IBER values, including modeling uncertainty and population variability?

3:45 P.M. Charge to Panel

Charge Question 3b. What are strengths and limitations of using the IBER approach to prioritize chemicals for further EDSP screening based on the ratio between the ER bioactivity dose range, and the expected exposure range?

4:30 P.M. Charge to Panel

Charge Question 3c. What are strengths and limitations of using the IBER approach to prioritize chemicals for further EDSP screening based on the ratio between the AR bioactivity dose range, and the expected exposure range?

5:15 P.M. Adjourn

Note: Please be advised that agenda times are approximate; when the discussion for one topic is completed, discussions for the next topic will begin. For further information, please contact the Designated Federal Official for this meeting, Dr. Fred Jenkins, via telephone: (202) 564-3327; fax: (202) 564-8382; or email: jenkins.fred@epa.gov.