UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

FEB 27 2018

MEMORANDUM

SUBJECT: Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Virtual Meeting Held November 6, 2017

TO: Stanley Barone, Ph.D.,
Acting Director
Office of Science Coordination and Policy

FROM: Todd Peterson, Ph.D.,
Designated Federal Official
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

THRU: Steven M. Knott, M.S.,
Executive Secretary
FIFRA Scientific Advisory Panel
Office of Science Coordination and Policy

Attached, please find the meeting minutes of the FIFRA Scientific Advisory Panel virtual preparatory meeting held by webcast and teleconference on November 6, 2017. This report addresses the clarity and scope of charge questions in relation to scientific issues being considered by the Environmental Protection Agency regarding the Continuing Development of Alternative High-Throughput Screens to Determine Endocrine Disruption, Focusing on Androgen Receptor, Steroidogenesis, and Thyroid Pathways.

Attachment

cc:

Nancy Beck
Louise Wise
Charlotte Bertrand
Seema Schappelle
Ronnie J Bever
Scott Lynn
Katie Paul-Friedman
Richard Judson
Rusty Thomas
Richard Keigwin
Anna Lowit
Anita Pease
Wayne Miller
Robert McNally
Marietta Echeverrria
Jackie Mosby
Dana Vogel
Delores Barber
Yu-Ting Guilaran
Mike Goodis
Linda Strauss
OPP Docket

FIFRA Scientific Advisory Panel Members
Dana Boyd Barr, Ph.D.
Marion F. Ehrich, PhD, DABT, ATS
David A. Jett, PhD
James McManaman, PhD
Joseph Shaw, PhD
Sonya K. Sobrian, PhD

FQPA Science Review Board Members
Ionnis Androulakis, PhD
Scott Belcher, PhD
Veronica Berrocal, Ph.D.
Rebecca Clewell, Ph.D.
Kristi Pullen Fedinick, Ph.D.
J. David Furlow, Ph.D.
Susan Nagel, Ph.D.
Michael Pennell, Ph.D.
Edward Perkins, Ph.D.
Thomas Zoeller, Ph.D.

SAP Minutes No. 2018-02

Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel Minutes

Scope and Clarity of Charge Questions for the Continuing Development of Alternative High-Throughput Screens to Determine Endocrine Disruption, Focusing on Androgen Receptor, Steroidogenesis, and Thyroid Pathways

November 6, 2017
FIFRA Scientific Advisory Panel
Virtual Meeting
Held via Webcast and Teleconference

Contents

SAP Minutes No. 2018-02

Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel Minutes

Scope and Clarity of Charge Questions for the Continuing Development of Alternative High-Throughput Screens to Determine Endocrine Disruption, Focusing on Androgen Receptor, Steroidogenesis, and Thyroid Pathways

November 6, 2017
FIFRA Scientific Advisory Panel
Virtual Meeting
Held via Webcast and Teleconference

Marion Ehrich

Marion Ehrich, Ph.D.
FIFRA SAP Session Chair
FIFRA Scientific Advisory Panel Staff

Date: FEB 27 2018

Todd Peterson

Todd Peterson, Ph.D.
Designated Federal Official
FIFRA Scientific Advisory Panel Staff

Date: FEB 27 2018

NOTICE

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act and established under the provisions of FIFRA as amended by the Food Quality Protection Act (FQPA) of 1996. The FIFRA SAP provides advice, information, and recommendations to the U.S. Environmental Protection Agency (EPA or Agency) Administrator on pesticides and pesticide-related issues regarding the impact of regulatory actions on health and the environment. The SAP serves as a primary scientific peer review mechanism of the EPA, Office of Pesticide Programs (OPP), and is structured to provide balanced expert assessment of pesticide and pesticide-related matters facing the Agency. FQPA Science Review Board members serve the FIFRA SAP on an *ad hoc* basis to assist in reviews conducted by the FIFRA SAP. The meeting minutes are provided as part of the activities of the FIFRA SAP.

The FIFRA SAP carefully considered all information provided and presented by the Agency, as well as information presented by the public. The minutes represent the views and recommendations of the FIFRA SAP and do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the Federal government. Mention of trade names or commercial products does not constitute an endorsement or recommendation for use.

The meeting minutes do not create or confer legal rights or impose any legally binding requirements on the Agency or any party. The meeting minutes of the November 6, 2017 FIFRA SAP virtual preparatory meeting represent the SAP's consideration and review of the scope and clarity of the draft charge questions in light of scientific issues associated with "Continuing Development of Alternative High-Throughput Screens to Determine Endocrine Disruption, Focusing on Androgen Receptor, Steroidogenesis, and Thyroid Pathways." Steven Knott, M.S., FIFRA SAP Executive Secretary, reviewed the minutes. Marion Ehrich, Ph.D., FIFRA SAP Session Chair, and Todd Peterson, Ph.D., FIFRA SAP Designated Federal Official, certified the minutes which are publicly available on the SAP website (http://www.epa.gov/sap/) under the heading of "Meetings" and in the public e-docket, Docket No. EPA-HQ-OPP-2017-0214, accessible through the docket portal: http://www.regulations.gov. Further information about FIFRA SAP reports and activities can be obtained from its website at http://www.epa.gov/sap/. Interested persons are invited to contact Todd Peterson, Ph.D., SAP Designated Federal Official, via e-mail at peterson.todd@epa.gov.

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Virtual Meeting
November 6, 2017

Scope and Clarity of Charge Questions for the Continuing Development of Alternative High-Throughput Screens to Determine Endocrine Disruption, Focusing on Androgen Receptor, Steroidogenesis, and Thyroid Pathways

PARTICIPANTS

FIFRA SAP, Session Chair
Marion F. Ehrich, Ph.D., Co-director, Laboratory for Neurotoxicity Studies,
Professor, Pharmacology and Toxicology, Department of Biomedical Sciences & Pathobiology,
Virginia-Maryland College of Veterinary Medicine, Blacksburg, VA

Designated Federal Official
Todd Peterson, Ph.D., FIFRA Scientific Advisory Panel Staff, Office of Science Coordination and Policy, EPA

FIFRA Scientific Advisory Panel Members
Dana Barr, Ph.D., Research Professor, Department of Environmental and Occupational Health, Rollins School of Public Health, Emory University, Atlanta, GA

David A. Jett, Ph.D., Director, National Institute of Health Counter ACT Program National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD

Joseph Shaw, Ph.D., Associate Professor, School of Public and Environmental Affairs, Indiana University, Bloomington, IN

Sonya K. Sobrian, Ph.D., Associate Professor, Department of Pharmacology,
Howard University College of Medicine, Washington, DC

FQPA Science Review Board Members
Ioannis Androulakis, Ph.D., Professor, Department of Chemical & Biochemical Engineering, School of Engineering, Rutgers, The State University of New Jersey, Piscataway, NJ

Scott M Belcher, Ph.D., Professor, Department of Biological Sciences, North Carolina State University, Raleigh, NC

Veronica J. Berrocal, Ph.D., Associate Professor, Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI

Rebecca Clewell, Ph.D., Chief Scientific Officer, Scitovation, Research Triangle Park, NC

J. David Furlow, Ph.D., Professor, Dept. of Neurobiology, Physiology and Behavior, University of California, Davis, CA

Susan Nagel, Ph.D., Associate Professor, Obstetrics, Gynecology & Women's Health University of Missouri, Columbia, MO

Michael Pennell, Ph.D., Associate Professor, Division of Biostatistics, College of Public Health, The Ohio State University, Columbus, OH

Edward J. Perkins. Ph.D., Environmental Laboratory, U.S. Army Engineer Research and Development Center (ERDC), US Army Corps of Engineers (USACE), Vicksburg, MS

Kristi Pullen Fedinick, Ph.D., Staff Scientist, Health and Environment Program, Natural Resources Defense Council, Washington, DC

Grant Weller, Ph.D., Research Statistician, Savvysherpa, Inc., Minneapolis, MN

Thomas Zoeller, Ph.D., Chair, Department of Biology, University of Massachusetts, Amherst, MA

Introduction

The November 6, 2017 virtual preparatory meeting focused on the scope and clarity of the charge questions and was not for Panel discussion of responses to the charge questions. The in-person public meeting of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) was held November 28 – 29, 2017.

A list of panel members for this virtual meeting is listed above. In addition, links to the supporting documents for the meeting are available on the FIFRA SAP website https://www.epa.gov/sap. There is a public docket for this meeting and copies of all meeting materials are available at https://www.regulations.gov under the docket number EPA–HQ–OPP–2017–0214.

The virtual meeting was attended by all panelists who participated in the November 28-29, 2017 meeting with the exception of Dr. Jim McManaman, FIFRA SAP Chair. Therefore, Dr. Marion Ehrich served as the Session Chair for the virtual meeting.

Dr. Todd Peterson, the Designated Federal Official (DFO) for the FIFRA SAP meeting, welcomed everyone to the virtual meeting and provided opening administrative remarks. The DFO introduced everyone present in the Agency's meeting room for the virtual meeting. The DFO thanked the panelists and Agency colleagues for all their efforts in preparing for the meeting. Dr. Marion Ehrich next led the Panel members in brief introductions including a few words about their expertise and backgrounds.

Several interesting topics were covered during this meeting: (1) U.S. Environmental Protection Agency (Agency) presentations; (2) public comments; and (3) the Panel's discussion.

Agency Presentations:

Dr. Seema Schappelle, Director of the EPA Exposure Assessment Coordination and Policy Division (EACPD) gave an overview of the Endocrine Disruptor Screening Program (EDSP). Topics addressed during the presentation include:

- EPA's statutory authority for endocrine testing.
- Scope and structure of the Endocrine Disruptor Screening Program (EDSP).
- Approach to screening and testing.
- Implementation of computational toxicology tools.
- Incorporation of alternative methods.

Dr. Ronnie Bever from the EPA, EACPD, gave an overview of the charge questions as related to the white paper topics:

- Background.
- Androgen Receptor Pathway Activity.
- Steroidogenesis Pathway Activity.
- Thyroid Conceptual Framework.

Oral Public Commenters:

Commenters who called into the virtual meeting to address the clarity and scope of the charge questions are as follows:

- Christopher Borgert, Ph.D., Is with Applied Pharmacology and Toxicology Incorporated and is representing the Endocrine Policy Forum EPF. He deferred his speaking time to Dr. Ellen Mihaich.

- Ellen Mihaich, Ph.D., Is with Environmental and Regulatory Resources and is representing the EPF. A document containing Dr. Mihaich's oral comments, as read to the panel during the virtual meeting, is posted to the docket (ID: EPA-HQ-OPP-2017-0214) at http://regulations.gov.

Panel Discussion of Scope and Clarity of Charge Questions:

The Agency read each charge question prior to the Panel's discussion of the scope and clarity. The following summarizes the Panel's discussion.

Androgen Receptor (AR) Pathway Model:

Question 1: Please comment on the Agency's efforts to address the suggestions of the previous Scientific Advisory Panel (SAP or Panel), thus confirming the suitability of the current HT AR pathway model to be used as an alternative to the low-throughput (LT) Tier 1 AR binding assay (OCSPP 890.1150).

An SAP Member asked how specific is the Panel to be about the utility of this method in terms of the Tier 1 testing or for other applications? Is this something that the Panel would be considering only in terms of a Tier 1 prioritization and schema?

The Agency responded that the goal of the alternative assays is to use them in conjunction with our high-throughput exposure modeling for prioritization and to use them in the Tier 1 testing as alternatives. Specifically, these questions are simply asking for feedback on using them as alternatives for the Tier 1 test.

Steroidogenesis Pathway Model:

Question 2: Based on the comparison of the performance of the HT H295R assay with the LT H295R assay, and the effects of reference chemicals on the synthesis of T and E2 levels only, please comment on the suitability of the HT H295R assay as an alternative to the LT H295R assay. See Sections 3.3 and 3.4**.**

There was no discussion regarding clarification for this question and the Panel moved on to the next question.

Question 3: Please comment on the strengths and limitations of integrating multiple hormone responses beyond T and E2 (*i.e.* 11 hormones vs 2 hormones) in a pathway-based analysis of the HT H295R assay. Please comment on the suitability of this HT H295R pathway model (using 11 hormones) to serve as an alternative to the LT H295R assay. See Section 3.7.2.

> One Panel member asked if the question was comparing the 11 hormone pathway based model to the low throughput and not to the high throughput 2 hormone assay?
>
> The Agency responded that this is correct.
>
> The SAP Member also asked if at any point the Panel would compare the high throughput 2 hormone to the high throughput 11 hormone.
>
> The Agency noted this was addressed in the White Paper and that there were improvements that the model offered. Overall the SAP is basically looking for high-throughput alternatives. Question 2 refers to measures with two hormones and if that would be suitable. Question 3 addresses measuring 11 hormones. Both questions address comparisons with the current validated low- throughput assay.

Question 4: The work herein presents a novel statistical integration of multiple hormone responses indicative of steroid biosynthesis in the HT H295R assay. A summary statistical metric, the maximum mean Mahalanobis distance (maxmMd), has been suggested as a tool for use in prioritization of chemicals. In addition to the use of the maxmMd to indicate the magnitude of potential effects on the steroid biosynthesis pathway expressed in H295R cells, an examination of the hormone responses that contribute to the maxmMd may provide valuable biological information to inform the weight-of-evidence evaluations performed for chemicals subjected to EDSP Tier 1 evaluation. Please comment on the strengths and limitations of using the maxmMd and the pattern of steroid hormone responses in the HT H295R assay for chemical prioritization and weight-of-evidence applications. See Sections 3.2.4, 3.3.2, and 3.7.2.

> The Session Chair asked the statisticians on the SAP if they understood this question because they may have to provide input.
>
> An SAP Member asked if the Panel was to consider and evaluate the strengths and limitations of the high throughput result, in terms of the maxmMD, as a method for prioritization prior to Tier 1 applications of the high-throughput method itself? And after that, as well, for the weight-of-evidence applications? So is there a before and after assessment of potential Tier 1 displacement?

The Agency responded yes referring to the slide that Dr. Seema Schappelle presented earlier. There is prioritization, Tier 1 evaluation, and weight of evidence before it goes to Tier 2. In the weight of evidence, the Agency decides which chemicals need to go to Tier 2 or back to a holding bin to await further analysis. This question is asking about the statistical method the Agency is using. The question asks about the metric, the strengths and limitations, and further about prioritization, the Tier 1 evaluation as part of a proposed alternative and then the weight-of-evidence application.

The SAP Member clarified by asking if the Agency would be evaluating the strengths and limitations of use in prioritization, the strengths and limitations of use in Tier 1 replacement, and then the strengths and limitations of the weight-of-evidence applications.

The Agency responded in the affirmative.

The Panel member next asked if the Agency would want the strengths and limitations of each approach and that it doesn't have to be that they would all be equal, based upon the fit for purpose type of thinking. The Member further asked whether or not the method is fit for purpose for each of these specific decisions along this pathway?

The Agency stated if this is not acceptable for use in a Tier 1 test, then the Agency would not use it in weight-of-evidence applications but could use this in prioritization.

Thyroid Conceptual Framework:

Question 5: Please refer to White Paper Section 4.2. EPA has identified AOPs for thyroid hormone disruption related to potential xenobiotic-induced alterations of thyroid homeostasis. Please comment on the completeness of the MIEs (Table 4-1), KEs, and adverse outcomes within the thyroid AOP network (Figure 4-1). Also, please provide information on any missing pathways, adverse outcomes, or other AOP-related information (*e.g.* MIEs or KEs) critical for capturing the complexity of systems biology controlled by thyroid hormones.

A Panel member asked if the panel should comment on the appropriateness of using an AOP or is it outside the scope of this question? This question seems to assume that AOPs are the right way in which to identify whether or not there are impacts to thyroid homeostasis. Does the question also include whether an AOP network approach is appropriate for this particular hormone pathway? If so, the question is whether the AOP is the right way to go? Is the panel to comment on whether or not the AOP approach itself is appropriate for thyroid homeostasis?

The Agency responded in the affirmative by saying the Panel's response on the use of the AOP approach would help the Agency in assessing the correct approach for this pathway model. However, this question's focus concerns the comprehensiveness of the network as presented. The Agency is providing the initial genesis of an approach in development. The

Agency seeks the SAP's feedback on the comprehensiveness of the approach and on the approach itself.

Question 6: Please refer to White Paper Section 4.3. EPA has summarized currently available assays and test guidelines informative of thyroid AOPs and is developing HT assays for a number of MIEs. Please comment on the ranked importance of MIEs (Table 4-3) and on whether assays for environmentally important MIEs are missing, and include information on both the biological and environmental relevance of these MIEs. In addition, please comment on other assays that would supplement or be orthogonal to the assays currently identified in Table 4.3 or for other KEs or AOs in the thyroid AOP framework (Figure 4-2).

The session chair stated that part of the answer from question 5 may fit for question 6.

One Panel member noted that part of the question appears to ask: Does the AOP capture all the relevant things that we should be thinking? The member stated this seems fair and this basically is a check in on the direction of examination of the thyroid pathway and all of its complications. It seems like the charge questions are pretty broad, which is fine, but the Agency is asking us essentially at this juncture about where things stand and where things should go.

The Agency responded that this is correct.