AGENDA

Federal Insecticide, Fungicide, and Rodenticide Act

Scientific Advisory Panel Open Meeting

May 21-23, 2013

FIFRA SAP WEB SITE http://www.epa.gov/scipoly/sap/

EPA Docket Number: EPA-HQ-OPP-2013-0075

Potomac Yard One South

2777 Crystal Drive

Arlington, VA 22202

Scientific Review of the Endocrine Disruptor Screening Program (EDSP); Tier I Assay and Battery Performance

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

Tuesday, May 21, 2013

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,** Daniel Schlenk, Ph.D., Chair FIFRA Scientific Advisory Panel

9:15 A.M. **Opening Remarks,** David Dix, Ph.D.**,** Acting Director, Office of Science Coordination and Policy, EPA: Steve Bradbury, Ph.D**.,** Director, Office of Pesticide Programs, EPA

EDSP Program Overview, Mary Manibusan, Director, Exposure Assessment Coordination and Policy Division, Office of Science Coordination and Policy, EPA

10:00 A.M. **Background: Current Validated EDSP Tier 1 Screening Assays and Battery,** Leslie Touart, Ph.D**.**, Exposure Assessment Coordination and Policy Division, Office of Science Coordination and Policy, EPA

10:30 A.M. **Break**

Scientific Review of Tier 1 Assay and Battery Performance

10:45 A.M. ***In Vitro*** **Assays,** Gregory Akerman, Ph.D., Health Effects Division, Office of Pesticide Programs, EPA

11:30 A.M. ***In Vivo*** **Mammalian Assays,** John Liccione, Ph.D., Health Effects Division, Office of Pesticide Programs, EPA

12:00 P.M. **Lunch**

1:00 P.M. **Fish Assay,** Amy Blankinship, M.S., Environmental Fate and Effects Division, Office of Pesticide Programs, EPA

1:30 P.M. **Frog Assay,** Catherine Aubee, M.P.A., Environmental Fate and Effects Division, Office of Pesticide Programs, EPA

2:00 P.M. **Battery Performance,** Tom Steeger, Ph.D, Catherine Aubee, M.P.A, Amy Blankinship, M.S., Gregory Akerman, Ph.D., Office of Pesticide Programs, EPA

2:45 P.M. **Break**

3:00 P.M. **Summary of Assay and Battery Review,** Tom Steeger, Ph.D., Environmental Fate and Effects Division, Office of Pesticide Programs, EPA

3:15 P.M. **Adjournment**

Wednesday, May 22, 2013

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. **Follow-up from Previous Day's Meeting,** Daniel Schlenk, Ph.D., Chair, FIFRA Scientific Advisory Panel

9:20 A.M. **Public Comments**

10:30 A.M. **Break**

10:45 A.M. **Public Comments (Cont'd)**

12:15 P.M. **Lunch**

1:15 P.M. **Panel Discussion of Charge Questions**

Charge Question 1. Based on the analysis of the data presented in Section III, please comment on the proficiency of the contributing laboratories to execute each assay in accordance with the test guidelines and achieve the performance criteria.

2:15 P.M.

Charge Question 2. The performance criteria for each *in vitro* assay are clearly stated in the test guidelines for the ER binding (OCSPP 890.1250), AR binding (OCSPP 890.1150), ERα Transcriptional Activation (OCSPP 890.1300, OECD 455), H295R steroidogenesis (OCSPP 890.1550) and aromatase human recombinant (OCSPP 890.1200) assays. Although contributing laboratories did not always demonstrate that results were within the specified boundaries of the performance criteria, the majority of the deviations were still close to the performance criteria. In this regard, the EPA concluded that the data were still adequate for use. Please comment on the EPA's conclusion. Please comment on when a deviation from the recommended performance criteria would render the study unreliable.

3:15 P.M.

Charge Question 3. Unlike the Hershberger and Uterotrophic assays, a positive control is not required in the male (OCSPP 890.1500) and female (OCSPP 890.1450) pubertal assays. For these *in vivo* assays with rats, coefficient of variation (CV) limits are specified in the test guidelines for most endpoints. Submissions from different laboratories sometimes fell short of meeting all the test guideline-recommended CV limits for the endpoints evaluated. However, in most cases these shortcomings were considered of minor importance to the overall results, and EPA concluded that the data are still adequate for endocrine screening. Please comment on the EPA's conclusion. Please comment on when a deviation from the recommended CV limits would render the study unreliable.

4:15 P.M.

Charge Question 4. The test guidelines for the six *in vivo* assays (Hershberger assay - OCSPP 890.1400, OECD 441; Uterotrophic assay- OCSPP 890.1600, OECD 440; Male Pubertal assay- OCSPP 890.1500; Female Pubertal assay - OCSPP 890.1450; FSTRA - OCSPP 890.1350, OECD 229 and AMA - OCSPP 890.1100) offer some guidance on setting the dose/concentration range when testing for specific effects on the E, A, or T signaling pathways. In some of the *in vivo* assays, overt toxicity was noted based on effects on growth, other sublethal effects, and even mortality at the highest dose/concentration tested. Positive Tier 1 findings indicating the potential for endocrine activity can be difficult to interpret in the presence of overt toxicity.

5:15 PM Adjourn

Thursday, May 23, 2013

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. **Follow-up from Previous Day's Meeting,** Daniel Schlenk, Ph.D., Chair, FIFRA Scientific Advisory Panel

9:20 A.M. **Panel Discussion of Charge Questions (Cont'd)**

Charge Question 5. Spinal curvature, usually manifesting as "bent tail" in *X. laevis* tadpoles, was reported in 15 of 18 AMA studies reviewed thus far. The anomaly appears to be first observed several days after study initiation, and prevalence increases with time. Overall, the prevalence of spinal curvature in these studies ranged from "a few per replicate" to 92% of a given treatment group by test termination. Experimental work by the EPA Office of Research and Development suggests that overfeeding can be a primary cause of spinal curvature in their *Xenopus* test populations; however, spinal curvature remained prevalent (range: 16-92%) in the five industry AMA studies in which feed was reduced by 50% compared to guideline recommendations.

Overall, the incidence of spinal curvature appears to be highly variable. From a qualitative review of the data, there appear to be no consistent differences in the incidence or variability of spinal curvature when studies using guideline versus reduced feeding regimes are compared. Please comment on whether the presence or prevalence of spinal curvature in test specimens, including controls, compromises the utility or validity of an AMA submission. If so, when does the prevalence of spinal curvature render the study unreliable? What technical guidance may be useful for laboratories in reducing the occurrence of spinal curvature and determining if, or at what point within the study, a study may be compromised because of this phenomenon?

10:20 A.M. **Break**

10:30 A.M.

Charge Question 6. With the exception of thyroid gross pathology findings (thyroid gland atrophy and hypertrophy) in the AMA, severity grades are generally assigned based on comparison to "normal" *X. laevis* thyroid findings depicted in the guidance or based on the professional opinion of the pathologist conducting the assessment; they are not assigned in comparison to concurrent control findings from a given study. (Please refer to Section III.2.f in the document entitled "Interpreting Amphibian Thyroid Histopathology Diagnoses" and supporting documents, OECD Guidance Document on Amphibian Thyroid Histology No. 82, 2007 and Grim et al., 2009).

a. In one study, the pathologist's report identified a lower incidence and severity of follicular cell hypertrophy when compared to the incidence and severity of this trait in control specimens. Similar trends have been observed in other studies. In this case, the pathologist concluded that the finding was potentially consistent with treatment-related delay of metamorphosis because thyroid follicular cells normally increase in height during tadpole development. Please comment on the validity of this conclusion.

11:30 A.M.

b. What guidance may be given to better distinguish between histological changes in the thyroid associated with the normal progression of metamorphosis and treatment-related effects? Are there certain lesions or diagnoses which may, by their *absence or lessened severity* as compared to controls, be indicative of treatment-related HPT effects such as delayed metamorphosis?

12:30 P.M. Lunch

1:30 P.M.

Charge Question 7. In 2008, the SAP acknowledged that the *in vivo* assays included in the Tier 1 battery provide both redundancy and complementarity for evaluating interactions with the E, A, or T signaling pathways. The panel also noted that all of the Tier 1 assays and the broad range of endpoints appeared to be necessary to "*discriminate positive and negative results*".

a. Please comment on the battery performance with respect to the anticipated complementary nature of the more complex, multi-parameter *in vivo* assays in the context of the observed responses with the case studies. Please comment separately on the E-, A-, and T-related assays and endpoints.

2:30 P.M. Break

2:45 P.M.

b. Please comment on the battery performance with respect to the anticipated redundancy across the 11 assays in the context of the observed responses with the case studies. Please comment separately on the E-, A-, and T-related assays and endpoints.

3:45 P.M.

c. The EPA concluded that the battery has performed as anticipated by the 2008 SAP. Please comment on this conclusion.

4:45 P.M.

Charge Question 8. The EPA is committed to minimizing animal usage in the screening battery while maintaining the effectiveness of the battery to answer the question of whether a chemical has the "potential" to interact with the endocrine system.

a. In 1998, the EDSTAC described the conceptual framework for Tier 1 assays and recommended the strategy to "*require the minimal number of screens and tests necessary to make sound decisions, thereby reducing the time needed to make these decisions*", and that the screens should be conducted at a minimal cost necessary to make decisions. Based on the preliminary battery performance evaluation, to what extent can the current Tier 1 battery of 11 assays be modified to reduce animal usage and/or lower cost while adequately ensuring the EPA's ability to answer the question of "*whether a chemical has the potential to interact with the endocrine system?*" More specifically, please comment on whether the Uterotrophic and Hershberger assays provide necessary redundancies in the Tier 1 battery based on this preliminary analysis. Please include in your comments what information may be lost and what uncertainties may be introduced by absence of either or both of these assays.

b. Please comment on the scientific criteria the Agency should consider in evaluating necessary redundancies and eliminating assays from the current battery.

5:45 P.M. **Closing Remarks,** Daniel Schlenk, Ph.D., Chair FIFRA Scientific Advisory Panel**;** Fred Jenkins, Ph.D., Designated Federal Official, Office of Science Coordination and Policy, EPA

6:00 P.M. **Adjournment**

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.