AGENDA

Meeting of the Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (FIFRA SAP) to Consider and Review Scientific Issues Associated with Weight-of-Evidence: Evaluating Results of EDSP Tier 1 Screening

July 30 - August 2, 2013

Docket Number: EPA-HQ-OPP-2013-0230 **OPP Docket Tel: 703-305-5805**

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

Tuesday, July 30, 2013

8:30 A.M. **Opening of Meeting and Administrative Procedures** – Joseph Bailey, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:35 A.M. **Introduction and Identification of Panel Members** – Daniel Schlenk, Ph.D., Chair, FIFRA Scientific Advisory Panel

8:45 A.M. **Opening Remarks** – David Dix, Ph.D., Acting Director, Office of Science Coordination and Policy (OSCP); Steven Bradbury, Ph.D., Director, Office of Pesticide Programs (OPP), EPA

9:00 A.M. **Overview of the Endocrine Disruptor Screening Program (EDSP) -** Mary Manibusan, Director, Exposure Assessment Coordination and Policy Division (EACPD), OSCP, EPA

9:30 A.M. **EDSP Weight-of-Evidence (WoE) Process-** Thomas M. Steeger, Ph.D., Environmental Fate and Effects Division (EFED), OPP, EPA

10:00 A.M. **Case Study Chemicals: Chemical A -** Gregory Akerman, Ph.D., Health Effects Division (HED), OPP, EPA

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

10:45 A.M. **Case Study Chemicals: Chemical S -** John Liccione, Ph.D., HED, OPP, EPA

11:15 A.M. **Case Study Chemicals: Chemical J -** Amy Blankinship, M.S., EFED, OPP, EPA

11:45 A.M. **Case Study Chemicals: Chemical N -** Catherine Aubee, M.P.A., EFED, OPP, EPA

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

1:15 P.M. **Case Study Chemicals: Chemical X -** Patience Browne, Ph.D., EACPD, OSCP, EPA

1:45 P.M. **Concluding Remarks -** Thomas M. Steeger, Ph.D., EFED, OPP, EPA

2:15 P.M. **Break**

2:30 P.M. **Public Comments**

5:00 P.M. **Adjournment**

AGENDA

Wednesday, July 31, 2013

8:30 A.M. **Opening of Meeting and Administrative Procedures** – Joseph Bailey, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:35 A.M. **Introduction and Identification of Panel Members** – Daniel Schlenk, Ph.D., Chair, FIFRA Scientific Advisory Panel

8:45 A.M. **Follow-up from Previous Day's Meeting**

9:00 A.M. **Panel Discussion of Charge**

Charge 1.1. Please comment on whether the agency has transparently described the conduct and results of the individual Tier 1 studies and the OSRI for each of the case studies (Sections 6-9 of the white paper), and specifically whether the level of detail is sufficient to ensure that a study is reliable for determining the potential to interact with E, A, or T signaling pathways and the rationale for the preliminary study conclusion.

10:15 A.M. **Break**

10:30 A.M. **Panel Discussion of Charge**

Charge 1.2. For each of the case studies, please comment on whether the performance criteria are clearly stated for the Tier 1 assays and, when results were not within the boundaries of the performance criteria, whether EPA has clearly expressed why the data are still considered reliable.

11:30 A.M. **Panel Discussion of Charge**

Charge 1.3. The test guidelines for Tier 1 assays recommend that the organism is challenged by attaining sufficiently high treatment doses/concentrations. Difficult to test substances may be encountered in Tier 1 screening. Chemical S is an illustration of this situation. In the case of Chemical S, consistent exposure was not achieved in the Amphibian Metamorphosis assay (AMA) due to the physical-chemical characteristics of the test substance. The compound has low solubility and is highly lipophilic (high Kow) and prone to sorbing to surfaces (high Koc). Due largely to these properties, the contributing laboratory performing the AMA with Chemical S did not achieve a concentration level high enough to produce a response indicative of a maximum tolerated dose. Nonetheless, the agency concluded that the data were still useful in the WoE analysis. This determination was based on the agency's understanding that while measured exposure concentrations were lower than the targeted nominal concentrations, exposure was reasonably quantified and that it is not likely that the chemical would be any less problematic to test if the study were repeated. Further, while higher exposure concentrations could have been achieved in the AMA, the FSTRA indicates that these higher concentrations likely would have resulted in overt toxicity.

Please comment on the agency's conclusion regarding the utility of the AMA data for Chemical S to still reliably evaluate its potential endocrine interaction in a WoE analysis.

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

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

Charge 2.1.a. Chemical A can result in cholinergic toxicity given that its pesticidal mode of action is cholinesterase inhibition. In particular, overt toxicity was observed at high concentrations in the FSTRA. Although a number of endocrine responses were observed (e.g., decrease in female VTG, fecundity/fertility, GSI, male tubercles) at the highest concentration in the FSTRA, there was also pronounced overt toxicity that included abnormal behavior and significant body weight reductions consistent with cholinergic intoxication. Given the directionality of the FSTRA responses (i.e., decreases in the measured endpoints), EPA concluded that the effects found at the high concentration in the FSTRA may not necessarily be reflective of an endocrine-mediated response, but rather a reflection of a compromised organism with limited ability to maintain reproductive function and homeostasis. Although in male fish, overt toxicity was not observed at the intermediate

concentration, possible endocrine responses were limited to two effects that lacked diagnostic specificity (i.e., altered GSI and histology).

Please comment on how the agency has applied its decision logic to integrate an understanding of overt toxicity in the context of observed Tier 1 in vivo responses , and in particular, the agency's determination not to place weight on the FSTRA high concentration responses coincident with overt toxicity.

2:15 P.M. Panel Discussion of Charge

Charge 2.1.b. The pesticidal mode of action of Chemical S involves the uncoupling of mitochondrial oxidative phosphorylation and resulting in the depletion of ATP. Another plausible mode of toxic action is related to its irritation properties including irritation that compromises the integrity of the gastro-intestinal tract in mammals leading to restricted caloric intake due to reduced food consumption. Reflective of these toxic modes of action, observations in the Tier 1 studies and OSRI included body weight reductions, behavioral effects, and decreased survival. The majority of potential androgen and estrogen-related responses (decreases in testosterone, decreases in male and female gonadal weights, delays in VO and PPS, decreases in male fertility, an increase in male GSI and VTG) were coincident with this overt toxicity. At concentrations where no apparent overt toxicity occurred, there were no endocrine related responses in the FSTRA, and responses in female rats were limited to a 2 day delay in VO, and for male rats, a decrease in the weights of two androgen-dependent tissues. The majority of Tier 1 responses were decreases in the measured endpoints, which were largely expressed in the presence of overt toxicity, are consistent with a depletion of ATP and restricted caloric intake. Although male VTG was increased in fish this is likely an artifact of a single elevated response.

Please comment on how the agency has applied its decision logic to integrate an understanding of overt toxicity in the context of observed Tier 1 in vivo responses, and in particular, on the agency's determination to place less weight on the Tier 1 in vivo responses in the presence of overt toxicity.

3:15 P.M. Break

3:30 P.M. Panel Discussion of Charge

Charge 2.1.c. Chemical N is a cyclic unsaturated ketone whose acute mode of toxic action is nonpolar narcosis (toxicologically induced and reversible stages of neural disruption, i.e. general anesthesia). Unlike the other case study chemicals, there is no pesticidal mode of toxic action for N given that it is an inert ingredient. Testing required reaching limit doses/concentrations in order to sufficiently challenge the animal. Potential androgen responses only occurred in the FSTRA (decrease female VTG, decrease fecundity/fertility, altered histology) and in the male pubertal assay (decreases in testosterone, decreases in androgen sensitive tissue weights, delays in PPS) near limit doses/concentrations (as described in the white paper and test guidelines). However, a significant decrease in female VTG was observed at the intermediate dose. Observations of overt toxicity (decreased body weights and feeding) were reported in the highest treatment group (i.e., near limit concentrations) in the FSTRA, but no overt toxicity was reported in the male pubertal assay. Unlike Chemicals A and S, the overt toxicity is not as pronounced for Chemical N. The responses in fish and rats at the high dose could be due to a compromised metabolic ability and inability to reduce chemical load.

Please comment on the agency's analysis in characterizing Tier 1 responses that are expressed at or near limit doses where some degree of overt toxicity occurs, and the extent to which such responses are considered in the WoE analysis.

4:15 P.M. Panel Discussion of Charge

Charge 2.1.d. The case study analyses described above all involve situations in which overt toxicity was observed coincident with Tier 1 responses.

Please comment on the agency's overall approach to characterizing Tier 1 responses coincident with overt toxicity and determining the weight to be given to such responses.

5:00 P.M. Adjournment

AGENDA

Thursday, August 1, 2013

8:30 A.M. **Opening of Meeting and Administrative Procedures** – Joseph Bailey, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:35 A.M. **Introduction and Identification of Panel Members** – Daniel Schlenk, Ph.D., Chair, FIFRA Scientific Advisory Panel

8:45 A.M. **Follow-up from Previous Day's Meeting**

9:00 A.M. **Panel Discussion of Charge**

Charge 2.2. In certain case studies, there was a lack of anticipated complementary and redundant responses (within an in vivo assay or across assays) at different levels of biological organization (molecular, cellular, tissue/organ, and organism) indicative of a chemical interaction with an endocrine signaling pathway. The estrogen signaling pathway will be used as an illustration. In the case of Chemical N, the mammalian assays were negative and responses within the FSTRA did not progress to higher level responses (e.g., an effect on VTG did not translate to an effect on gonadal-tissue or on fecundity). In the case of Chemical A, the rat uterotrophic and female pubertal assays (i.e., an organism with an intact hypothalamic-pituitary-gonadal axis) were negative for estrogen-related responses, and although there were some responses in the FSTRA in the absence of overt toxicity, they lacked diagnostic specificity (e.g., effects on male gonadal tissue or GSI). Given the lack of complementarity and redundancy in responses within and across assays, the agency considered these situations as insufficient to support a robust conclusion of an interaction with endocrine signaling pathways.

Please comment on the decision logic the agency has used to characterize these types of situations where there is a lack of robustness in terms of complementarity and redundancy, and the transparency and reasonableness of the approach.

10:00 A.M. **Break**

10:15 A.M. **Panel Discussion of Charge**

Charge 2.3. In contrast to the situation described in question 2.2., Chemical J appears to interact with the estrogen signaling pathway in terms of complementarity and redundancy across multiple levels of biological organization as evidenced through altered steroidogenesis, resulting in decreased VTG in female fish which in turn translates to a higher-level response (e.g., reduced fecundity) in fish. However, this biological continuum was not observed in the Tier 1 rat female pubertal assays and the Part 158 mammalian data.

Please comment on the how the agency has characterized this endocrine interaction at different levels of biological organization across taxa, and the transparency and reasonableness of the conclusions drawn. Please include in your response, comments regarding the agency's conclusion about differences in sensitivities between taxa (i.e., fish and rats), regarding chemicals that appear to alter steroidogenesis.

11:15 A.M. **Panel Discussion of Charge**

Charge 2.4. Chemical A illustrates a situation where a molecular event has been initiated along a pathway via binding to the androgen receptor and by altered steroidogenesis, with corroborative evidence from the Hershberger assay. However, at a higher level of biological organization, an anti-androgenic response is not expressed within the context of the mammalian intact hypothalamic-pituitary-gonadal axis (based on the Tier 1 mammalian assays and the mammalian in vivo OSRI). In the absence of overt toxicity, there were some possible endocrine-related responses in the FSTRA, but they lacked diagnostic specificity (e.g., reduced GSI and altered histology). The agency concluded that although there is evidence of an endocrine interaction (i.e., the androgen signaling pathway) at lower levels of biological organization, clear endocrine-driven responses are not expressed at higher levels of biological organization in organisms with an intact HPG-axis, presumably due to compensatory processes.

Please comment on how the agency has integrated different sources of data along a biological continuum to characterize endocrine interactions of Chemical A and the transparency and reasonableness of the decision logic.

12:00 P.M. Lunch

1:00 P.M. Panel Discussion of Charge

Charge 2.5. In some chemical situations, the in vitro Tier 1 data are negative. Nonetheless, this does not necessarily detract from a conclusion of a potential endocrine interaction in vivo either because a different molecular initiating event (MIE) may be occurring than what the in vitro assay evaluates or because an activated metabolite may be responsible for the in vivo effects. Chemicals N and S provide an illustration of this situation in that the MIE is uncertain due to the negative Tier 1 in vitro assays. But, there were Tier 1 in vivo responses that are consistent with potential interactions with the androgen or estrogen signaling pathways.

For Chemical N, anti-androgen related responses were observed in the male pubertal assay that were complementary within the assay (i.e., decreased in testosterone levels that progressed to effects at the organ (tissue weight decreases in androgen sensitive tissues) and organism level (delay in PPS). In the FSTRA, more limited responses were observed in the absence of overt toxicity, i.e., a decrease in female VTG that did not manifest into higher level effects. In this case, there is in vivo evidence of an endocrine interaction but compared to other case studies (e.g., as Chemical J), the complementarity and redundancy in responses are not as robust.

In the case of Chemical S for the A pathway, in the Hershberger there was a decrease in androgen-sensitive tissue weights. In the case of the male pubertal assay, there were complementary responses in that a cellular response (i.e., decreases in testosterone levels) progressed to effects at the organ (tissue weight decreases in androgen sensitive tissues) and organism level (delay in PPS). In the FSTRA, there were altered male gonadal weights and reduced tubercles. Although these effects in the fish lack specificity, they are supported by the mammalian responses. Tier 1 in vivo responses are not observed at the lower concentrations in organisms with an intact HPG-axis, presumably due to compensatory processes.

Please comment on the how the agency has integrated different sources of data along a biological continuum to characterize this endocrine interaction and the transparency and reasonableness of the conclusion drawn.

2:00 P.M. Panel Discussion of Charge

Charge 2.6. In each of the cases studies, there was a lack of anticipated complementary and redundant responses indicative of a chemical's interaction with the thyroid signaling pathway. In the rat, there were T4 changes that were either marginal or equivocal (Chemical A), or isolated organ weight changes (Chemicals J and S) or histopathological changes of the thyroid gland (Chemical J) that were not coincident with hormone changes. In the AMA, there were some isolated responses not necessarily indicative in terms of the endpoint specificity of a hypothalamic-pituitary-thyroid axis perturbation (Chemicals A and N). The agency considered the lack of complementarity and redundancy in responses to support a conclusion of no interaction with the HPT axis, and viewed these isolated responses insufficient to support a conclusion of an interaction with the thyroid signaling pathway.

Please comment on the how the agency has characterized this endocrine interaction at different levels of biological organization, and the transparency and reasonableness of the conclusion drawn.

3:00 P.M. Break

3:15 P.M. Panel Discussion of Charge

Charge 2.7. In the absence of Tier 1 data, OSRI was available for Chemical X that indicated effects on thyroid endpoints in the rat but the results were inconsistent within and among studies and there was no OSRI presented from amphibian studies. Because of studies that were not specifically validated to detect an interaction with the thyroid hormonal pathway, limited data, and ambiguous results, the potential for Chemical X to interact with the thyroid pathway cannot be excluded.

Please comment on the how the agency has characterized this endocrine interaction at different levels of biological organization, and the transparency and reasonableness of the conclusion drawn.

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4:15 P.M. **Panel Discussion of Charge**

Charge 3. Based on all of the case study analyses, please provide overall comments on how the agency has employed its WoE guidance and characterized the evidence and conclusions and include in your response the following points:

a. How consistent and transparent the cases studies are in terms of documentation.

b. How adequately the agency has described the extent of complementarity and redundancy of responses and has integrated and interpreted diverse lines of evidence across different biological levels of organization and taxa to reach preliminary conclusions regarding endocrine interactions.

c. How the agency has used OSRI data to further characterize the observations from EDSP Tier 1 assays in determining potential chemical interactions with the E, A, and T signaling pathways.

d. How the agency has considered the understanding of a chemical's mode of action and how that informs the weight that is placed on Tier 1 responses in the presence of uncertainties introduced by dose setting, overt toxicity, and portal of entry issues.

5:00 P.M. **Adjournment**

Friday, August 2, 2013

8:30 A.M. **Opening of Meeting and Administrative Procedures** – Joseph Bailey, Designated Federal Official, Office of Science Coordination and Policy, EPA

8:35 A.M. **Introduction and Identification of Panel Members** – Daniel Schlenk, Ph.D., Chair, FIFRA Scientific Advisory Panel

8:45 A.M. **Follow-up from Previous Day's Meeting**

9:00 A.M. **Panel Discussion of Charge**

10:00 A.M. **Break**

10:15 A.M. **Panel Discussion of Charge**

11:00 A.M. **Panel Discussion of Charge**

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

1:00 P.M. **Panel Discussion of Charge**

3:00 P.M. **Break**

3:15 P.M. **Panel Discussion of Charge**

5:00 P.M. **Adjournment**

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: Joseph Bailey, telephone: (202)-564-2045, fax: (202) 564-8382, or email: bailey.joseph@epa.gov.