PETROVA Nevyana (ENV)

From: KORYTAR Peter (ENV)
Sent: 14 February 2013 09:46
To: [redacted]@epamail.epa.gov'
Subject: RE: Criteria for identification of endocrine disruptors
Attachments: ED_AD-hoc-5_2012_04_Possible elements for the criteria for EDs.doc

Dear [redacted]

Thank you for your willingness to review the draft and provide us with comments.

The document with draft criteria (which is a public document) is enclosed. It represents our initial thoughts on how such horizontal criteria could look like. As you might see, we were inspired by GHS approach for classification and labelling of CMRs.

The paper in the 1st section gives definitions – we are considering using WHO/IPCS definition, which means that to proof a substance to be an ED, one would need to demonstrate endocrine mode of action, adversity and causal relation. The 2nd section defines categories based on level of evidence. The 3rd section provides criteria for placing a substance into category. The 4th section lists other elements which are under discussion to potentially become a part of criteria; e.g. do we need to define endocrine system and if yes, how; shall we incorporate potency as a criterion, etc. There are some options provided for each parameter.

We would appreciate your comments preferably by the end of February but not later than 10 March. By the middle of March we intend to come with the final draft.

The document is a Microsoft word file. The comments can be in track changes or in a separate document. Simple e-mail to me from you or your colleagues is fine.

In case you would need any clarifications to the document, please do not hesitate to contact me. Happy to explain over the phone.

Best regards,

Peter

From: [redacted]@epamail.epa.gov [mailto:[redacted]@epamail.epa.gov]
Sent: Wednesday, February 13, 2013 7:34 PM
To: KORYTAR Peter (ENV)
Subject: Re: Criteria for identification of endocrine disruptors

Dear Peter,

We would be very pleased to review the draft criteria and provide any additional comments. In your email, please let me know the time frame in which you will need our comments and how you would prefer to have them transmitted.

Hope this message finds you well and I very much look forward to working with you on this very important development.

[redacted]

[redacted], Director
Exposure Assessment Coordination and Policy Division
Office of Science Coordination and Policy
(202) 564-[redacted]

---02/13/2013 12:38:17 PM---Dear[redacted], As you are certainly well aware, there are two Regulations in the EU (pesticides and bioc

From: <Peter.KORYTAR@ec.europa.eu>
To: [redacted]/DC/USEPA/US@EPA
Date: 02/13/2013 12:38 PM
Subject: Criteria for identification of endocrine disruptors

Dear[redacted]

As you are certainly well aware, there are two Regulations in the EU (pesticides and biocides) which requires the European Commission to develop criteria for identification of endocrine disruptors. The criteria should be adopted by the end of 2013.

Discussions on how such criteria could look like have been going on for some time. At the end of last year we have produced the first preliminary draft of such criteria on which we are collecting comments.

Last week we met with Environmental Officer at the US mission to the EU, [redacted]. We agreed that it might be a good idea to ask you whether you (or somebody from your EPA colleagues) would be interested to provide us with the comments. We are interested to both types of comments, official/unofficial/formal/informal.

If you would be interested, please, let me know and I will send you the draft document with some more explanation.

Greetings from Brussels,

Peter

Peter KORYTÁR
Policy officer

European Commission
DG ENVIRONMENT
Unit D.3 – Chemicals, Biocides and Nanomaterials

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B-1049 Brussels/Belgium
+32 2 299 17 86
Peter.Korytar@ec.europa.eu

EUROPEAN COMMISSION
DIRECTORATE-GENERAL
ENVIRONMENT
Directorate D - Water, Marine Environment & Chemicals
ENV.D.3 – Chemicals, Biocides and Nanomaterials

Brussels, 22 November 2012
ED-AD-HOC-5/2012/04

THE COMMUNITY STRATEGY FOR ENDOCRINE DISRUPTORS

5TH AD HOC MEETING OF

COMMISSION SERVICES, EU AGENCIES AND MEMBER STATES

Centre de Conférence A. Borschette, room 4B, rue Froissart 36, Brussels
30 November 2012 (10:00 – 17:30)

Concerns: **Initial thoughts on the criteria for endocrine disruptors**

Agenda Point: **4**

Action Requested: **This paper sets out possible elements for the definition, identification and categorisation of Endocrine Disruptors (EDs) based on the discussions which have so far taken place in the Expert Group and the Ad-hoc Group. This document was developed by DG ENV for the 4th meeting of the expert advisory group to better steer and frame discussions at that meeting. The members of the expert group were asked to provide their comments which are summarised in the separate document.**

During the ad-hoc meeting the possible elements for the horizontal criteria for EDs as currently considered by DG ENV will be presented and the ad-hoc group may wish to provide comments (from the policy perspective).

The participants to the meeting are invited to:

- take note of this document

- provide comments (from the policy perspective)

Possible Elements for Criteria for Identification of Endocrine Disruptors

1. Definition

An *endocrine disruptor* is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations. (WHO/IPCS)

A *suspected endocrine disruptor* is an exogenous substance or mixture that may alter function(s) of the endocrine system and consequently may cause adverse health effects in an intact organism, or its progeny, or (sub)populations. (DK)

A *potential endocrine disruptor* is an exogenous substance or mixture that possesses properties that might be expected to lead to endocrine disruption in an intact organism, or its progeny, or (sub)populations. (WHO/IPCS)

2. Categories of Endocrine Disruptors

For the purpose of categorisation of endocrine disruptors, substances are allocated to one of three categories based on [weight of evidence] / [level of evidence] / [strength of evidence and additional considerations (weight of evidence)].

Categories for endocrine disruptors

- Category 1: Known or presumed endocrine disruptors
    - Category 1a: Known endocrine disruptors
    - Category 1b: Presumed endocrine disruptors
- Category 2: Suspected endocrine disruptors
- Category 3: Potential endocrine disruptors

3. Criteria for Placing Substances in Categories

Category 1 – Known or presumed endocrine disruptors

Substances are placed in category 1 when they are known to have caused ED mediated adverse effects in humans or [animal species living in the environment] / [population relevant effects on animal species living in the environment] / [ecosystem relevant adverse effects] or when there is evidence from [animal studies] / [experimental animal studies], possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to cause ED mediated adverse effects in humans or [animals living in the environment] / [population relevant effects on animal species living in the environment] / [ecosystem relevant adverse effects].

The [animal studies] / [experimental animal studies] shall provide clear evidence of ED-mediated adverse effects in the absence of other toxic effects, or if occurring together with other toxic effects,

the ED-mediated adverse effects should be considered not to be a secondary non-specific consequence of other toxic effects. However, when there is e.g. mechanistic information that raises doubt about the relevance of the effect for humans or [animal species living in the environment] / [population of animal species living in the environment], category 2 may be more appropriate.

Category 1 is further divided into two sub-categories on the basis of whether the evidence for classification is primarily from human data or data from [animals living in the environment] / [field studies] (Category 1A – Known Endocrine Disruptors) or from [laboratory animal studies] / [experimental animal studies] (Category 1B – Presumed Endocrine Disruptors).

Substances can be allocated to the sub-category 1A based on evidence from humans or from [animal species living in the environment] / [field studies] where it is plausible that the observed adverse effect is ED-mediated.

Substances can be allocated to the sub-category 1B based on:

- [Animal studies] / [experimental animal studies] where it is plausible that the observed adverse effects are caused by an ED mode of action
- [Animal studies] / [experimental animal studies] showing an ED activity *in vivo* which is clearly linked to adverse effects *in vivo* (e.g. through read-across)

Category 2 – Suspected endocrine disruptors

Substances are placed in category 2 when there is some evidence for ED mediated effects from humans or experimental animals, and where the evidence is not sufficiently convincing to place the substance in category 1. If, for example, limitations in the study (or studies) make the quality of evidence less convincing, category 2 could be more appropriate. Such effects should be observed in the absence of other toxic effects, or if occurring together with other toxic effects, the ED mediated effect should be considered not to be a secondary non-specific consequence of other toxic effects.

Substances can be allocated to this category based on:

- Experimental animal studies where it is suspected that the observed adverse effects are caused by an ED mode of action
- Experimental animal studies showing endocrine activity *in vivo* which is suspected to be linked to adverse affects *in vivo* (e.g. through read-across)
- *in vitro* studies showing endocrine activity, combined with toxicokinetic *in vivo* data which is suspected to be linked to adverse effects *in vivo* (e.g. through read-across, chemical categorisation and QSAR predictions).

Category 3 – Potential endocrine disruptors

Substances are placed in Category 3 when there is some *in vitro/in silico* evidence indicating a potential for endocrine disruption mediated adverse effects in intact organisms and where the evidence is not sufficiently convincing to place the substance in category 1 or 2.

The evidence could also be observed effects *in vivo* where there is general but not specific evidence relating those to ED mediated adverse effects (i.e. that may, or may not, be ED-mediated).

4. Further issues for consideration to be part of the criteria

4.1 Endocrine system

Should the endocrine system be defined and if so, what definition should be used?

Human health

Option 1: In humans, endocrine glands include the pituitary, thyroid, adrenal glands and gonads, and parts of the kidney, liver and heart. The three important endocrine axes are the Hypothalamus-pituitary-gonad (HPG) axis, Hypothalamus-pituitary-adrenal (HPA) axis, Hypothalamus-pituitary-thyroid (HPT) axis. These axes describe the boundaries within which the endocrine system and endocrine disruption have been confined from the perspective of classical endocrinology.

Option 2: Signalling pathways considered under OECD DRP ENV/JM/MONO(2012)23: Hypothalamus-pituitary-adrenal (HPA) axis, Hypothalamus-pituitary-gonad (HPG) axis, Hypothalamus-pituitary-thyroid (HPT) axis, Somatotropic axis, Retinoid signalling pathway, Vitamin D signalling pathway, Peroxisome proliferator-activated receptor (PPAR) signalling pathway, epigenomic regulatory mechanisms

Option 3: Any type of receptor-mediated signalling pathway

Option 4: Does any general definition exists for endocrine system in humans (e.g. in endocrinology)?

Environment:

Does any suitable definition exist for endocrine system across all animal species?

4.2 Route of exposure

Should the route of exposure be specified in the definition, categories, criteria or possibly guidance?

Human health and environment

Option 1: Any route of exposure is relevant

Option 2: Only physiological routes of exposure are considered relevant

4.3 Adversity

Should adversity be defined in greater detail in the definition, categories, criteria or possibly guidance?

Human health

Option 1: No specific consideration

Option 2: A change in morphology, physiology, growth, reproduction, development or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences. (WHO/IPCS)

Option 3: More detailed description

Environment

Adverse effect should be observed or presumed at the population level.

4.4 Mode of action

Should the mode of action be elaborated or better defined in the definition, categories, criteria or possibly guidance?

4.5 Proof of causality

Does what we mean with causality need to be elaborated further?

4.6 Data

Categorisation of a substance as an endocrine disruptor is made on the basis of evidence from reliable and acceptable studies. The evaluations shall be based on all existing data, peer-reviewed published studies and additional acceptable data.

4.7 Potency

Option 1: No potency consideration

Option 2: Potency cut-off

Option 3: Potency as part of weight of evidence

4.8 Lead toxicity

Should the consideration of the lead toxicity be included?

4.9 Severity

Should the consideration of severity be included?

4.10 Irreversibility

Should the consideration of irreversibility be included?

4.11 Specificity

Should the consideration of specificity be included?

4.12 Step by step procedure

1. Gather all available data
2. Consider adversity and mode of action in parallel
3. Evaluate human and wildlife relevance

4. Final (eco)toxicological evaluation, classification and categorisation

PETROVA Nevyana (ENV)

From: [redacted] <[redacted]@epa.gov>
Sent: 01 March 2013 16:07
To: KORYTAR Peter (ENV)
Subject: RE: Criteria for identification of endocrine disruptors
Attachments: USEPA Comments.Proposed EU Criteria for EDC.3.01.13.doc

Dear Peter,

Thank you for the opportunity to provide comment on the draft proposed criteria for identification of endocrine disruptors. If you have any additional questions, please do not hesitate to contact me.

Best regards,

[redacted]

From: Peter.KORYTAR@ec.europa.eu [mailto:Peter.KORYTAR@ec.europa.eu]
Sent: Thursday, February 14, 2013 3:46 AM
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Exposure Assessment Coordination and Policy Division
Office of Science Coordination and Policy
(202) 564[redacted]

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Greetings from Brussels,

Peter

Peter KORYTÁR
Policy officer

European Commission
DG ENVIRONMENT
Unit D.3 – Chemicals, Biocides and Nanomaterials

Avenue de Beaulieu 9, 04/36
B-1049 Brussels/Belgium
+32 2 299 17 86
Peter.Korytar@ec.europa.eu

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

March 1, 2013

Dr. Peter Korytar,

Thank you for the opportunity to provide comment on the draft criteria for endocrine disruptors, issued on November 22, 2012. As the proposed draft criteria presents a preliminary framework to determine specific levels of endocrine activity, considerations summarized below are primarily intended to encourage additional clarity so as to more fully understand the classification scheme, the distinctions between the proposed classification categories and the nature of the data, and data interpretation methods which will inform classification decisions. We appreciate the challenge of integrating biological mechanisms, different types of data and varying levels of scientific evidence in a classification scheme. Our suggestions are intended to assist in further clarification of these specific issues to enhance transparency as you further develop these criteria. To provide some additional context to our suggestions, we also summarize the current status of the U.S. Endocrine Disruptor Screening Program.

Background

Based on US legislative mandate, the U.S. EDSP was developed to screen chemicals using validated test methods for endocrine activity similar to those associated with naturally occurring estrogen; the program has been in existence since 1999 and has evolved to a two-tiered screening and testing program based on the Endocrine Disruptor Screening and Testing Advisory Committee recommendations. The Tier 1 screening battery is intended to determine whether a chemical has the potential to interact with the endocrine system for estrogen, androgen and thyroid pathways, while Tier 2 test methods are definitive studies that would provide quantitative dose response information for use in risk assessments. As a two-tiered testing program, a chemical is advanced for Tier 2 testing only if positive in the Tier 1 battery and weight of evidence analyses warrant further testing.

Since 1999, the EDSP program has validated 11 Tier 1 screening assays; issued Tier 1 test orders for 67 pesticide chemicals and is currently in the process of evaluating the incoming EDSP Tier 1 data. The program is also in the process of validating Tier 2 test methods; all test method development activities are conducted in conjunction with OECD to enhance global harmonization of test guidelines and performance standards. In conjunction with these various efforts, in 2013, the EDSP is undertaking the following external peer reviews through the Agency's Scientific Advisory Panel (1-4) and the National Academy of Sciences (5):

(1) Use of Computational Toxicology to Prioritize the EDSP Universe of Chemicals for Tier 1 Screening
(2) EDSP Tier 1 assay and battery performance evaluation
(3) EDSP Tier 2 test methods validation for multi-generation reproduction studies on invertebrates, birds and fish and amphibian growth and development study.
(4) EDSP weight of evidence analyses based on Tier 1 screening data and other scientifically relevant information to determine if a chemical has the potential to interact with estrogen, androgen and/or thyroid systems.
(5) State of the science on non monotonic dose response curves for endocrine disrupting chemicals.

Based on recommendations from these external scientific peer reviews, the agency will advance the EDSP to reflect the current state of the science, using validated screening and testing methodologies and data evaluation processes. The agency is required to ensure strong scientific rigor in the applied test methods, transparency in the data review and regulatory processes with full and open public participation, broad stakeholder engagement and international partnerships through OECD.

General Considerations:

1. As the US EDSP has engaged in public participation, will the EC anticipated providing a formal public comment period for the next version of the document and any supporting documents?
2. Is there going to be a support document(s) prepared that provides additional information as to how best available information will be evaluated to determine the assignment of specific categories? What are the minimum data quality standards for different types of information for each category?
3. How will a chemical be classified if there is no endocrine related data available? How will a chemical be classified if there is sufficient data indicating it does not have endocrine effects? It seems at least two more categories are needed, a) Insufficient data to make a determination and b) sufficient data to determine the chemical does not have endocrine effects.
4. The classification scheme seems to correlate with the OECD EDTA Tiers that progress from prioritization through definitive testing, but the OECD Tiers are not designed to provide a categorization scheme. Does the EC anticipate using the OECD Tiers in a process to require data submission from manufacturers to the appropriate authorities and/or as a process to gather and evaluate existing data.
5. If a chemical has, for example, appropriately vetted in silico or in vitro data to indicate it has the potential to interact with an endocrine system, if subsequently additional, more definitive data is generated and it indicates a chemical does or does not interact with the endocrine system, will the chemical be re-classified?
6. The difference between the suspected (may alter functions of the endocrine system) and potential (might be expected to lead to endocrine disruption) categories is unclear. Additional detail is needed, perhaps with hypothetical examples of data sets, to provide a

better understanding of the differences between these categories. Additional clarification is also needed to ascertain the difference between category 1B and 2.

7. Category 1A requires clear evidence of an effect independent of other effects or an ED effect that is not secondary to other effects. This implies an extensive in vivo data set that addresses dose response information for a wide variety of endpoints will be required to make a determination for this category. Additional descriptions of the data sets required to make a determination for this category would be helpful.
8. Category 1A also indicates human data/evidence is needed. What data/evidence is envisaged – human epidemiological studies or intentional human dosing studies? We assume the former, not the latter, but clarification is needed. With regard to human epidemiological data, additional information is required to understand how cause-effect relationships from an epidemiological study will be ascertained (e.g., control of confounding effects or effect modifiers, etc.)
9. The definitions for categories 2 and 3 are unclear. For example, for category 2 the term "suspected" is used in the definition of the data types that could be used to make a determination of a "suspected" endocrine chemical. However, the word "suspected" is never defined; hence, it is difficult to understand the attributes of a data set that would result in a determination of suspected endocrine activity. The same circular description occurs for category 3. This lack of clarity makes it difficult to ascertain the difference between these two categories as well as the nature of the data that would support a classification. Examples of hypothetical chemicals with hypothetical data sets that illustrate how a chemical could be suspected or could have potential is needed to ascertain the differences between these categories and the nature of the data that would support a classification in either category.

Specific Comments by Section:

10. Section 4.1: The WHO definitions seem appropriate and consistent with those adopted by the US EDSP.
11. Section 4.2: An elaboration of exposure is critical, including the route and level of exposure. The need for this information is implied in the category definitions (e.g., dose-response information is needed in evaluating whether or not a chemical falls into category 1).
12. Section 4.3: Option 2 is needed to provide transparency.
13. Section 4.4: A definition of mode of action is needed as this concept is at least implicitly required to make a classification – such a definition will provide transparency. In addition, it would be helpful to better understand how the AOP concept or IPCS MOA WOE approach would be considered in the proposed classification scheme.
14. Section 4.5: Causality needs to be elaborated to provide transparency; doing so may help explain the distinction between categories 1A, 1B, 2, and 3, which is presently not clear.
15. Section 4.7: Option 3 would be optimal for clarity and transparency. Option 1 should not be used.
16. Section 4.8-4.11: These sections have options to provide additional information and in all cases the options for expanded descriptions and detail should be implemented. More detailed descriptions are needed for these terms to provide clarity and transparency in the distinctions between the categories.

17. Section 4.12: The four steps seem reasonable. There may, however, be a need for additional steps once there is elaboration of the issues previously highlighted. Also, a discussion of the process for data and evaluation, as well as an estimated timeline by which the EC regulatory authorities will undertake this effort would be helpful.

Thank you again for the opportunity to provide comments on the draft proposed criteria. If you have any additional questions, please feel free to contact me at (202) 564-2827 or Manibusan.mary@epa.gov. I look forward to our continued partnership and collaboration on endocrine disrupting chemicals.

Sincerely,

[redacted], Director
U.S. Endocrine Disruptor Screening Program

PETROVA Nevyana (ENV)

From: [redacted] <[redacted]@epa.gov>
Sent: 29 July 2013 16:05
To: HANSEN Bjorn (ENV); BEREND Klaus (ENTR); EMBERGER Geraldine (TRADE); [redacted] (USEU); KORYTAR Peter (ENV)
Subject: FW: FIFRA Scientific Advisory Panel will meet July 30 - August 2, 2013 to consider and review scientific issues related to Weight-of-Evidence: Evaluating Results of EDSP Tier 1 Screening
Attachments: Final Agenda JulAug 2013 SAP.docx

For your information.

From: [redacted]
Sent: Friday, July 26, 2013 10:07 AM
To: OCSPP ALL
Subject: FIFRA Scientific Advisory Panel will meet July 30 - August 2, 2013 to consider and review scientific issues related to Weight-of-Evidence: Evaluating Results of EDSP Tier 1 Screening

The US EPA FIFRA Scientific Advisory Panel will meet July 30 - August 2, 2013 to consider and review scientific issues related to *Weight-of-Evidence: Evaluating Results of EDSP Tier 1 Screening.* The meeting will be held at the Environmental Protection Agency, Conference Center, Lobby Level, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA 22202.

All meeting materials (e.g., Background Documents, Charge to the Panel, Agenda, Panel Roster, and Public Comments) are available in the e-docket, EPA-HQ-OPP-2013–0230 http://www.regulations.gov).

This meeting will be accessible thru a live online webcast. The live webcast will enable interested persons to listen to the entire public meeting and to view the PowerPoint presentations displayed at the meeting. To participate in the live webcast, please click on the link below to access the webcast instructions. The webcast link will not be active until 15 minutes prior to the start of the meeting. You must use a PC and Internet Explorer as your browser.

Link to webcast and webcast instructions (see "Announcements" block on right side of page): http://www.epa.gov/scipoly/sap/

Please note that the webcast is a supplementary public process provided only for convenience. If difficulties arise resulting in webcasting outages, the meeting will continue as planned.

Additional general information concerning the meeting, including the webcast information, is posted on the SAP website, http://www.epa.gov/scipoly/sap/meetings/2013/073013meeting.html. An agenda is attached to this email.

[redacted]

US Environmental Protection Agency

FIFRA Scientific Advisory Panel

☎: 202-564-[redacted]
fx: 202-564-[redacted]

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 Manibusin, 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.

AGENDA

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.