Docket ID No. EPA-HQ-OPPT-2007-1080

Additional Materials Provided to OMB During EO 12866 Review of the Draft Federal Register document entitled: “Endocrine Disruptor Screening Program (EDSP); Policies and Procedures for Initial Screening; Notice” (08/11/2008).

The following attached documents regarding the **Specific EPA Responses to OMB Comments** were also provided to OMB:

1. Response to OMB document entitled: “EPA Responses to OMB Comments of 01/12/2008 on EDSP Documents” (01/26/2009).

2. Response to OMB document entitled: “Response to OMB entitled: “EPA Responses to OMB Follow-up Comments of March 13 & 14, 2009 on the EDSP Materials” (03/18/2009).

EDSP-EPA_Responses2OMB-2009-01-26.doc

EPA Responses to OMB Comments of 01/12/2008 on EDSP Documents

EPA responses to OMB's comments and suggested edits appear below after each comment and are grouped with the document upon which the comment was made. Comments have been numbered and line numbering has been added to simplify referencing, and a line separates the different documents upon which comments were made.

Table of Contents:

Revised Policies & PROCEDURES Document

1) **OMB Edit:** On page 4, lines 144 – 146. Revise as follows:

> The fact that a substance may interact with a hormone system, however, does not mean that when the substance is used, it will cause adverse effects and/or have endocrine effects in humans or ecological systems.

EPA Response: The beginning of the sentence states "the fact that a substance may interact with a hormone system" indicates that the substance does indeed have "endocrine effects." Ultimately, EPA would only regulate on adverse endocrine effects not "beneficial" endocrine effects. EPA will not make this change.

2) **OMB Edit:** On page 4, lines 146 - 149

> The purpose of Tier 2 testing (referred to as "testing"), is to identify and establish a dose-response relationship for any endocrine ~~adverse~~ effects that might result from the interactions identified through the Tier 1 assays (Ref. 1).

EPA Response: This same phrasing describing Tier 2 has been used by EPA since the establishment of the EDSP in 1998. The purpose of Tier 2 is not just to identify an effect, but to identify an adverse effect. EPA regulates chemicals on the basis of adverse effects, not just any effects (e.g., beneficial). EPA will not make this change.

3) **OMB Edit:** On page 4, lines 150 - 152

> EPA is implementing its EDSP in three major parts developed in parallel. This document deals only with one ~~the third~~ component of the EDSP (i.e., the administrative policies and

procedures related to the issuance of orders). The three parts are briefly summarized as follows:

EPA Response: Edit is accepted.

4) **OMB Edit:** On page 4, Line 162

~~At this moment, validation is complete for all but 1 of the assays (ER Binding) that were included in the proposed Tier 1 screening battery. The ER Binding assay is expected to complete the validation process in March 2009.~~

EPA Response: Edit is accepted.

5) **OMB Edit:** On page 5, Line 166

~~The status of each assay can be viewed on the EDSP website in the Assay Status table: http://www.epa.gov/scipoly/oscpendo/pubs/assayvalidation/status.htm.~~

EPA Response: We are not sure why giving the reader this link is unwanted. The status link is still relevant to those interested in where we are on the validation effort for the Tier 2 assays.

6) **OMB Comment:** On page 5, Line 167, Comment A1: Is it really priority setting or should the tile say Substance list as the FR notice refers to the final list and does not mention priority setting.

EPA Response: EPA has referred to the "list making" effort as "priority setting" throughout the history of EDSP (e.g., see the 1998 policy statement, and the Approach related documents from 2000 and 2005). EPA prefers to retain this terminology to be consistent with previous documents and the Agency's Website.

7) **OMB Comment:** On page 5, Line 188, Comment A2: Page 3 describes the document in 6 bullets—this just uses 4. Has anything been dropped? Why the change in framing?

EPA Response: Nothing was dropped. The first list presents bullets which are intended to serve as a roadmap to the FR document - linking the Agency's stated objectives to the specific sections in the FR document where the issue is discussed. The bullets here serve a different purpose, and are intended to provide a quick overview of the policy and procedures. We believe that the distinction between these bullets is clear in the text that introduces them.

8) **OMB Comment:** On page 6, Lines 226 - 228, Comment A3 (highlighting the first sentence): Is Tier 1, Tier 2, or the whole thing? If Tier 1, is this the standard we're applying, or is the standard the question of whether the chemical must proceed to Tier 2?

EPA Response: The first sentence refers to the entire program. The next sentence addresses Tier 1, followed by Tier 2.

9) **OMB Edit:** On page 6, Line 227: Delete this word in the first sentence:

In general, EPA intends to use the data collected under the EDSP, along with other information, to determine if a pesticide chemical, or other substances, ~~that~~ may pose a risk to human health or the environment due to disruption of the endocrine system.

EPA Response: EPA accepts the edit.

10) **OMB Comment:** On page 6, Lines 226 – 228, Comment A4 (highlighting the first sentence): Is this new language or is EPA quoting what has been previously stated?

EPA Response: This is not new language. EPA has used this description previously to describe EDSP, including on its Web site and in the documents that underwent public review and comment, including the draft Policy & Procedures document and related documents issued for comment last year.

11) **OMB Comment:** On page 6, Lines 233 – 235, Comment A5: What is meant by saying "scope of" in this sentence: "Chemicals that go through Tier 1 screening and are found to have the potential to interact with the estrogen, androgen, or thyroid hormone systems will proceed to be evaluated for the scope of Tier 2 testing." ? does this mean that all chemicals that have endocrine effects in Tier 1 will have to go through ALL tier 2 tests?

EPA Response: No. This does not mean that all chemicals that have endocrine effects in Tier 1 will have to go through ALL tier 2 tests. EPA will evaluate the chemical's Tier 1 Battery response, along with other available data, to make a weight of the evidence determination of whether or what Tier 2 testing is needed. To clarify, EPA will revise this sentence as follows:

Chemicals that go through Tier 1 screening and are found to have the potential to interact with the estrogen, androgen, or thyroid hormone systems will proceed to ~~be evaluated for scope of Tier 2 testing~~ the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data.

12) **OMB Edit:** On page 6, Lines 235 – 237: Revise as follows

Tier 2 testing data will be designed to identify any adverse endocrine-related effects caused by the substance, and establish a quantitative relationship between the dose and that endocrine ~~adverse~~ effect.

EPA Response: EPA accepts the edit, but will correct the tense.

13) **OMB Comment:** On page 6, Lines 235 – 237, Comment A6: What is the history of defining effects as adverse?

EPA Response: The term and concept of "adverse effects" under the EDSP is not any different than what is understood generally – for which there is an even longer history. In the context of EDSP, if a chemical is determined to interact with the hormone system and Tier 2 testing is required, the ultimate end product of the EDSP will be a risk assessment. Risk assessments are written to describe the risk surrounding the use of a substance based on the *adverse* effects - not

the *beneficial* effects. This construct is consistent with that established by our implementing statute and upon which the Agency has regulated pesticides since the beginning of EPA.

14) **OMB Comment:** On page 12, Line 468, Comment A7 (refers to mention of the Test Order Templates): See comments on these documents

EPA Response: Go to the Response to Comments on the Templates section below.

15) **OMB Comment:** On page 12, Lines 478 – 479, Comment A8 (linked to the following quote: "[t]o the extent practicable, the Administrator shall minimize duplicative testing of the same substance for the same endocrine effect. . . ."): Why is EPA interpreting this to deal only with cost sharing and data compensation and not the issue that commenters mention regarding lack of utility of requiring screening tests when other data that answers the question already exists—repetition of assays without utlity? Where is this discussed in the notice? It is mentioned on page 9 of the R2C and EPA should discuss in the FR that duplicative testing can also mean this as well (and then cite where its discussed further in the FR).

EPA Response: EPA is not. This first paragraph attempts to introduce this complex topic, which is then discussed in detail and is not limited to cost sharing and data compensation. It is important to understand that EPA defines "duplicative testing" as testing the same chemical using the same test. OSRI involves the testing of a chemical using some other test, whose results should be considered as responsive to the request in the Order, or may even involve another chemical with the same structure. Using OSRI to address this issue is specifically identified in the bullets that follow and is discussed in more detail later in this section (see Section IV.C.1.c.), as well as again in Section IV.F.1.b.

16) **OMB Comment:** On page 13, Line 513, Comment A9: See previous comment regarding clarifying the 2 meanings of this term ("duplicative testing").

EPA Response: See previous response. There are not two meanings. See third paragraph, where EPA identifies its approach to reduce duplicative testing consistent with how that phrase has been used by EPA. Some comments, however, do provide a different interpretation as reflected in the discussion of their comments. However, that interpretation does not change the traditional meaning of the phrase.

17) **OMB Edit:** On page 15, 596 – 604; Revise as follows:

Other scientifically relevant information is information that is scientifically credible and that provides information that that informs the determination as to whether the substance may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, androgen or thyroid (e.g., information that identifies substances as having the potential to interact with the estrogen, androgen, and/or thyroid system(s); information demonstrating whether substances have an effect on the functioning of the endocrine system). OSRI may be functionally equivalent to Tier 1 assays—that is data from assays that perform the same function as EDSP Tier 1 assay or may include data that provide information on a consequence or effect that could be altered by producing

effects on the estrogen, androgen or thyroid systems. ~~affects the confidence with which conclusions may be made about the potential for substances to have an effect that is similar to an effect produced by a substance that interacts with the estrogen, androgen, and/or thyroid hormonal systems (e.g., information that identifies substances as having the potential to interact with the estrogen, androgen, and/or thyroid system(s); information demonstrating whether substances have an effect on the functioning of the endocrine system).~~

EPA Response: To reflect the final language on OSRI, this will be revised as follow:

c. *Submission/Citation of existing data*. As under FIFRA, EPA provides the recipients of FFDCA 408(p) test orders with the option of submitting or citing existing data, along with a rationale that explains how the cited or submitted study satisfies the requirements of the Order. Existing data may include data that has already been generated using the assay(s) specified in the Order, or "other scientifically relevant information." Other scientifically relevant information is information that informs the determination as to whether the substance may have an effect that is similar to an effect produced by a substance that interacts with the estrogen, androgen, and/or thyroid hormonal systems (e.g., information that identifies substances as having the potential to interact with the estrogen, androgen, and/or thyroid system(s); information demonstrating whether substances have an effect on the functioning of the endocrine system). OSRI may either be functionally equivalent to information obtained from the Tier 1 assays—that is, data from assays that perform the same function as EDSP Tier 1 assays—or may include data that provide information on a potential consequence or effect that could be due to effects on the estrogen, androgen or thyroid systems.~~is scientifically credible and that provides information that affects the confidence with which conclusions may be made about the potential for substances to have an effect that is similar to an effect produced by a substance that interacts with the estrogen, androgen, and/or thyroid hormonal systems (e.g., information that identifies substances as having the potential to interact with the estrogen, androgen, and/or thyroid system(s); information demonstrating whether substances have an effect on the functioning of the endocrine system).~~ Some "other scientifically relevant information" may be sufficient to satisfy part or all the requirements of the Test Order. The submission or citation of other scientifically relevant information in lieu of the data specified in the Order is discussed in Unit IV.F.1.b. of this document.

18) OMB Edit: On page 15, Line 608, Comment A10: Suggest adding all the bullets from the OSRI 2 pager to this FR notice here.

EPA Response: EPA will not make this edit. The 2 pager was developed to provide guidance to EPA staff and managers who will be reviewing the responses to Tier 1 Orders, and is not intended to be binding on either EPA or any outside parties. Even though EPA has worked hard to ensure that it is clear that this 2-pager does not contain any binding requirements, including it in the preamble increases the likelihood that a Court will consider it to have greater weight than otherwise – which could have the undesired effect of limiting submissions of or citations to other scientifically relevant information. The Agency believes that the salient points from that 2-pager are captured appropriately already.

19) **OMB Comment:** On page 24, Lines 999 - 1001, Comment A11 (linked to "EPA has created a simple Initial Response Form that it intends to pre-populated with the basic information about the chemical and recipient to connect it to the specific order."): Should EPA mention that this will be released as part of the ICR package? Has EPA already taken comment on this form as part of the draft ICR release? If so, should mention this.

EPA Response: Yes. A draft form was included as an attachment to the draft ICR that underwent public review at the same time as the proposed procedures, and was included in BOTH the procedures and the ICR dockets. During OMB review, EPA decided to simplify the form further by creating a separate streamlined form tailored to Consortia. To reflect that here, EPA will revise the text as follows:

> To facilitate completion of this initial response within the 90 days, EPA has created ~~a~~two simple Initial Response Forms that EPA ~~it~~ intends to pre-populated with the basic information about the chemical and recipient to connect it to the specific order. One form is for use by the Individual Order recipient and the other is for use when a Consortium provides their group's response. EPA intends to include both of the Initial Response Forms in the EDSP Order Packet that is sent to the recipients. Please note that in calculating the due date for the Initial Response Form, the Agency intends to include an additional 10 calendar days to account for the Agency processing of the final order package for delivery to the Post Office.

In addition, the discussion about our compliance with the PRA's comment process fits better in Section V.B., which specifically addresses EPA's compliance with the PRA. In that section, EPA will revise the related discussion (starts on line 1603) as follows:

> A copy of the final ~~Information Collection Request (~~ICR~~) document~~ package (~~prepared by EPA and~~ identified under EPA ICR No. 2249.01) has been placed in the docket for this policy. A draft of the ICR package ~~In addition, the Agency has established a docket for the ICR under Docket ID No. EPA-HQ-OPPT-2007-1081, which~~ was issued for public comment ~~under~~ pursuant to the PRA and 5 CFR 1320.8(d) on December 13, 2007 (72 FR 70839) (FRL-8155-8). The ICR has been revised to address comments received, and the following is a brief summary of the final ICR ~~document,~~package that was submitted to OMB for approval under the PRA and which describes the information collection activities discussed in the final policy and procedures document, along with ~~and~~ EPA's estimated burden in more detail.

20) **OMB Edit:** On page 25, Lines 1032 – 1033 Revise as follows:

> Order, including, where appropriate, a cogent and complete rationale for why it believes the information is or ~~not~~ is sufficient to satisfy part or all of the requirements in the Order.

EPA Response: We understand the intended edit and will revise this sentence as follows:

Order, including, where appropriate, a cogent and complete rationale for why it believes the information is ~~or not is~~ sufficient to satisfy part or all of the ~~requirements in~~ the Order.

21) OMB Comment: On page 25, Lines 1034 - 1038, Comment A12 (refers to the following text): Does this apply to all OSRI? Doesn't makes sense that a comparison to Tier 1 test protocols is needed—focus should be on what it tells EPA about endocrine effects. In addition, is the 'validation' of each piece of OSRI going to need to be addressed? If so, EPA needs a bullet on this in the OSRI, for instance their should be a presumption that standard Part 158 data would be considered valid for the purposes of being accepted as OSRI so that this 'validation' doesn't become a hurdle of all OSRI.

If the data cited or submitted are from a study that was not conducted exactly as specified in the protocols referenced in the test order, the recipient would also identify the deviations from the applicable protocol(s), along with an explanation for the deviations, including an explanation as to why, notwithstanding the deviations, the protocol it used could still be considered "validated," and any other information relevant to a decision to accept the data as satisfaction of the Order.

EPA Response: In this context, "validation" is used with its standard scientific definition and is not intended to refer to the EDSP Validation Process. The request for an explanation when the protocols differ is consistent with existing requirements, and applies to all studies submitted to EPA under FIFRA or FFDCA that do not follow an established test guidelines, including when data is submitted under part 158. We revised similar test in response to OMB's comment, and will change this as follows:

If the data cited or submitted are from a study that was not conducted exactly as specified in the protocols referenced in the test order or in accordance with accepted scientific methodology or protocol, including but not limited to those presented in EPA's harmonized test guideline compendium (see http://www.epa.gov/oppts and select "Test Methods & Guidelines" on the left), the recipient would also identify the deviations from the applicable protocol(s), along with an explanation for the deviations, including an explanation as to why, notwithstanding the deviations, the protocol ~~it~~ used for developing the cited or submitted data could still be considered "scientifically valid~~ated~~," and any other information relevant to a decision to accept the data as satisfaction of the Order.

22) OMB Edit: On page 25, Lines 1040 – 1042; Revise the first sentence as follows:

EPA would review any existing relevant information submitted or cited to determine whether the information is acceptable and satisfies the requirements of the Order and/or is acceptable OSRI.

EPA Response: See explanation below regarding "acceptable" as used in this context. Instead of the suggested edit, EPA will revise as follows:

EPA would review any existing relevant information submitted or cited (including other scientifically relevant information) to determine whether the information is acceptable

(i.e., the study was not rejected by the Agency for any reason related to completeness or quality) and satisfies ~~the requirements of~~ the Order ~~and/or is acceptable OSRI~~.

23) OMB Edit: On page 25, Lines 1042 – 1044: revise as follows:

Decisions about whether the information informs the determination as to whether the substance may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, androgen or thyroid ~~satisfies part or all of the Test Order testing requirements~~ will be based on the weight of the evidence from all relevant information available.

EPA Response: As discussed previously, the suggested edit is incorrect and can not be made. EPA will, however, revise "Test Order testing requirement" to read "Tier 1 Order," which is consistent with the rest of the document.

24) OMB Edit: On page 25, Lines 1046 – 1049; Revise as follows:

If the Agency determines that the information cited or submitted as part of the initial response informs the determination as to whether the substance may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, androgen or thyroid, ~~satisfies all of the requirements of the Order,~~ the Initial Response Form is the only response required to satisfy the Order.

EPA Response: The context of the discussion here is focused on the decision about whether the submitted or cited data satisfies the Order. That determination is different from the ultimate EDSP determination itself. EPA will revise as follows.

If the Agency determines that the information cited or submitted as part of the initial response received from an Order recipient satisfies ~~all of the requirements of~~ the Tier 1 Order, which will be based on the weight of evidence from all relevant information available to the Agency, the Initial Response Form is the only response required ~~to satisfy the Order~~.

25) OMB Edit: On page 25, Lines 1049 – 1054; Revise as follows:

If, however, EPA determines that the information cited or submitted as part of the initial response is not acceptable or is acceptable but insufficient to inform the determination as to whether the substance may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, androgen or thyroid, ~~satisfy all the requirements of the Order,~~ the recipient must still satisfy the necessary requirements of the Order.

EPA Response: The first edit is incorrect. To clarify, EPA will revise this as follows:
If, however, EPA determines that the information cited or submitted as part of the initial response is ~~not acceptable or is acceptable but~~ insufficient to satisfy all of the requirements of the Order, although in may satisfy part of the Order, the recipient ~~must~~ would still need to satisfy the ~~requirements~~ remainder of the Order.

26) OMB Comment: On page 26, Line 1059, Comment A13 (refers to the text highlighted in the following sentence): This implies that E, A, or T positive findings are sufficient to trigger the need for tier 2—thus implying that is someone submits data on one endpoint only (eg E but not A or T) then the A or T testing is not needed as Tier 2 is automatically triggered. If this is not correct, this needs to be clarified and discussed in this policies and procedures document. Perhaps it should be clarified even if this is a correct interpretation.

Chemicals that go through Tier 1 screening and are found to have the potential to interact with the estrogen, androgen, or thyroid hormone systems will proceed to be evaluated for the scope of Tier 2 testing.

EPA Response: As already explained, the Agency can not specifically state that providing any data on a single axis (e.g., E but not A or T) will satisfy the Order. This violates the Safe Harbor Principle. We believe that the policy document is clear that EPA will evaluate all OSRI and determine whether the OSRI 1) answers one or more of the questions that make up the Tier 1 determination, or 2) satisfies all or part of the Tier 1 Order. Based on those determinations, and using a weight or the evidence approach to consider the available information, EPA will assess whether and what is needed for Tier 2. Once we make decisions on OSRI submitted, EPA intends to publish the decision so that they become the examples for future reference.

27) OMB Comment: On page 26, Line 1059, Comment A14 (refers to highlighted text in the following sentence): What is meant by "scope of"? does this mean that all Tier 2 test wills be required for all chemicals that must go to Tier 2. If not, this should be clarified/revised.

Chemicals that go through Tier 1 screening and are found to have the potential to interact with the estrogen, androgen, or thyroid hormone systems will proceed to be evaluated for the scope of Tier 2 testing.

EPA Response: See response #11. EPA will revise this as follows:

Chemicals that go through Tier 1 screening and are found to have the potential to interact with the estrogen, androgen, or thyroid hormone systems will proceed to ~~be evaluated for the scope of Tier 2 testing.~~the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data.

28) OMB Edit: On page 26, Lines 1060 – 1062: Revise as follows:

Tier 2 testing data will be designed to identify any adverse endocrine-related effects caused by the substance, and establish a quantitative relationship between the dose and that endocrine ~~adverse~~ effect.

EPA Response: See response #12. EPA accepts the edit, but will correct the tense.

29) OMB Comment: On page 26, Line 1060, Comment A15: Where does the term "adverse" come from?

EPA Response: See response #2.

30) **OMB Comment:** On page 29, Line 1211, Comment A16: Where is the section that allows for submission of OSRI?

EPA Response: Section IV.C.1.c. first introduces OSRI, and Section IV.F.1.b. of the document specifically addresses how an order recipient can submit other scientifically relevant information.

31) **OMB Edit:** On page 38, Lines 1595 – 1596: Revise as follows:

The information collection requirements associated with issuing orders for Tier 1 screening under the EDSP have been submitted for review ~~and approval~~ by OMB under the Paperwork Reduction Act (PRA), 44 U.S.C. 3501 et seq.

EPA Response: Does OMB no longer approve the ICRs under the PRA? This is longstanding standard language that directly reflects the requirement in the statute. At the time of signature, the Agency will have submitted the ICR for OMB review and approval. The copy provided in October was an advance draft for OMB's informal review along with the final procedures document.

Agency's R2C document for the Policy & PROCEDURES Document

1) **OMB Comment**: On page 2, Section 2.8 and 2.81, change page number "24" to "23".

EPA Response: We will be sure to regenerate the Table of Contents before finalization to make sure it is accurate.

2) **OMB Comment**: On pages 3 and 4, Section 1.2 Background, Comment A1 [linked to yellow highlight text below]. Does the statute say adverse or endocrine? Revise text as follows:

The necessary information includes identifying any adverse effects that might result from the interaction of a substance with the endocrine system and establishing a dose-response curve. Section 1457 of the Safe Drinking Water Act (SDWA) also authorizes EPA to screen substances that may be found in sources of drinking water, and to which a substantial population may be exposed, for endocrine disruption potential. [42 U.S.C. 300j–17].

[…] The fact that a substance may interact with a hormone system, however, does not mean that when the substance is used, it will cause adverse or endocrine effects in humans or ecological systems.

> […] The purpose of Tier 2 testing (referred to as ‘‘testing’’), therefore, is to identify and establish a dose-response relationship for any ~~adverse~~ endocrine effects that might result from the interactions identified through the Tier 1 assays.
>
> […] This paper deals only with ~~the third~~ one component of the EDSP (i.e., policies and procedures related to the issuance of orders). The other aspects of the EDSP have been or will be addressed in separate documents published in the Federal Register.

EPA Response: EPA will change “the third” to “one,” but will not make the other changes related to “adverse.” As explained in a previous response, the term and concept of “adverse effects” under the EDSP is not any different than what is understood generally, and has been used consistently since 1998.

3) **OMB Comment**: On page 6, in the text between the Tables 1 and 2. Comment A2 [see yellow highlighted text below]. Does this include comments from the June 5 mtg with ACC/Croplife and also from the mtg with PCRM? If not, where and when will those comments be addressed. What about the croplife july 11 2008 petition? Where are those comments addressed? At one point we saw a draft response to that—will that be released now?

   After carefully analyzing the twelve submissions, EPA determined that 257 distinct comments had been submitted that could be grouped in thirteen subject/topic areas. Table 2 (below) outlines this analysis.

EPA Response: The tables solely consist of information related to comments submitted during the public comment period to the Docket. The Agency is responding to the post public comment period comments in separate documents (i.e., a separate response to comments document for each of these additional submitters – which were sent to OMB in draft form back in October). These response to comments documents will be placed in an appropriate docket based on the principle topic of the comments (e.g., comments on the assay or battery will be placed in the Battery FRN docket, etc.).

4) **OMB Comment**: On page 9, the first paragraph under Submitted Comment(s), Comment A3 [yellow highlighted text below]. This is missing from the FR.

   Submitted Comment(s):

   EPA appears to consider the goal of minimizing duplicative testing only in the context of reducing the number of screening tests of the same chemical, rather than whether such a screening test is needed at all. “Duplicative testing” in this context can also mean the repetition of assays that would not bring additional quality information to the EDSP assessments.

EPA Response: This is part of the comment – not EPA’s interpretation. EPA has consistently defined “duplicative testing” as testing the same chemical using the same test. Sections IV.C.1.c. and IV.F.1.b. of the Policies and Procedures document specifically addresses this point

and describes how an order recipient can submit other scientifically relevant information. To clarify, EPA will move the sentence to the Response and revise it as follows:

> "Duplicative testing" (as used by the commenters)~~in this context can also~~ appears to mean the repetition of assays that would not bring additional ~~quality~~ information to the EDSP assessments. To reiterate, EPA defines "duplicative testing" as testing the same chemical using the same test. Nevertheless, even though EPA does not interpret the statute in the manner suggested by the commenter, EPA has adopted procedures intended to address the substance of the commenter's concern: that assays should not be required where the assay would not result in the submission of additional information needed for the EDSP assessment. Elsewhere in this Response to Comments document, and in Section IV.C.1.c. and IV.F.1.b. of the Policies and Procedures Federal Register Notice, EPA discusses the process by which order recipients may submit other scientifically relevant information that they believe already provide the information that would be provided by the generation of Tier one data, in response to the Order.

5) **OMB Comment**: On page 9, the last paragraph and the first paragraph on page 10. Revise text as follows:

> As under FIFRA, EPA provides the recipients of FFDCA §408(p) test orders with the option of submitting or citing existing data, along with a rationale that explains how the cited or submitted study informs the determination as to whether the substance may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, androgen or thyroid ~~satisfies the requirements of the order~~. Existing data may include data that has already been generated using the assay(s) specified in the Order, or "other scientifically relevant information." Other scientifically relevant information is information that is ***scientifically credible*** and that or thyroid (e.g., information that identifies substances as having the potential to interact with the estrogen, androgen, and/or thyroid system(s); information demonstrating whether substances have an effect on the functioning of the endocrine system). OSRI may be functionally equivalent to Tier 1 assays—that is data from assays that perform the same function as EDSP Tier 1 assay or may include data that provide information on a consequence or effect that could be altered by producing effects on the estrogen, androgen or thyroid systems.~~Information that is scientifically credible and that provides information that affects the confidence with which conclusions may be made about the potential for substances to have an effect that is similar to an effect produced by a substance that interacts with the estrogen, andarogen, and/or thyroid hormonal systems (e.g., information that identifies substances as having the potential to interact with the estrogen, androgen, and/or thyroid system(s); information demonstrating whether substances have an effect on the functioning of the endocrine system). Some "other scientifically relevant information" may be sufficient to satisfy part or all of the requirements of the Test Order.~~ The submission or citation of other scientifically relevant information in lieu of the data specified in the Order is discussed in Unit IV.F.1.b. of the revised Policies and Procedures document.

EPA Response: As explained previously, the first edit is incorrect. Consistent with the other documents, EPA will revise this second part of this text as follows:

Existing data may include data that has already been generated using the assay(s) specified in the Order, or "other scientifically relevant information." Other scientifically relevant information is information that informs the determination as to whether the substance may have an effect that is similar to an effect produced by a substance that interacts with the estrogen, androgen, and/or thyroid hormonal systems (e.g., information that identifies substances as having the potential to interact with the estrogen, androgen, and/or thyroid system(s); information demonstrating whether substances have an effect on the functioning of the endocrine system). OSRI may either be functionally equivalent to information obtained from the Tier 1 assays—that is, data from assays that perform the same function as EDSP Tier 1 assays—or may include data that provide information on a potential consequence or effect that could be due to effects on the estrogen, androgen or thyroid systems~~is scientifically credible and that provides information that affects the confidence with which conclusions may be made about the potential for substances to have an effect that is similar to an effect produced by a substance that interacts with the estrogen, andarogen, and/or thyroid hormonal systems (e.g., information that identifies substances as having the potential to interact with the estrogen, androgen, and/or thyroid system(s); information demonstrating whether substances have an effect on the functioning of the endocrine system)~~. Some "other scientifically relevant information" may be sufficient to satisfy part or all of the requirements of the Test Order. The submission or citation of other scientifically relevant information in lieu of the data specified in the Order is discussed in Unit IV.F.1.b. of the revised Policies and Procedures document.

6) **OMB Comment**: Page 25, third paragraph, under "EPA Response" line 7, change "Neither" to "neither," and on line 11, change "are as" to "will be."

EPA Response: EPA agrees with the edit.

FFDCA 408(p) Order TEMPLATE for Pesticide Registrants

1) **OMB Comment**: Similar changes as requested here, should also be made to the Inert Ingredients Order Template.

EPA Response: OK, to the extent that the change is relevant to the other Template.

2) **OMB Comment**: On page 4, Section III. A. Data Required – The Tier 1 Battery, Comment A1 (linked to the section header). If the order must have a list of the required assays, then the draft orders cannot be released until the final assay list is released.

EPA Response: The Draft Order Templates were already released as part of the proposed Policy and Procedures and ICR packages last December 2007 for public review and comment. As indicated in the December 18, 2008 email about the Battery announcement, the Agency intends to begin issuing the Orders only after the last assay completes validation at the end of March. To clarify this in the **Draft** Order Template. It serves the sole purpose of illustrating

what the Order might look like and is not intended to otherwise bind the Agency. To clarify, EPA will insert the following language at the beginning of the templates:

> This template was developed by EPA to provide guidance to EPA staff and managers who will be preparing the Tier 1 Orders that will be issued under the Endocrine Disruptor Screening Program (EDSP). This template is not a rule or regulation, nor does it create or confer legal rights or impose any legally binding requirements on EPA or any party. In preparing a final Tier 1 Order, EPA may depart from the guidance presented in this template where circumstances warrant and without prior notice.

We will also insert the following language in the introduction to this section, which already appears in the ICR:

> [NOTE: The availability of the final Tier 1 screening battery will be announced in the Federal Register before any 408(p) orders will be issued. Until that is done, the list of assays presented in this template is only a list of the assays that **are expected to be** in the battery based on the proposed Tier 1 screening battery that underwent peer review by the FIFRA Scientific Advisory Panel (SAP) in March 2008. When the orders are issued, the order will reflect the final Tier 1 Battery.]

3) OMB Comment: On page 5, Section III. B. Conducting the Battery – Testing Protocols, first paragraph, Comment A2 (linked to the 2nd and 3rd sentences presented below). Need to discuss OSRI as well.

> Pursuant to section 408(p)(1), testing conducted for the EDSP must be based on "validated test systems and other scientifically relevant information." 21 U.S.C. § 346a (p)(1). As such, the assays identified above must be conducted using the test protocols that have been validated and the Agency has made available for use by all Order recipients. All of the applicable testing protocols have been validated and are available on the Agency's web site at: [insert URL to website, which will include a list of the Protocols and links to the appropriate documents in the Docket].

EPA Response: To clarify this, EPA will revise as follows:

> Pursuant to section 408(p)(1), testing conducted for the EDSP must be based on "validated test systems and other scientifically relevant information." 21 U.S.C. § 346a (p)(1). "Other scientifically relevant information" is information that informs the determination as to whether the substance may have an effect that is similar to an effect produced by a substance that interacts with the estrogen, androgen, and/or thyroid hormonal systems (e.g., information that identifies substances as having the potential to interact with the estrogen, androgen, and/or thyroid system(s); information demonstrating whether substances have an effect on the functioning of the endocrine system). OSRI may either be functionally equivalent to information obtained from the Tier 1 assays—that is, data from assays that perform the same function as EDSP Tier 1 assays—or may include data that provide information on a potential consequence or effect that could be due to effects on the estrogen, androgen or thyroid systems. See also the discussion in Section IV. of this Order.

~~As such, t~~The assays identified ~~above~~in Section III.A. of this Order must be conducted using the test protocols that have been validated and ~~the Agency has~~ made available for use by ~~all~~ the Order recipients that are completing the assays to generate new data to respond to this Order. All of the applicable testing protocols have been validated and are available on the Agency's web site at: [insert URL to website, which will include a list of the Protocols and links to the appropriate documents in the Docket].

4) OMB Comment: On page 5, Section III. B. Conducting the Battery – Testing Protocols, second paragraph, Comment A3 (linked to the second paragraph). Need to first discuss that it is ok to submit other existing test data instead—eg the OSRI.

You may not deviate from an approved testing protocol unless you first consult with the Agency and obtain Agency approval of any deviation. If you wish to use a protocol that differs from those identified in this Order, you must submit a detailed description of the proposed protocol (including a precise description of any deviations from the protocol attached to this Order) and your reason for wishing to use it.

EPA Response: To clarify, EPA will revise as follows:

If you choose to generate the data to respond to this Order, y~~Y~~ou may not deviate from an approved testing protocol unless you first consult with the Agency and obtain Agency approval of any deviation. If you wish to use a protocol that differs from those identified in this Order, you must submit a detailed description of the proposed protocol (including a precise description of any deviations from the protocol attached to this Order) and your reason for wishing to use it.

If you choose to cite or submit existing data, including other scientifically relevant information, you must indicate whether the information provided follows a validated protocol, and provide a cogent and complete rationale for why you believe the information is sufficient to satisfy part or all of this Order. EPA's decisions about whether the OSRI satisfies part or all of the Tier 1 Order will be based on the weight of evidence from all relevant information available to the Agency. See the instructions for submitting your response, which appear in Section IV.

You must also adhere to the good laboratory practice (GLP) standards described in 40 CFR part 160, which require you to follow certain practices when conducting studies ~~in response to a FFDCA section 408(p) test order~~, and to indicate whether data cited or submitted addresses the GLPs.

5) OMB Comment: On page 8, Option 2: Submit or Cite Existing Data, revise 1st paragraph. Comment A4. Language edited to match 408(p) language.

If you choose to submit or cite an existing study in response to this Order (including data previously submitted to the Agency), your Initial Response must include either the data or a reference to the data for each test that is required, along with a rationale that explains how the study provides information to determine whether the substance may have an

effect in humans that is similar to an effect produced by a naturally occurring estrogen, androgen or thyroid ~~satisfies the requirements in this order~~. Existing studies are studies that predate issuance of this Order. In order to be accepted as satisfaction of the requirements imposed in this Order, the Agency expects that any such hazard-related data would be of high quality and achieves the objective of Tier 1 assays to provide reasonable assurance that a chemical does or does not have the potential to produce effects on the estrogen, androgen, or thyroid systems ~~scientifically comparable to data that would be generated by the EDSP.~~

EPA Response: The first suggested phrasing incorrectly attempts to limit the EDSP determination to effects *in humans*, and effects produced *by naturally occurring* E, A or T, which is inconsistent with the Agency's implementation of the EDSP as first articulated in 1998. The 1998 EDSP Policy Statement underwent review by the FACA, the public, and OMB in draft before it was reviewed by OMB again and then issued in final form. In addition, the context of the discussion here is focused on the decision about whether the submitted or cited data satisfies the Order. That determination is different from the ultimate EDSP determination itself. Therefore, EPA will not make this suggested edit.

The second suggested edit will be made, with the following addition to be consistent with our discussion about the Agency's approach to OSRI:

If you choose to submit or cite an existing study in response to this Order (including data previously submitted to the Agency), your Initial Response must include either the data or a reference to the data for each test that is required, along with a rationale that explains how the study you cited or submitted satisfies the requirements in this Order. Existing studies are studies that predate issuance of this Order. In order to be accepted as satisfaction of the requirements imposed in this Order, the Agency expects that any such hazard-related data would be of high quality and achieves the objective of Tier 1 assays to provide reasonable assurance that a chemical does or does not have the potential to interact with ~~produce effects on~~ the estrogen, androgen, or thyroid systems ~~scientifically comparable to data that would be generated by the EDSP~~. EPA's decisions about whether the data cited or submitted satisfies part or all of the Tier 1 Order will be based on the weight of evidence from all relevant information available to the Agency.

6) OMB Comment: On page 8, Option 2: Submit or Cite Existing Data, 2nd paragraph, Comment A5. This paragraph sets an inappropriate bar for other scientific information and is too narrow. Suggest revising to be consistent with description of OSRI or need to add discussion about how OSRI, such as part 158 testing would be considered 'validated' for the purposes of informing the objectives of Tier 1.

The submitted or cited study must have been conducted in accordance with a scientifically validated protocol. If the existing study cited or submitted was not conducted exactly as specified in the protocols validated for the Tier 1 assays, you must identify the deviations from the protocol(s), along with an explanation for the deviations, including an explanation as to why, notwithstanding the deviations, the protocol should still be considered "validated," and any other information to support a decision to accept the data in satisfaction of this Order.

EPA Response: In this context, "validated" is used with its standard scientific sense and is not intended to refer to the EDSP Validation Process. The request for an explanation when the protocols differ is consistent with existing standards, and applies to all studies submitted to EPA under FIFRA or FFDCA that do not follow an established test guideline or other accepted scientific methods, including those studies submitted under part 158. To clarify this, the discussion will be revised as follows:

> The submitted or cited study must have been conducted in accordance with accepted scientific~~ally~~ methodology or ~~validated~~ protocol, including but not limited to those presented in EPA's harmonized test guideline compendium (see http://www.epa.gov/oppts and select "Test Methods & Guidelines" on the left). Deviations from the ~~If the existing study cited or submitted was not conducted exactly as specified in the~~ protocols validated for the Tier 1 assays, ~~you~~ must be identify~~ied the deviations from the protocol(s)~~, along with an explanation for the deviations, including an explanation as to why, notwithstanding the deviations, the protocol used should still be considered "scientifically valid~~ated~~," and any other information you think the Agency should consider in deciding whether ~~to support a decision~~ to accept the data in satisfaction of this Order.

7) **OMB Comment**: On page 9, second paragraph, Comment A6. In what context is the term « acceptable » used?

> If you choose to cite a study that has been previously submitted to EPA, that study must have been previously classified by EPA as acceptable or it must be a study which has not yet been reviewed by the Agency.

EPA Response: It refers to the status of a study that has been submitted to EPA, reflecting that EPA has completed its initial review in terms of completeness (no pages missing), scientifically sound (used scientific methods and standards) and quality (reproducible, reliable, relevant etc). This has been a standard step for "data submissions" since the beginning, and is reflected in the guidance referenced with regard to how to submit the data. Recipients of the Orders will certainly be familiar with this term as it is used here. However, to clarify for others, EPA will the sentence as follows:

> If you choose to cite a study that has been previously submitted to EPA, that study must have been previously classified by EPA as acceptable (i.e., the study was not rejected by the Agency for any reason related to completeness or quality) or it must be a study which has not yet been reviewed by the Agency.

8) **OMB Comment:** On page 9, second paragraph, Comment A7. What if the agency reviewed it for a different purpose and perhaps here it would be acceptable? This statement seems too broad.

EPA Response: The purpose is not considered. The phrasing "acceptable" only relates to whether the study meets basic submission standards in terms of completeness and quality. This phrasing has been used historically by EPA to only refer to the preliminary screening done for a submission BEFORE it is then reviewed. In other words, we may accept a study, and then later

determine that it does not satisfy the intended purpose.

9) **OMB Comment:** Comment A8. So EPA wants some OSRI referred to but not re-submitted? This contradicts the statement in the policies and procedures document that all data must be submitted.

   Do not resubmit a study that has previously been submitted to EPA for another purpose.

EPA Response: There is no contradiction at all. We consistently say "CITE or submit." As you know, if the data was previously submitted to EPA for other purposes, the PRA does not allow the Agency to require it to be resubmitted. This is consistent with existing instructions to pesticide registrants that the Agency issued back in 1986 (PR Notice 86-5, available at http://www.epa.gov/PR_Notices/pr86-5.html), in which EPA explains that Registrants should not resubmit a study because it saves the Registrant the cost of sending more copies of the study to EPA, and helps prevent duplicate entries in the Agency files.

10) **OMB Comment**: On page 12, second paragraph, Comment A9. What does this mean "EPA will only accept the data in satisfaction of the test order for those assays for which the testing has been conducted"? As opposed to data from tests that have not been conducted? How does this apply to OSRI?

EPA Response: This is not really related to the OSRI issue. This ONLY refers to those few chemicals used in the EDSP validation process. Since none of those chemicals were used for all the assays in the Tier 1 Battery, the results from the validation effort can not be used to assert that the Order is satisfied by that effort. They can only assert that part of the Order is satisfied, specifically that part of the request related to the assay whose validation effort used that chemical. To clarify, EPA will revise as follows:

   Your chemical was used by EPA as a ''positive control'' to validate one or more of the screening assays ~~and that EDSP screening has already been conducted~~. EPA will only accept th~~e~~is data in satisfaction of that part of the test order related to ~~for~~ those assays for which the chemical was used to complete the testing ~~has been conducted~~ as part of the validation effort.

11) **OMB Comment**: On page 13, Section IV.F. Procedures for Data Protection, first paragraph, Comment A10. The response to comments leaves this a little fuzzy. Can EPA withhold this information as a rule, or can it be forced to release it, either by Congress or by internal agency discretion?

IV.F. Procedures for Data Protection

FOIA requires agencies to make information available to the public upon request, except for information that is "specifically made confidential by other statutes" or data that are "trade secrets and commercial or financial information obtained from a person and is privileged or confidential" [5 U.S.C. § 552]. Any information that you wish to have EPA protect as confidential business information should be clearly identified as such. Note that substantive criteria must be met to support a claim confidentiality of business information, as specified in 40 CFR § 2.208.

EPA Response: Information claimed to be confidential business information (CBI) is protected from public release, unless the Agency follows the procedures in 40 CFR part 2 to release it. This includes procedures for releasing the CBI to a specific party – like a contractor doing work for us, a member of Congress, or in the context of litigation. In general, release to specific parties requires that party to accept the responsibility of protecting the information from public release, as well as the consequences for failing to do so. This is discussed in more detail in the Policy and Procedures document.

Final LIST FR Notice

1) **OMB Comment**: On page 5, line 166, Comment A1 (linked to the following sentence that starts on this line). Is this a quote? If so from where? Is the word "adverse" needed?

   The purpose of Tier 2 testing (referred to as "testing") is to identify and establish a dose-response relationship for any adverse effects that might result from the interactions identified through the Tier 1 assays

EPA Response: This same phrasing describing Tier 2 has been used by EPA since the establishment of the EDSP in 1998. The purpose of Tier 2 is not just to identify an effect, but to identify an adverse effect. EPA regulates chemicals on the basis of adverse effects, not just any effects (e.g., beneficial).

2) **OMB Comment:** On page 5, line 177 (Comment A2, linked to "may have estrogenic effects in humans or other endocrine effects" in the following sentence). Is this a direct quote from 408p?

   Under FFDCA section 408(p), EPA is required to use "appropriate validated test systems and other scientifically relevant information" to determine whether substances may have estrogenic effects in humans or other endocrine effects as the Administrator may designate.

EPA Response: The wording within the quotations is a direct quote, while the remainder of this sentence is a paraphrasing that EPA has used in describing EDSP in the past – including in the three prior List related FR notices that OMB also reviewed.

3) **OMB Comment:** On page 5, line 183. Delete this text: "At this moment, validation is complete for all but 1 of the assays (ER Binding) that were included in the proposed Tier

1 screening battery. The ER Binding assay is expected to complete the validation process in March 2009."

EPA Response: OK.

4) **OMB Comment:** On page 6, line 211, Comment A3 (linked to "EPA developed a draft template for the test order and a draft information collection request (ICR) to obtain the necessary clearances"). See OMB comments on these templates.

EPA Response: OMB comments on these templates are addressed in the Template discussion later in this document.

5) OMB Comment: On page 6, line 226. Insert "and how" as follows:
"One of the main concerns was whether and how EPA would consider existing data in determining what screening assays were necessary."

EPA Response: OK.

6) **OMB Comment:** On page 6, line 227, Comment A4 (linked to "Although EPA will not tailor test orders based on existing information, as articulated in the "Draft List Comment Summaries and Agency Responses" (Ref. 2),"). See comments in the response document and revise to match.

EPA Response: OMB comments are addressed in the Draft List's Response to Comment discussion later in this document.

7) **OMB Comment:** On page 6, line 231, Comment A5 (linked to "~~meets one or more of the data requirements of the order~~to inform the determination as to whether the substance may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, androgen or thyroid."). Language edited to match the 408p language.

EPA Response: As discussed in the Agency's response to OMB's comments on the OSRI paper, the context of the discussion around line 231 is focused on the decision about whether the OSRI satisfies the Order – which is different from the EDSP determination itself.

In addition, the suggested language is not a direct match with 408(p). This suggested phrasing incorrectly attempts to limit the EDSP determination to effects *in humans*, and effects produced *by naturally occurring* E, A or T, which is inconsistent with the Agency's implementation of the EDSP as first articulated in 1998. The 1998 EDSP Policy Statement underwent review by the FACA, the public, and OMB in draft before it was reviewed by OMB again and then issued in final form. Therefore, EPA will not make this suggested edit.

8) **OMB Comment:** On page 6, line 237. Revise the text as follows:

The recipient's response to test orders for Tier 1 assays will be evaluated by EPA to determine whether the cited data ~~fulfills the testing required by the order~~provides the information needed for EPA to determine whether or not the chemical has the effect

described above. This will require a case-by-case determination of whether the information submitted is of high quality and achieves the objective of Tier 1 assays to provide reasonable assurance that a chemical does or does not have the potential to produce effects on the estrogen, androgen, or thyroid systems.

EPA Response: EPA will insert the suggested revision, modified as follows:

The recipient's response to test orders for Tier 1 assays will be evaluated by EPA to determine whether the cited data fulfills the ~~testing required by~~ requirements in the order, and provides the information needed for EPA to determine whether or not the chemical has the effect described above. This will require a case-by-case determination of whether the information submitted is of high quality and achieves the objective of Tier 1 assays to provide reasonable assurance that a chemical does or does not have the potential to produce effects on the estrogen, androgen, or thyroid systems.

9) **OMB Comment:** On page 6, line 245, Comment A6. Suggest putting this in the policy and procedures FR notice and referring to this. Should also provide similar details in the response to comments document for this FR—so perhaps cite both.

Further detail on this is provided in XXX.

EPA Response: EPA will revise the last paragraph of this section as follows, and add a similar reference to the Draft List Response to Comment document:

These comments have been addressed in a document, entitled: *Draft List Comment Summaries and Agency Responses* (Ref. 2), available in the Docket ~~supporting~~ for this action, under Document ID No. EPA-HQ-OPPT-2004-0109-XXXX. In addition, the Agency's final policy and procedures describe the Agency's approach for considering other scientifically relevant information under the EDSP, see Docket ID No. EPA-HQ-OPPT-2007-1080.

Agency's R2C Document for the Final LIST FR Notice

1) **OMB Comment**: On page 7, first paragraph (at the top of the page), line 2, Comment A1 (linked to "Thus, the Agency is not removing chemicals from the list on the basis of claims of adequate data. The registrants and/or manufacturers of chemicals appearing on the final initial list will therefore receive Test Orders for the full battery of Tier 1 assays."). This paragraph responds to a comment that commenters are not necessarily making. Commenters are not saying that chemicals with functionally equivalent or higher tier data be removed from the list—they are asking that EPA exempt these substances from Tier 1 testing. These are two different things."

EPA Response: The statute specifically addresses the issue of "exemption" from testing under the EDSP, without discussing the concept reflected in the comments, i.e., an exemption from

Tier 1 screening or just part of the EDSP. To clarify, EPA will insert the following as a new introductory paragraph for 4.2:

> It is important to first clarify the concept of "exemption" as it relates to the EDSP. FFDCA section 408(p)(4) provides that "the Administrator may, by order, exempt from the requirements of this section a biologic substance or other substance if the Administrator determines that the substance is anticipated not to produce any effect in humans similar to an effect produced by a naturally occurring estrogen." The Agency's final policy and procedures document specifically addresses the Agency's approach regarding requests to exempt chemicals under FFDCA section 408(p)(4). The statute does not, however, provide for partial exemptions. Although the commenters request that EPA "exempt" chemicals from Tier 1 screening (i.e., creating a partial exemption from EDSP), the Agency has interpreted the comments as requesting that EPA allow certain chemicals to *skip* Tier 1 screening.

2) **OMB Comment**: On page 7, second paragraph, line 1, Comment A2 (linked to "On an assay-by-assay basis"). What if someone wants to simply say their compound has endocrine effects—does this still need to be assay by assay?

EPA Response: Although the order recipient "can elect" to cite or submit existing data on an assay-by-assay basis as this response explains, they are not REQUIRED to do so. If an order recipient wants to cite or submit existing data for all of the assays, they would simply check all the boxes in the applicable column of the table on the Initial Response Form and attach the related explanation with the data or citation. There is nothing in the procedures or the Order Templates that **requires** the order recipient to reply on an assay-by-assay basis. The assay-by-assay approach reflected in the procedures and on the forms is specifically in response to stakeholders who told us that they want to have the flexibility to address each assay differently.

3) **OMB Comment**: On page 7, second paragraph, line 6, Comment A3 (linked to the first inserted language as indicated in red below). Language edited to match the 408p language and make other edit as follows:

> On an assay-by-assay basis, a Test Order recipient can elect to cite or submit existing data that the recipient believes meets informs the determination as to whether the substance may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, androgen or thyroid and provides reasonable assurance that the substance does or does not have the potential to produce effects on the estrogen, androgen, or thyroid systems. ~~one or more of the data requirements of the order~~ Existing data may be of several types. It may be functionally equivalent to Tier 1 assays—that is data from assays that perform the same function as EDSP Tier 1 assay or data that provide information on a consequence or effect that could altered by producing effects on the estrogen, androgen or thyroid systems.

EPA Response: See EPA's response to OMB Comment #7 for the Final List FR Notice. The suggested language is incorrect.

4) **OMB Comment**: On page 7, second paragraph, line 13, Comments A5 (links to the

OSRI language that had been inserted). Revise to be consistent with the OSRI document, and revise as follows:

Other scientifically relevant information" is information that is ***scientifically credible*** and that provides information that ~~***affects the confidence with which***~~ ***informs*** conclusions that may be made about the potential for substances to have an effect that is similar to an effect produced by a substance that interacts with the estrogen, androgen, and/or thyroid hormonal systems (e.g., information that identifies substances as having the potential to interact with the estrogen, androgen, and/or thyroid system(s); information demonstrating whether or not substances have an effect on the functioning of the endocrine system). Other scientifically relevant information can include Part 158 studies or studies from the scientific literature or unpublished studies. In all cases a scientifically sound rationale must be submitted for each data requirement that is cited or submitted.

EPA Response: OK, but we will use the final language, which was subsequently revised after OMB's suggested changes above.

5) **OMB Comment**: On page 7, end of second paragraph, Comment A4 (links to the suggested new language). Suggest citing the policy and procedures FR that would provide more detail:

Further information on information EPA will consider is provided in XXXX.

EPA Response: EPA will insert the following language:

For additional information about the Agency's approach for considering other scientifically relevant information under the EDSP, go to the Agency's final policy and procedures and related documents in Docket ID No. EPA-HQ-OPPT-2007-1080.

6) **OMB Comment**: On page 7, third paragraph, line 2. Revise text as follows:

The recipient's response to Test Orders for Tier 1 assays will be evaluated by EPA to determine whether the submitted or cited data fulfills ~~the testing required by the order~~ information need as described in Section 408(p) of FFDCA. This will require a case-by-case determination whether the data ~~set as a whole~~ achieve(s) the objective of Tier 1 assays to provide reasonable assurance that a chemical does or does not have the potential to produce effects on the estrogen, androgen, or thyroid systems.

EPA Response: EPA will revise this as follows:

The recipient's response to Test Orders for Tier 1 assays will be evaluated by EPA to determine ~~whether~~ the extent to which the submitted or cited data satisfies the Tier 1 Order~~fulfills the testing required by the order information need as described in Section 408(p) of FFDCA~~. EPA will generally make ~~This will require~~ a case-by-case determination based on ~~whether~~ the data available, including whether the data ~~set as a whole~~ achieve(s) the objective of the Tier 1 Battery~~assays~~ to provide reasonable

assurance that a chemical does or does not have the potential to ~~produce effects on~~interact with the estrogen, androgen, or thyroid systems.

7) **OMB Comment**: On page 14, first paragraph, line 5, Comment A1 (linked to the sentence that follows). EPA does not seem to respond to this comment. What are EPAs plans for data release and will data be FOIAable once EPA receives the data? Can EPA provide any assurances that the data will be withheld?

Therefore, data obtained from Tier 1 screening of the initial 73 chemicals should not be publicly disclosed, and should only be used to assist the Agency in making future EDSP policy and management decisions.

EPA Response: EPA will insert the following paragraph to specifically address this comment:

Finally, one commenter suggested that the data obtained from Tier 1 screening of the initial chemicals not be publicly disclosed, and only be used to assist the Agency in making future EDSP policy and management decisions. The Agency's final policy and procedures specifically addresses how EPA will generally handle Confidential Business Information (CBI).

As explained in Unit IV.C. of that document, because EPA considers much of the data submitted in response to FFDCA section 408(p) orders to be submitted in support of a tolerance or tolerance exemption, such submissions are entitled to confidential treatment to the same extent as under FIFRA section 10, pursuant to FFDCA section 408(i). In addition, CBI submitted by pesticide registrants in response to a FFDCA section 408(p) test order is considered as part of the registration process, and is therefore considered to be submitted in support of a registration.

In general, the Agency believes that data obtained from Tier 1 screening of the initial chemicals should be released to the extent permitted by law. The Agency generally intends to release summary data when all of the test data on a particular chemical has been submitted and evaluated by EPA.

8) **OMB Comment**: On page 19, fourth paragraph, line 1, Comment A7 (linked to "equivalent" in the following sentence). Is it hard to agree with this characterization based simply on the language provided? Is there any other support to show that these are functionally the same definition? Comment A8 (linked to "adverse effects"). Edit made because the 1st definition ("intereferes") does not necessarily imply that there will be adversity. Comment A9 (linked to "or its offspring and may be seen as individual effects and/or effects on populations"). The first quote above doesn't talk about offspring or individual vs population effects. Revise this paragraph as follows:

EPA regards these definitions as equivalent: they both express that 1) an endocrine disruptor is an exogenous agent, and 2) that alters or interferes with normal function of the endocrine system~~, and causes adverse effects~~. The ~~adverse effects~~ alteration or interference of function can be on the exposed organism or its offspring and may be seen as individual effects and/or effects on populations.

EPA Response: EPA will revise this response as follows:

One commenter stressed the importance of consistent communication throughout EPA, particularly with respect to the definition of "endocrine disruptor." Although the commenter indicated that the description in the context of the screening program is accurate, they questioned whether it correlated with a description provided by EPA's Office of Research and Development (ORD). Specifically, they indicated that ORD's ***Multi-Year Plan For Endocrine Disruptors (FY2007-2013)***[1], which describes the research program that is specifically designed to address the Agency's science needs, indicates that for the purposes of that document and the research discussed therein, the Agency is "using the World Health Organization's definition of a potential endocrine disrupting chemical which is 'an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function' (IPCS/WHO 2002)."

EDSTAC adopted an interim working definition, but the Committee was divided regarding the inclusion of the term "adverse." One view held that the definition must include the term "adverse," whereas the second view held that the term "adverse" should be excluded from the definition. Proponents for including adverse reasoned that a definition should distinguish disruption from the wide range of hormone fluctuations necessary for normal physiological function. An example is insulin: one's insulin levels change all of the time in response to what and how much one eats and this change is essential for regulating metabolism. Proponents for excluding adverse reasoned that hormone function is so sensitive to xenobiotic challenge that any biochemical alternation during key developmental stages above background may lead to serious, but subtle, pathology later in life or in subsequent generations. While certain prescription drugs are intended to interfere with the endocrine system to produce beneficial effects, EPA is not concerned about the pharmaceutical use of such drugs (e.g., birth control pills) in intended targets but is concerned about effects in non-target species including humans. Therefore EPA's interest is in unintended and adverse consequences and, therefore, has adopted the sense that an endocrine disruptor is a substance that results in adverse health or environmental effects.

The Agency believes that the WHO definition is consistent with the sense of the term "endocrine disruptor" as it has been used in the EDSP since 1998. As such, the Agency has accepted the WHO definition as the definition of endocrine disruptor for purposes of the EDSP because it has gained widespread usage throughout the world and within the Agency.

~~There are several definitions of endocrine disruptor that EPA has referenced. The oldest one appears in the Special Report on Environmental Endocrine Disruption: An Effects Assessment and Analysis (EPA Report 630/R-96/012; February 1997). It defined an endocrine disruptor as…~~

[1] http://www.epa.gov/ord/npd/pdfs/Draft-EDCs-MYP-091407.pdf.

> ~~An exogenous agent that interferes with the synthesis, secretion, transport, binding action or elimination of natural hormones in the body that are responsible for the maintenance of homeostatis, reproduction, development and/or behavior.~~

~~Another frequently used definition is that used in the ICPS Global Assessment of the State-of-the-Science of Endocrine Disruptors (WHO/PCS/EDC/02.2; 2002):~~

> ~~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.~~

~~EPA regards these definitions as equivalent: they both express that 1) an endocrine disruptor is an exogenous agent, 2) that alters or interferes with normal function of the endocrine system and 3) causes adverse effects. The adverse effects can be on the exposed organism or its offspring and may be seen as individual effects and/or effects on populations.~~

9) **OMB Comment**: On page 21, fourth paragraph, line 7, Comment A10 (linked to the language below). What is EPAs response to this?

The commenter suggests that EPA is sending mixed messages – some saying that the available endocrine data are insufficient for consideration until the chemicals have gone through Tier 1 screening "when the appropriate screening and/or testing protocols being considered under the agency's EDSP have been developed…" and others saying that chemicals may not need to go through the EDSP if there are existing data.

EPA Response: EPA will revise the first sentence to read "There are really ~~three~~four separate issues related to this topic." And will insert the following at the end:

> The fourth issue involves the comment that EPA is sending mixed messages – some saying that the available endocrine data are insufficient for consideration and others saying that chemicals may not need to go through the EDSP if there are existing data. As discussed in more detail in the Agency's final policy and procedures document, although a relatively broad range of toxicity data are available for pesticide active ingredients regulated under FIFRA and some pesticide inert ingredients, in most cases EPA has not yet established how the available data might be confidently used to predict the endocrine disruption potentials of these chemicals at this time. The Agency intends to consider existing data or other scientifically relevant information that is submitted or cited in response to the Tier 1 Order.

10) **OMB Comment**: On page 22, first paragraph, line 3, Comment A11 (linked to "and be removed from the list" in the following sentence). Removed from the list or from Tier I testing? This should likely be Tier I testing. From the framing of the comments, it's not clear that requestors are asking for complete removal.

First, with respect to the issue of EPA's not providing sufficient guidance regarding what evidence would be required to demonstrate that a chemical is an endocrine disruptor and be removed from the list, the Agency has never stated that the identification by a test

order recipient of a compound as an endocrine disruptor will necessarily allow the recipient to avoid all EDSP testing.

EPA Response: EPA will revise this as follows:

First, with respect to the issue of EPA's not providing sufficient guidance regarding what evidence would be required to demonstrate that a chemical is an endocrine disruptor and be removed from the screening list, the Agency has never stated that the identification by a test order recipient of a compound as an endocrine disruptor will necessarily allow the recipient to avoid all EDSP testing.

11) OMB Comment: Page 22, 1st paragraph, last sentence, Comment A12 (linked to the following language). Couldn't data also provide scientific support that no Tier 2 testing is needed? This should be mentioned—the balance is needed.

At most, this response, provided it was accompanied with sufficient support, would allow recipients to proceed directly to or avoid Tier 2 testing, which will provide information to determine whether the substance causes ~~adverse~~ estrogen, androgen or thyroid effects, identify the ~~adverse~~ effects, and establish a quantitative dose-response relationship.

EPA Response: Yes. If the respondent says they want to by-pass Tier 1 because they are an endocrine disruptor, they would only be able to avoid Tier 2 testing if they have existing data that identifies an adverse effect, and provides the quantitative dose-response relationship. In addition, the deletion of "adverse" before effects is incorrect. Instead, EPA will revise as follows:

At most, this response from a Tier 1 Order recipient, provided it was accompanied with sufficient support, would allow the recipient~~s~~ to proceed to the next stage of the EDSP where EPA will determine which**, if any**, of the ~~directly to or avoid~~ Tier 2 tests are necessary based on the available data. ~~ing, which will provide information to determine whether the substance causes adverse estrogen, androgen or thyroid effects, identify the adverse effects, and establish a quantitative dose-response relationship~~.

12) OMB Comment: On page 22, second paragraph, Comment A13 (linked to the last part of the last sentence, which is highlighted in yellow). Does this mean EPA will be releasing test data results to the public as it is received? Can EPA feasibly wait until the Tier 2 assays are ready to provide results?

The second issue relates to the process for making these determinations and the lack of an apparent opportunity for organizations or individuals to comment or supply information before EPA's decisions on its response to test orders become final. EPA agrees with the commenter that there should be a role for the public. EPA will provide a mechanism whereby the public can provide other scientifically relevant information (including information they believe is functionally equivalent to the Tier 1 screening assays in the test order) for the specific chemicals that receive test orders. EPA intends to use a weight-of-evidence basis to determine whether the chemical has the potential to interact with the endocrine system, taking into account data from the Tier 1 assays and any other

scientifically relevant information available (see page 7 for a more detailed response on this topic). As described in the Policy and Procedures document, the Agency will publish in the Federal Register the pertinent information about EDSP orders that are issued (e.g., chemical covered by the order, recipients of the order, dates associated with the order), and will also publish in the Federal Register any final decisions related to those orders. The status of the orders, including responses to the order and related decisions, will be maintained on EPA's Web site.

EPA Response: OK to the edit. In terms of the question, the "responses to the Order" refers to the initial response – e.g., whether the order recipient will join a consortium or intends to generate the data, and then EPA's decisions related to that initial response. The data itself will not be posted on the Website. To clarify, EPA will revise this last sentence as follows:

> The status of the orders, including the initial response~~s~~ to the order and related decisions, will be maintained on EPA's Web site.

13) **OMB Comment**: On page 23, second paragraph, line 4, Comment A14 (linked to "In addition, both methyl ethyl ketone and acetone were recently subject to thorough review and assessment for potential effects on children in EPA's VCCEP, in which EPA concluded that no further toxicity testing or exposure assessment was needed to conclude that no regulatory action was needed."). EPA does not appear to respond to this comment. Please revise.

EPA Response: EPA will replace the first paragraph with the following:

> EPA is following the established approach, criteria and priorities for selecting the list of chemicals for screening in the EDSP. These are detailed in the September 2005 and June 2007 Federal Register notices and underwent considerable public and interagency review before being applied. These criteria are based solely on exposure. Thus, the Agency did not consider hazard information when listing a chemical and declined to do so when considering comments on the list.
>
> Although a relatively broad range of toxicity data are available for pesticide active ingredients regulated under FIFRA and some pesticide inert ingredients, in most cases EPA has not yet established how the available data might be confidently used to predict the endocrine disruption potentials of these chemicals at this time. Instead of tailoring the Tier 1 Orders based on existing information, EPA intends to provide a mechanism whereby test order recipients and the public can provide information on specific chemicals for which test orders are issued. A test order recipient can elect to cite or submit existing data the recipient believes meets one or more of the data requirements of the order. A scientifically sound rationale must be submitted for each data requirement that is cited. The recipient's response to test orders for Tier 1 assays will be evaluated by EPA to determine whether the cited data fulfills the requirements in the order, and provides the information needed for EPA to determine whether or not the chemical has the effect described above. This will require a case-by-case determination of whether the information submitted is of high quality and achieves the objective of Tier 1 assays to provide reasonable assurance that a chemical does or does not have the potential to

produce effects on the estrogen, androgen, or thyroid systems. This approach is consistent with ensuring effective and efficient use of societal and government resources in generating and reviewing data, as well as minimizing the use of animals in regulatory testing, to achieve the information base needed to support a specified objective.

14) **OMB Comment:** On page 25, third paragraph, line 5, Comment A15 (linked to "The January 2003 Atrazine Interim Reregistration Eligibility Decision (IRED), stated that the Agency did not have reliable evidence that atrazine caused endocrine effects in the environment and, based on existing uncertainties in the available database, that atrazine should be subject to more definitive testing once the appropriate testing protocols had been established.") This seems to speak to findings that would come out of Tier 2 testing, not tier 1 testing. Thus if EPA already knows that atrazine has endocrine effects, EPA should clearly state that the tier 1 tests for those specific endpoints are not needed. If this information is enough to trigger Tier 2, why would any other Tier 1 assays be needed? EPA needs to explain this more clearly if EPA still believes that Tier 1 data are needed for atrazine.

EPA Response: See response to previous comment. EPA is not reviewing any existing hazard data in connection with the determination of which chemicals will receive a Tier 1 Order, and is not otherwise tailoring each order. As described in the final policy and procedures document, the Tier 1 Orders will include the Tier 1 Battery. Order recipients with existing data need only provide the 90 day response submitting or citing the data they want the Agency to consider, with an explanation.

15) **OMB Comment:** On page 25, third paragraph, Comment A16 (linked to third line from the bottom of the paragraph). So does this mean that androgen is likely not affected and thus Tier 1 testing on androgen effects is not needed?

EPA Response: No. At this time, the Agency has determined that Tier 1 testing on androgen effects should be included in the Tier 1 Battery – as reflected in our proposed Tier 1 Battery that was submitted to the FIFRA SAP for review. It is otherwise premature for the Agency to draw this conclusion at this time.

16) **OMB Comment:** On page 25, third paragraph, Comment A17 (linked to last line of the paragraph). Please include these examples in the policies and procedures document of OSRI that may be used in lieu of Tier 1 test orders. These examples demonstrate that there is OSRI that EPA will accept and use to avoid Tier 1 testing.

EPA Response: As discussed previously, the policy and procedures document provides non-binding guidance for EPA staff and others in terms of the issuance of the Tier 1 Orders for the initial list of chemicals. As such, EPA is legally precluded from including binding statements or examples that purport to bind the Agency. At this time, EPA has not yet conducted an OSRI review or made any such determinations. However, the Agency generally intends to publish such determinations, which will then serve as examples for others. In addition, although the Tier 1 Orders will be issued, the recipient is still able to avoid the testing by submitting or citing the other scientifically relevant information that they want the Agency to accept in lieu of the data requested by the Order.

17) **OMB Comment:** On page 25, fourth paragraph on Endosulfan, line 2, Comment A18 (linked to "However, further investigation is necessary to determine the relevance and impact of such findings on public health and the environment."). As per comments above, this argues for the need for Tier 2 testing and sounds as if we know enough to say that their would be Tier 1 effects thus there does not appear to be practical utility in requiring Tier 1 tests.

EPA Response: See the previous answer.

18) **OMB Comment:** On page 26, second paragraph, line 2, Comment A19 (linked to "the the remaining active ingredients will be screened based on their schedule for docket opening in the registration review program"). Does this imply that EPA is not going to wait til all Tier 1 testing is finished and evaluated to look at the utility of the battery before beginning to test other AI's?

EPA Response: In 1999, when EPA accepted the SAP's recommendation to review the Tier 1 results of the first group of 50-100 chemicals before full implementation of the testing phase of the program, the Agency envisioned the testing phase beginning in 2005 and anticipated having data by 2007. Assuming that test orders are issued in May 2009, it will be spring of 2011 before the first test data are received by the Agency and 2012 before a review of the performance of the battery could be conducted in consultation with the SAP. This would mean that a second group of chemicals would not begin screening or testing under the EDSP until 2013.

At this time, however, the Agency has not made a final decision about considering additional chemicals for screening under the EDSP. As you know, before the Agency would be able to issue Tier 1 Orders to additional chemicals, EPA would need to amend the existing ICR, or prepare a new ICR because the existing draft ICR only identifies the initial List of chemicals.

19) **OMB Comment:** On page 26, second paragraph, last sentence. Insert the following text:

EPA will also consider testing data conducted as part of reregistration and registration eligibility decisions to help inform whether or not and to what extent Tier 1 testing may be needed.

EPA Response: OK, but correcting "Tier 1" to read "Tier 2." Using Tier 1 is incorrect – as explained in an earlier answer.

End..

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EPA Responses to OMB Follow-up Comments of March 13 & 14, 2009 On the EDSP Materials 03/18/2009

As before, EPA's responses follow OMB's comments. Before addressing document specific comments, EPA is responding to several reoccurring comments. For ease in referencing to specific responses in this document, EPA has replaced the bullets used in OMB's comments with sequential numbering and added line numbering.

I. General Reoccurring Comments:

1) OMB Comment: OMB remains concerned about the need to satisfy the test order itself rather than satisfying the goals of the tier 1 testing, which is to determine what, if any, tier 2 testing is needed. EPA talks about "satisfying the order"—what exactly does this mean? Has EPA ever defined what it means to satisfy the order? This would be useful. What would it mean to satisfy part of the order (as stated on page 26)—this implies a test by test requirement. Is this the intent?

EPA Response: The Order involves the full Battery, but each assay is listed separately to provide complete flexibility to the recipient in terms of responding to the Order. In the Policy & Procedures and in the Order itself, the Agency explains the various ways that a recipient can satisfy the Order, including that the individual recipient may satisfy all or part of the Order by using one or more of the response options. For example, the recipient may choose to cite or submit other scientifically relevant information to address 3 of the assays, and join a consortium that will address the other assays.

Since Orders are issued to individual registrants or manufacturers/importers of the chemicals, the critical determination from the recipient's perspective is whether and when the Order that they received is satisfied. This determination is separate and apart from the overall Tier 1 determination, which will be made by EPA on a per chemical basis – NOT a per Order basis. For example, EPA may determine that the Order for a particular recipient has been satisfied even though it can not yet make the overall Tier 1 determination for that chemical either because another Order recipient for that chemical has indicated that they would be the one submitting the data on one or more of the assays, or other available data to be considered in the determination is still being compiled.

There is an important distinction between satisfying the Order and the overall Tier 1 determination. The Order recipient is responsible for satisfying the Order – the Order recipient is NOT responsible for EPA's overall Tier 1 determination. In discussing the submissions in response to the Order, the Agency's determination is whether that submission satisfies all or part of the Order. The submission of OSRI, however, can be done by anyone either to satisfy the Order or to inform EPA's consideration of the overall Tier 1 determination. In a few places where OSRI is discussed, EPA will revise the language to provide this clarification.

This concept is well established in the DCI program which served as a model for the EDSP Orders. EPA believes that attempting a last minute shift to a stricter interpretation that requires Order recipients to be responsible for the Tier 1 determination or to otherwise wait to learn if they have satisfied the Order until EPA makes the overall Tier 1 determination for the chemical, is inappropriate and unnecessary.

2) OMB Comment: Provide specific examples of what OSRI could satisfy the Order. Please explain to us why clarifying that an E, A or T finding automatically triggers Tier 2 violates the safe Harbor Principle. We think information of this type is very useful for a policies and procedures document and does not create any legal vulnerability for the Agency.

EPA Response: As we have previously explained, it is legally inappropriate for EPA to provide such specific examples in a non-binding guidance document because the examples purport to bind the Agency to a specific decision. The same is true with respect to the statement you are requesting that a finding that a chemical interferes with E, A, or T "automatically triggers Tier 2." This statement defines how the Agency will act in the future with respect to a general class. The courts have been consistent that the only way in which EPA may publish such statements is through rulemaking. It is also premature for the Agency to attempt to make such decisions without actually considering a specific circumstance and/or the data. As indicated throughout the documents, EPA will make these determinations on a case-by-case basis. Once made based on actual circumstances, the Agency has committed to making the decisions and our rationale publicly available so that the actual decisions may be considered by others in the same or similar circumstances, as well as be used to inform the development of more specific guidance in the future.

With that said, EPA will incorporate the following at the end of our response to the CLA petition in section in II.B.2.c. on page 7:

> "Furthermore, although EPA is not currently able to provide definitive examples of the specific circumstances in which a chemical would be able to go directly to Tier 2 testing, an Order recipient may provide a justification for EPA to consider such a request. In general, it may in some cases be possible for EPA to determine that a particular chemical has the potential to interact with the endocrine system and therefore could proceed to Tier 2 even if Tier 1 data are limited. However, if only some of the Tier 1 data are available to EPA, there may not be sufficient information for EPA to determine that some of the Tier 2 data are not necessary. These determinations will be made in a weight of the evidence judgment on a case-by-case basis and made publicly available for consideration by others with the same or similar circumstances."

3) OMB Comment: Please cite the OSRI guidance document—this will help ease some concerns. We do not believe that mention of this or its contents in a preamble increases an legal vulnerability of the 2 pager. Revise Note to clarify that the 2-pager is intended to provide guidance to public too.

EPA Response: EPA will cite the OSRI 2-pager in the preamble and Response to Comment documents when OSRI is first mentioned and will place the document in the Procedures docket.

"The Agency has written a paper entitled "EPA's Approach for Considering Other Scientifically Relevant Information (OSRI) under the Endocrine Disruptor Screening Program." (Ref. 4). This paper was developed by EPA to provide guidance to EPA staff and managers who will be reviewing the responses to Tier 1 Orders issued under the EDSP, and may also be of interest to parties considering whether to submit other scientifically relevant information to EPA. This paper provides general guidance and is not binding on either EPA or any outside parties. Anyone may provide other scientifically relevant information, and the Agency will assess the information for appropriateness on a case-by-case basis, responding to the submitter in writing, and making EPA's determination publicly available. A copy of the approach paper has been placed in the docket for this policy (Docket ID number EPA–HQ–OPPT–2007–1080)."

II. Policies and Procedures FR Document:

1) **OMB Comment:** Page 6, line 225, suggested edit: "The determination that a chemical does or is not likely to have the potential to interact with the endocrine system (i.e., disruption of the estrogen, androgen, or thyroid hormone systems) will be made on a weight-of-evidence basis taking into account data from the Tier 1 assays and/or other scientifically relevant information that is made available.

EPA Response: The second insert would limit OSRI to only that which is made available. We do not think OMB intended to limit EPA's consideration of OSRI in this way. Instead, EPA will accept the first edit, and instead of the second suggested insert, EPA will delete "available."

2) **OMB Comment:** Page 12 and 13, while we understand that EPAs meaning of duplicative testing is not what commenters think it is, should EPA address the commenter concern somewhere in the discussion? While other sections discuss OSRI, they do not mention how OSRI is being allowed to minimize duplicative testing. Shouldn't this be mentioned—it would be responsive to comments.

EPA Response: It is specifically mentioned in the bullets describing EPA's goals. To make this easier to link the bullets to the more detailed discussions, EPA will add a reference at the end of each bullet and will revise this bullet as follows:

The recipients of the FFDCA section 408(p) test orders may cite or submit existing data (i.e., other scientifically relevant information) in lieu of developing new data, and ask EPA to determine whether the data adequately responds to the requirements of the order. See Unit IV.C.1.c. of this document.

3) **OMB Comment:** Page 15, line 602, after describing OSRI as is done, please provide a link or cite to where readers can find the OSRI guidance for more information on what will be considered and how EPA will look at it. We do not believe that mention of this or its contents in a preamble increases an legal vulnerability of the 2 pager.

EPA Response: See response #3 in Section I. above.

4) **OMB Comment:** Page 25, line 2015 suggested edit: "In submitting or citing existing data, the order recipient or other party should follow, as appropriate, relevant format guidelines described in Unit IV.F.4. of this document and provide an explanation of the relevance of the data to the Order, including, where appropriate, a cogent and complete rationale for why it believes the information is ~~or is not~~ sufficient to satisfy part or all of the ~~requirements in the~~ Order."

EPA Response: OK.

5) **OMB Comment:** Page 25, line 1040, suggest not creating a new term of art "scientifically valid" and instead refer to quality standards and preexisting language.

EPA Response: EPA is not creating a new term of art. This phrasing and related concept has been used historically and is well understood. It is not related to the information quality standards imposed on Federal agencies, and is generally well understood in the scientific and regulated community involved in the identification of test methods and study protocols used in the testing of chemicals.

6) **OMB Comment:** Page 25, Lines 1042-1047, EPA should again make mention of the OSRI guidance and provide info as to where to find it in the docket.

EPA Response: See response #3 in Section I. above.

7) **OMB Comment:** Page 25 and elsewhere, EPA talks about "satisfying the order"—what exactly does this mean? Has EPA ever defined what it means to satisfy the order? This would be useful. What would it mean to satisfy part of the order (as stated on page 26)—this implies a test by test requirement. Is this the intent?

EPA Response: See response #1 in Section I. above.

8) **OMB Comment:** Page 26, please explain to us why clarifying that an E, A or T finding automatically triggers Tier 2 violates the safe Harbor Principle. We think information of this type is very useful for a policies and procedures document.

EPA Response: See response #2 in Section I. above.

9) **OMB Comment:** Page 29, suggested edit: "*Submit the data specified in the response to the test order*."

EPA Response: No. This edit is unnecessary. The first sentence makes it clear that this discussion applies when the Order recipient has decided to generate the data.

10) **OMB Comment:** Page 39, line 1602 suggested edit: "A copy of the final ICR package submitted to OMB for review (identified under EPA ICR No. 2249.01) has been placed in the docket for this policy."

EPA Response: OK, but to be accurate, the insert should be "submitted to OMB for review and approval under the PRA".

11) **OMB Comment:** Page 39, line 162, suggested edit: "Pursuant to 5 CFR 1320.12, the submission of the ICR to OMB is addressed in a separate document published elsewhere in today's Federal Register. EPA requests comments on all aspects of this information collection, including burden estimates."

EPA Response: EPA is NOT soliciting comments on the ICR through this document. Comments on the ICR are solicited in the FR Notice that is publishing elsewhere, which represents the mandated 2nd FR notice for ICRs and follows that prescribed format – including a specific solicitation of comments on the ICR. This is an important distinction because comments MUST be submitted to the ICR docket – not the Policy and Procedures docket. The standard ICR submission FR notice specifically addresses the point of submitting comments and that comments are sought on all aspects of the ICR, including those that we are specifically required to seek comment on under the PRA. Adding this sentence here is therefore misleading and confusing. This notice should point people to the ICR Notice. As such, to address OMB's point, we will change this to read as follows: "Pursuant to 5 CFR 1320.12, the submission of the ICR to OMB, along with a solicitation of comments on that ICR, is addressed in a separate document published elsewhere in today's Federal Register."

III. Policies and Procedures' Response to Comments Document:

1) **OMB Comment:** Page 9 Suggested edits: "Duplicative testing" (as used by the commenters) appears to mean the repetition of assays that would not bring additional information to the EDSP assessments. To reiterate, EPA defines "duplicative testing" as testing the same chemical using the same test. Nevertheless, even though EPA does not interpret the statute in the manner suggested by the commenter, EPA has adopted procedures intended to address the substance of the commenter's concern: that assays should not be required where the assay would not result in the submission of additional information needed for the EDSP assessment. Elsewhere in this Response to Comments document, and in Section IV.C.1.c. and IV.F.1.b. of the Policies and Procedures Federal Register Notice, EPA discusses the process by which order recipients may submit other scientifically relevant information that they believe ~~already provide the information that would be provided by the generation of Tier one data, in response to the Order.~~will inform the determination as to whether the substance may have an effect that is similar to an effect produced by a substance that interacts with the estrogen, androgen and/or thyroid hormonal systems." Edit made because OSRI does not need to provide the same information that tier 1 data provides, it needs to inform the same endpoint—whether or not there is E, A, or T interaction. For instance data which informs the same consequence or effect could be provided instead- rather than functionally equivalent test data.

EPA Response: See response #1 in Section I. above. EPA can accept this edit here with the following revision:

Elsewhere in this Response to Comments document, and in Section IV.C.1.c. and IV.F.1.b. of the Policies and Procedures Federal Register Notice, EPA discusses the process by which order recipients and other stakeholders may submit other scientifically relevant information that they believe ~~already provide the information that would be provided by the generation of Tier one data, in response to~~ will either satisfy the Order or ~~it~~ will otherwise inform the determination as to whether the substance may have an effect that is similar to an effect produced by a substance that interacts with the estrogen, androgen and/or thyroid hormonal systems."

2) **OMB Comment:** Page 9 suggested edits: "EPA has adopted a similar policy for the EDSP, as shown ~~in the list of~~ by the response options available to order recipients."

EPA Response: OK.

3) **OMB Comment:** Page 10: EPA states: "Some "other scientifically relevant information" may be sufficient to satisfy part or all the requirements of the Test Order." Shouldn't this refer to making the determination about whether or not tier 2 testing is needed, rather than focusing on meeting specific test order requirements. Focus for OSRI should be on meeting the broad goals of Tier 1 (to determine if and what tier 2 tests are needed), rather than meeting each testing requirement of Tier 1.

EPA Response: See response #1 in Section I. above.

IV. OSRI Approach Document:

1) **OMB Comment:** Opening paragraph suggested edit: "This paper was developed by EPA to provide guidance to test order recipients as well as EPA staff and managers who will be reviewing the responses to Tier 1 Orders issued under the Endocrine Disruptor Screening Program (EDSP)."

EPA Response: See response #3 in Section I. above. The document was developed for internal use, but certain may be of interest to others. To say that it was developed for them, however, is misleading.

"This paper was developed by EPA to provide guidance to EPA staff and managers who will be reviewing the responses to Tier 1 Orders issued under the Endocrine Disruptor Screening Program (EDSP), and may also be of interest to parties considering whether to submit other scientifically relevant information to EPA. This paper provides general guidance and is not binding on either EPA or any outside parties, and the use of language such as "will," "is," "may," "can" or "should" in this paper does not connote any requirement for either EPA or any outside parties. As such, EPA may depart from the guidance where circumstances warrant and without prior notice, and this guidance is not otherwise intended to limit ~~Tier 1 Order recipients'~~ anyone's submission of or citation to other scientifically relevant information. ~~In their response to a Tier 1 Order, the recipient~~ Anyone may provide other scientifically relevant information ~~as described in this paper~~,

and the Agency will assess the information for appropriateness on a case-by-case basis, ~~and will~~ responding to the submitter in writing, and making EPA's determination publicly available."

2) **OMB Comment:** Opening paragraph suggested edit: "In their response to a Tier 1 Order, the recipient may provide other scientifically relevant information as described in this paper, or other information, and the Agency will assess the information for appropriateness on a case-by-case basis and will respond in writing." Edit made because previous discussion mentions how this is just guidance, not binding and is not meant to limit submissions.

EPA Response: No. Instead, EPA will revise this sentence as follows: "In their response to a Tier 1 Order, the recipient may provide other scientifically relevant information ~~as described in this paper, or other information,~~ and the Agency will assess the information for appropriateness on a case-by-case basis and will respond in writing."

3) **OMB Comment:** Last bullet in the section on the relationship to the Tier 1 Orders: OMB had suggested the following edit on January 15th. It is unclear why this edit was not incorporated:

> Judgments about whether the OSRI satisfies part or all of the Tier 1 Order will generally consider the dataset as a whole for the subject chemical. The Tier 1 Order is satisfied when EPA has sufficient information to determine whether or not Tier 2 testing may be needed for each taxa (mammalian, amphibian, and avian) that is part of the planned Tier 2 battery. For instance, if EPA determines that sufficient data exist to know that mammalian Tier 2 testing is needed due to estrogen effects, additional Tier 1 data on androgen and thyroid systems in mammals may not be needed as the trigger for Tier 2 mammalian testing has already been met. If however, available data show that a substance does not have estrogenic effects in mammalian tests, EPA may still need some Tier 1 testing, or OSRI, on androgen and thyroid endpoints to determine if the Tier 2 trigger has or has not been met for mammalian systems. EPA will make separate determinations for mammalian, amphibian and avian systems based on a weight of the evidence evaluation. ~~This includes the Agency's determination of whether the data set addresses the estrogen, androgen or thyroid (EAT) hormonal systems.~~

EPA Response: See response #2 in Section I. above.

4) **OMB Comment:** OMB remains concerned about the need to satisfy the test order itself rather than satisfying the goals of the tier 1 testing, which is to determine what, if any, tier 2 testing is needed. If EPA will make clear that the test order can be satisfied without doing a test-by-test crosswalk, but instead by looking at the weight of evidence and how it informs if a compound may interact with E, A or T, this would be helpful.

EPA Response: See response #1 in Section I. above.

5) **OMB Comment:** Other questions we would like to discuss to ensure that we understand the programs approach: 1) other than determining what Tier 2 tests are needed and which taxa need to be tested, will the Tier 1 information be used for any other purposes? 2) if a

recipient submits data from a tier 2 test as OSRI in response to the Tier 1 test order, would EPA still require them to complete any of the Tier 1 assays or would EPA be able to conclude that the chemical can be moved directly to Tier 2 without Tier 1 testing? Can EPA use that data to make a final determination under Tier 2 or would more Tier 2 tests be needed?

EPA Response: As discussed, in addition to being used to determine whether Tier 2 data are needed for the particular chemical, Tier 1 data will assist EPA in determining which Tier 2 data are needed, and may be used in combination with other information available to help identify the potential mode of action when analyzing adverse effects. In particular, in the context of pesticide registration decisions where EPA is required to consider such adverse effects in decision making related to registration.

In general, even if there isn't a full dataset from the Tier 1 battery, it may in some cases be possible for EPA to determine that a particular chemical has the potential to interact with the endocrine system and thus should proceed to Tier 2. However, if only some of the Tier 1 data are available to EPA, there may not be sufficient information for EPA to determine which Tier 2 data are necessary. Again, ALL determinations involving less than the full dataset from the Tier 1 Battery will need to be made on a case-by-case basis. Once EPA makes a determination, EPA has committed to making that determination publicly available for consideration by others with the same or similar circumstances.

As discussed previously, any decision would really depend on a variety of factors, including what the submitted data say, the sensitivity in the study(ies) submitted, and the other factors mentioned in the OSRI paper. HOWEVER, given that the only available Tier 2 test currently available is for mammalian species, it is unlikely that the Agency would be able at this time to make any conclusions with respect to non-mammalian species for purposes of Tier 2 based on that single study. Again, these determinations will be made on a case-by-case basis and made publicly available for consideration by others with the same or similar circumstances.

V. Draft List's Response to Comments Document:

1) **OMB Comment:** Page 7, 2nd full paragraph talks about how recipients to a test order can respond. Can a recipient respond by saying their compound is an endocrine disruptor and thus they are willing to go to tier 2? Can they say this without providing documentation or is documentation required. The initial response form does not seem to have an option where a person volunteers to skip tier 1 without having documentation. Please respond and include this in the discussion in the response to comments document. Similarly, EPA responded to our comment, but did not include this discussion in the response document. Please include discussion which states that recipients do not need to respond on an assay to assay basis.

EPA Response: See response #5 in Section IV. above.

2) **OMB Comment:** Page 7, 3rd paragraph - OMB suggested here and elsewhere (in previous comments) that the focus be on whether or not the data fulfill the information need described in Section 408(p) of FFDCA. However, EPA remains focused on whether the data satisfy the Tier 1 test order. Why is this the EPA focus? If someone states that their chemical is an endocrine disruptor and volunteers to go to Tier 2, have they satisfied the Tier 1 test order? This is not clear.

EPA Response: See response #1 in Section I. above.

3) **OMB Comment:** Page 8, in citing the agency docket, it would be helpful if EPA were more specific and mentioned that there is a document called EPA's approach for evaluating OSRI.. that readers may find helpful.

EPA Response: See response #3 in Section I. above.

4) **OMB Comment:** Page 16, EPA states: "In general, the Agency believes that data obtained from Tier 1 screening of the initial chemicals should be released to the extent permitted by law. The Agency generally intends to release summary data when all of the test data on a particular chemical has been submitted and evaluated by EPA." Does this mean that EPA will release the data if there is a FOIA request? Does FOIA permit the release of CBI? Hypothetically, if EPA has tier 1 results evaluated in 2011 and the tier 2 battery is not yet validated, and likely wont begin being used until 2013 (hypothetically) would EPA still release the data as soon as the evaluation is complete? It was our original understanding that EPA was not planning to release results until the battery was ready for use- is this no longer EPA's position? Page 23 states that this information will be available on EPAs webpage. Again we wonder what the timing of this release will be.

EPA Response: It is important to first correct your understanding as reflected in this comment. We aren't sure where you obtained the 2013 date. As EPA reported to OMB in August, and as reflected in several of the documents submitted to OMB, the validation of the Tier 2 tests (this should never be referred to as a "Tier 2 Battery") is scheduled to be complete in 2011. Assuming that there are no further delays in implementing Tier 1, the earliest that the Tier 1 Orders can be issued is in May 2009. With the Tier 1 data due 2 years from issuance of the Orders, EPA expects to receive the Tier 1 data by May 2011. Accordingly, the validated Tier 2 tests are expected to be available BEFORE the Agency expects to be able to complete the Tier 1 evaluations and begin releasing the Tier 1 results, i.e., whether the chemical will go to Tier 2 and which Tier 2 tests will be sought.

It is important to distinguish the results information from the data submitted to EPA. Until EPA completes its Tier 1 evaluation for a chemical, EPA intends to treat its evaluation as deliberative and pre-decisional. Once the evaluation for a particular chemical is complete, EPA intends to make the evaluation and related decision publicly available. EPA does not intend to wait until the evaluations for all the chemicals are done. This is consistent with how the Agency has handled the release of Reregistration Eligibility Decisions and the procedures established for Registration Review.

The release of data submitted to EPA is specifically addressed in the Policy & Procedures document on page 20. Generally, these data may not be released in response to a FOIA if they

are protected from public release as CBI under FIFRA or as a trade secret under the Trade Secrets Act. If the data are submitted by a pesticide registrant, FIFRA section 10 also limits the release of these data to foreign or multinational pesticide producers.

5) **OMB Comment:** Page 20, EPA states: "EDSTAC adopted an interim working definition, but the Committee was divided regarding the inclusion of the term "adverse." One view held that the definition must include the term "adverse," whereas the second view held that the term "adverse" should be excluded from the definition. Proponents for including adverse reasoned that a definition should distinguish disruption from the wide range of hormone fluctuations necessary for normal physiological function. An example is insulin: one's insulin levels change all of the time in response to what and how much one eats and this change is essential for regulating metabolism. Proponents for excluding adverse reasoned that hormone function is so sensitive to xenobiotic challenge that any biochemical alternation during key developmental stages above background may lead to serious, but subtle, pathology later in life or in subsequent generations. While certain prescription drugs are intended to interfere with the endocrine system to produce beneficial effects, EPA is not concerned about the pharmaceutical use of such drugs (e.g., birth control pills) in intended targets but is concerned about effects in non-target species including humans. Therefore EPA's interest is in unintended and adverse consequences and, therefore, has adopted the sense that an endocrine disruptor is a substance that results in adverse health or environmental effects." Rather than discussing the discussion that led to the interim working definition, please simply provide the interim definition and its citation. This would provide more clarity then not providing a definition and talking about what EPA's interest isn. Similarly, in the next paragraph when EPA says the WHO term "is consistent with the sense of the term".. its not clear what EPA is comparing the WHO definition to. We suggest this section be revised to provide the interim working definition and its citation. Where on the EPA website does EPA accept the WHO definition for EDSP purposes? When we look at current EPA webpages (eg http://www.epa.gov/endo/pubs/edspoverview/whatare.htm) , we do not get the "sense" that EPA has adopted the WHO definition. Its unclear why EPA needs to state in their response whether or not they think the WHO definition is 'in its sense' similar. We would be happy to have a discussion with your about suggested revisions, once more information can be provided as to the current EPA interim working definition.

EPA Response: On second thought, there is no need to discuss the description that EDSTAC used prior to 1998. EPA will revise as follows:

> "One commenter stressed the importance of consistent communication throughout EPA, particularly with respect to the definition of "endocrine disruptor." Although the commenter indicated that the description in the context of the screening program is accurate, they questioned whether it correlated with a description provided by EPA's Office of Research and Development (ORD). Specifically, they indicated that ORD's ***Multi-Year Plan For Endocrine Disruptors (FY2007-2013)***[1], which describes the research program that is specifically designed to address the Agency's science needs, indicates that for the purposes of that document and the research discussed therein, the Agency is "using the World Health Organization's definition of a potential endocrine disrupting chemical which is 'an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function' (IPCS/WHO 2002)."

[1] http://www.epa.gov/ord/npd/pdfs/Draft-EDCs-MYP-091407.pdf.

~~EDSTAC adopted an interim working definition, but the Committee was, however, divided regarding the inclusion of the term "adverse." One view held that the definition must include the term "adverse," whereas the second view held that the term "adverse" should be excluded from the definition. Proponents for including adverse reasoned that a definition should distinguish disruption from the wide range of hormone fluctuations necessary for normal physiological function. An example is insulin: one's insulin levels change all of the time in response to what and how much one eats and this change is essential for regulating metabolism. Proponents for excluding adverse reasoned that hormone function is so sensitive to xenobiotic challenge that any biochemical alternation during key developmental stages above background may lead to serious, but subtle, pathology later in life or in subsequent generations. While certain prescription drugs are intended to interfere with the endocrine system to produce beneficial effects, EPA is not concerned about the pharmaceutical use of such drugs (e.g., birth control pills) in intended targets but is concerned about effects in non-target species including humans.~~

Given EPA's statutory mandates, ~~Therefore~~ EPA's interest is in ~~unintended and~~ adverse consequences and, therefore, the Agency's 1998 EDSP policy ~~has~~ adopted the ~~sense~~description that an endocrine disruptor is a substance that results in adverse health or environmental effects. The Agency believes that the WHO definition is consistent with the ~~sense~~description of the term "endocrine disruptor" as it has been used in the EDSP since 1998. As such, the Agency has accepted the 2002 WHO definition as the definition of endocrine disruptor for purposes of the EDSP because it has gained widespread usage throughout the world and within the Agency."

6) **OMB Comment:** Page 23 states: "At most, this response from a Tier 1 Order recipient, provided it was accompanied with sufficient support, would allow the recipient to proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data." This means that if someone wants to go to Tier 2 directly, and bypass tier 1, that they must have accompanying sufficient support. Is this correct—a recipient cant go to tier 2 without any data supporting endocrine effects even if they claim to have endocrine effects?

EPA Response: Yes, if someone wants to go to Tier 2 directly, and bypass Tier 1, they must provide a sufficient rationale upon which EPA can conclude that the particular chemical has the potential to interact with the endocrine system and thus should proceed to Tier 2. If no Tier 1 data are available to EPA, there may not be sufficient information for EPA to determine which Tier 2 data are necessary, so that entity will also need to agree to generate all of the Tier 2 data. Without the required explanation, entities would bypass Tier 1 simply to delay any potential testing consideration under the EDSP. As indicated previously, EPA believes that this approach is consistent with ensuring effective and efficient use of societal and government resources in generating and reviewing data, as well as minimizing the use of animals in regulatory testing, to achieve the information base needed to support a specified objective.

7) **OMB Comment:** Page 25/26, its not clear that revised language specifically addresses the commenters concerns regarding chemicals that went through the VCEEP process. A more transparent response should be provided.

EPA Response: We will make this clearer by revising the first paragraph in response 12.2 as follows:

> In finalizing this list of chemicals, EPA is ~~following~~ adhering to the established approach, criteria and priorities for selecting the ~~list of~~ chemicals for screening in the EDSP. These are detailed in the September 2005 and June 2007 Federal Register notices and underwent considerable public and interagency review before being applied. These criteria are based solely on the specific exposures described in the June 2007 document. Thus, the Agency did not consider hazard information when listing a chemical and declined to do so when considering comments on the draft list of chemicals.
>
> In implementing VCCEP, EPA asked companies that manufactured or imported one or more of 23 chemicals to which children have a high likelihood of exposure, to volunteer to provide information on health effects, exposure, risk, and data needs. Thirty-five companies and 10 consortia responded, volunteering to sponsor 20 of the 23 chemicals. VCCEP is being implemented first as a pilot -- the goal is to learn from this trial before a final VCCEP process is determined and before additional chemicals are selected. Although the Data Needs Decision documents prepared under the VCCEP were not considered in selecting the final list of chemicals for screening in the EDSP, anyone wishing EPA to consider specific data submitted under the VCCEP or other scientifically relevant information, may cite or submit that information in response to the EDSP Tier 1 Order as described in more detail in the Agency's final policy and procedures document, see Docket ID No. EPA-HQ-OPPT-2007-1080.

8) **OMB Comment:** Page 25 states: "A test order recipient can elect to cite or submit existing data the recipient believes meets one or more of the data requirements of the order. A scientifically sound rationale must be submitted for each data requirement that is cited. The recipient's response to test orders for Tier 1 assays will be evaluated by EPA to determine whether the cited data fulfills the requirements in the order, and provides the information needed for EPA to determine whether or not the chemical has the effect described above. This will require a case-by-case determination of whether the information submitted is of high quality and achieves the objective of Tier 1 assays to provide reasonable assurance that a chemical does or does not have the potential to produce effects on the estrogen, androgen, or thyroid systems. This approach is consistent with ensuring effective and efficient use of societal and government resources in generating and reviewing data, as well as minimizing the use of animals in regulatory testing, to achieve the information base needed to support a specified objective." This is written to presume that data provided must be to fulfill a particular data need—while in practice isn't it correct that a data requirement by data requirement approach is not needed but what is needed is information that informs whether the substance interacts with E, A or T systems? Please revise this to be consistent with that approach and the agreed to OSRI language. Its unclear where the 'reasonable assurance' language is coming from.

EPA Response: The explanation allows EPA to provide the greatest degree of flexibility in terms of submitting other scientifically relevant information to address one or more of the assays in the Tier 1 Order, while ensuring the effective and efficient use of societal and government resources in reviewing the information submitted. To clarify, EPA will delete "to provide reasonable assurance that a chemical does or does not have the potential to produce effects on the estrogen, androgen, or thyroid systems"

9) **OMB Comment:** Page 26, while EPA describes the status of Atrazine endocrine disruption, EPA does not address the comment that it is unlikely that further tier 1 or 2 testing may be needed. EPA needs to respond to this concern—perhaps something along the lines of "if this information is submitted to EPA as OSRI, EPA would likely rely on the previous agencys assessment and findings, and thus further Tier 1 testing on the androgen system would likely not be required and this chemical would move to Tier 2 testing." EPA should also address what the protocol would be for testing all the Tier 2 taxa, or if other Tier 1 information may inform that (although we don't think it would). If EPA has white papers and an SAP report that speak to endocrine endpoints, it is unclear why EPA cannot use these as good examples of OSRI in the policies and procedures document.

EPA Response: No. The question here is whether the chemical should be included on the final List – NOT whether this chemical can be declared to be an endocrine disruptor under the EDSP. See response #2 in Section I. above.

10) **OMB Comment:** Page 27, while EPA describes the endosulfan RED status, EPA needs to address the comment made regarding what it may mean for Tier 1 or 2 testing. If we already know Tier 2 testing would be needed, why not clearly state in the policies and procedures document that examples exist where the RED informs this and is an example of OSRI. The test order can still be sent, but EPA can provide this as an example where if the receiver cites the RED, this would be a good set of OSRI for EPAs consideration.

EPA Response: No. The question here is whether the chemical should be included on the final List – NOT whether this chemical can be declared to be an endocrine disruptor under the EDSP. See response #2 in Section I. above.

VI. Draft List FR Document:

1) **OMB Comment:** Page 6, line 230 EPA states: "A test order recipient can elect to cite or submit existing data the recipient believes meets one or more of the data requirements of the order. A scientifically sound rationale must be submitted for each data requirement that is cited. The recipient's response to test orders for Tier 1 assays will be evaluated by EPA to determine whether the cited data fulfills the requirements in the order, and provides the information needed for EPA to determine whether or not the chemical has the effect described above." OMB had previously provided edits such that information informs the overall determination of whether the substance has endocrine effects, as opposed to whether the substance has data available to meet each test order requirement. (Please see previous edits). It is unclear why these edits were not accepted. The new language does not address our concerns.

EPA Response: See response #1 in Section I. above.

VII. Order Template (comments apply to both):

1) **OMB Comment:** Page 1 EPA states: "This template was developed by EPA to provide guidance to EPA staff and managers who will be preparing the Tier 1 Orders that will be issued under the Endocrine Disruptor Screening Program (EDSP)." Isn't this also guidance for test order recipients? If so, please clarify. Additionally, should EPA clarify here and in the document name that this is only a draft template?

EPA Response: Once we issue the Procedures, this template will no longer be considered a "draft" template, it will be the template that EPA intends to use in developing the individual orders. The template was developed for both EPA and the recipients. EPA will revise this note as follows:

> "This template was developed by EPA to provide guidance to EPA staff and managers who will be preparing the Tier 1 Orders that will be issued under the Endocrine Disruptor Screening Program (EDSP), as well as for the recipients of the Tier 1 Orders."

2) **OMB Comment:** Page 6: "If you choose to cite or submit existing data, including other scientifically relevant information, you must indicate whether the information provided follows a validated protocol, and provide a cogent and complete rationale for why you believe the information is sufficient to satisfy part or all of this Order. EPA's decisions about whether the OSRI satisfies part or all of the Tier 1 Order will be based on the weight of evidence from all relevant information available to the Agency." We have a few concerns here: A) where is this concept of a validated protocol coming from? Suggest revising such that this tracks with the OSRI document –could cite to meeting the IQ assessment factors guidance or simply site the OSRI document as guidance on what EPA is looking for. B) Is the goal really to satisfy the test order or is it to be able to determine what, if any Tier 2 testing is needed? the goal should be to inform the same decision as the Tier 1 order, but not to satisfy the Tier 1 order itself. Suggest revising appropriately.

EPA Response: Yes. In the context of the Order, the determination is all about satisfaction of the Order – not the overall EDSP determination. See response #1 in Section I of this document.

In the context here, "validated protocols" does NOT refer to the EDSP Validation Effort, it refers to the long standing concept of using protocols and methods that are have been accepted as scientifically reliable. In the previous response, identical language was revised in a later discussion to clarify this, and EPA will make corresponding changes to this section:

> If you choose to cite or submit existing data, including other scientifically relevant information, you must indicate whether the information provided follows ~~a validated protocol~~ an accepted scientific methodology or protocol, including but not limited to those presented in EPA's harmonized test guideline compendium (see http://www.epa.gov/oppts and select "Test Methods & Guidelines" on the left), and provide a cogent and complete rationale for why you believe the information is sufficient to satisfy part or all of this Order. EPA's decisions about whether the ~~OSRI~~information satisfies part or all of the Tier 1 Order will be based on the weight of evidence from all

relevant information available to the Agency. See the instructions for submitting your response, which appear in Section IV.

3) **OMB Comment:** Page 6: "You must also adhere to the good laboratory practice (GLP) standards described in 40 CFR part 160, which require you to follow certain practices when conducting studies, and to indicate whether data cited or submitted addresses the GLPs." This is in effect setting a new GLP standard for OSRI. This does not seem appropriate. Suggest revising such that this focuses the GLP issue only to the test battery itself.

EPA Response: This is not at all new. Whenever anyone submits data to EPA under FIFRA or FFDCA (or TSCA for that matter), they must provide a GLP compliance statement indicating a) that the data were generated using GLPs; or b) describe in detail "all differences" between the GLPs and the practices used; or c) confirm that they did not sponsor or conduct the study and do not know whether the GLPs were followed. In fact, the GLPs were promulgated in 1989, and today they basically represent the standard accepted scientific procedures for managing studies and study facilities. To clarify this in the template, EPA will revise this sentence as follows:

> You must also adhere to the good laboratory practice (GLP) standards described in 40 CFR part 160, which require you to follow certain practices when conducting studies, and ~~to indicate whether data cited or submitted to EPA addresses the GLPs~~when you submit data to EPA you must provide a GLP compliance statement indicating a) that the data were generated using GLPs; or b) describe in detail "all differences" between the GLPs and the practices used; or c) confirm that you did not sponsor or conduct the study and do not therefore know whether the study was conducted in accordance with the GLPs.

4) **OMB Comment:** Page 9: "your Initial Response must include either the data or a reference to the data for each test that is required, along with a rationale that explains how the study you cited or submitted satisfies the requirements in this Order." As per previous comments, we remain concerned about the concept that the response must satisfy the order, rather than the goals for 408 (p).

EPA Response: See response #1 in Section I of this document. The recipient is responsible for satisfying the Order – which is directed to them individually, while EPA is responsible for making the determination under 408(p) – which will be done on a per chemical basis. If this approach were changed as suggested, then the Agency would not be able to consider OSRI unless it was submitted by that Order recipient. This is inconsistent with the more flexible approach adopted by EPA, allowing OSRI to be submitted by anyone – recipients and other interested parties.

5) **OMB Comment:** Page 9: "Deviations from the protocols validated for the Tier 1 assays, must be identified, along with an explanation for the deviations, including an explanation as to why, notwithstanding the deviations, the protocol used should still be considered "scientifically valid," and any other information you think the Agency should consider in deciding whether to accept the data in satisfaction of this Order." Rather than creating a "scientifically valid" construct, we suggest referring to the OSRI guidance that lays out all the factors that will be considered.

EPA Response: The OSRI paper does not purport to lay out all the factors that will be considered, i.e., binding or limiting the Agency in that way is inconsistent with "guidance." In addition, use of the "scientifically valid" phrasing here does not create a new construct. That phrasing has been used historically and is well established in this construct. We believe that its meaning in this context is understood by the pesticide industry as referring to the same construct used historically.

6) **OMB Comment:** Page 12 suggested edit: "You can demonstrate (supported by appropriate data) that the chemical is an endocrine disruptor and that EDSP Tier 1 screening is unnecessary."

EPA Response: Actually, this is intended to be broader than Tier 1. To clarify, EPA will revise as follows:

> "You can demonstrate (supported by appropriate data) that the chemical is an endocrine disruptor and that ~~EDSP Tier 1~~ additional screening or testing under the EDSP is unnecessary."

VIII. Comments from an OMB Meeting with ACC & Croplife:

1) **OMB Comment:** We have records of a June 5 2007 (?-likely was 2008?, EPA was present) mtg with ACC, croplife, and others. Issues raised included: duplicative testing (not EPAs definition, but commenters definition), procedures (equity issues of inerts v pesticides, testing opt out, 90 days too short, penalties), validation, and costs. Where are comments from this mtg addressed?

EPA Response: We do not have any records of anyone from EPA attending a meeting with OMB and CropLife or ACC on June 5, 2008. Assuming that OMB's records are correct, a meeting in 2007 would have been during the OMB review of the DRAFT documents that were subsequently issued for public comment in December 2007. To the extent that these entities raised similar concerns in the comments they submitted to EPA during the comment period, EPA has responded to those comments in the applicable Response to Comment document.

IX. Response to CRE's Comments Document:

1) **OMB Comment:** We note that the draft provided is dated 9-18-08 and doesn't appear to capture changes that would reflect the multiple conversations that OMB, OSTP and OPP had regarding the AMA assay. While much of this is in the crosswalk, the strong arguments OPP made in conversations regarding AMA validation, don't appear to come across very strongly in the provided response (for instance the final conclusion links back to SAP saying that these assays create a good battery- a point we all agree is not relevant to determining validation status as SAP was presuming complete validation through an alternative process).

EPA Response: EPA will integrate the Cross-Walk provided to OMB with this Response to Comment document.

2) **OMB Comment:** We suggest that EPA take a higher level approach than the one provided here and as such we have not provided line by line edits and suggest a broader reframing of the response. For instance, on page 2, EPA provides specific quotes from the peer review which support their findings, however, a factual review of the peer review report, finds that EPA could just as easily find relevant statements that contradict these. It seems silly to get into a back and forth about what the peer reviewers said. The higher level approach should focus on what has been done by OECD since the peer review to address reviewer concerns. As per the crosswalk EPA provided to OMB:
For Section 1:
   - EPA should mention that following from peer review there was an OECD expert group meeting in May 2008 which led to revisions to the test guidance. EPA should point to specific revisions that address the concerns of reproducibility, inter-lab variation, and other CRE concerns as relevant (some of this language does already exist in the response)
   - EPA could then mention what has happened at OECD since may process wise eg., Nov 2008 revisions and review, lack of comments, etc and how in Dec 2008 there were no revisions and approval is expected in April
   - EPA can note that if approval does not occur they will put a hold on test orders as it seems that EPAs strongest argument for addressing the outstanding peer reviewer concerns is that they have been addressed by OECD and EPA is deferring to the OECD expertise for validation. It thus follows that if something goes awry with the OECD process, EPA should be willing to put their use of the test on hold.
   - EPA should also explain how the test will be used qualitatively not quantitatively so this relieves some of the pressure from reviewer concerns-some of this language already exists.
   - EPA should not have language about Dr. Furlows role on the SAP implying endorsement—he was clearly wearing 2 different hats and the SAP role was not about validation of assays (thus suggest deleting page 3 language).
   - EPA should not be talking about SAPs support of the battery in this response-it is not relevant as SAP was answering a different question and presuming validation (thus language on page 4 and page 6 should be deleted as per previous OMB comments and much discussion).

EPA Response: EPA has made appropriate revisions. However, EPA disagrees with several of the bullets above. In fact, many are inconsistent with the Cross-Walk provided to OMB and ignore the previous extensive discussions with OMB. We believe that we have been clear that EPA determined the assay was validated, and that the OECD international expert group concurred on EPA's determination. Furthermore, EPA's acceptance of any assay validation is completely independent of any OECD acceptance of related Test Guidelines.

X. Response to PCRM Comments Document:

1) **OMB Comment:** Page 1, Response 1: Please clarify, as per comments elsewhere, that the goal is to inform the objectives of tier 1 testing, not to meet specific test requirements. The comment is linked to the following highlighted/underlined text in the Response: "EPA recognizes that several of the chemicals on the initial list have been studied in detail for endocrine disrupting effects. Some were reference chemicals in EPA's or OECD's validation programs as well as being on the ICCVAM list. EPA selected chemicals for the initial list on the basis of exposure, not hazard or completeness of data base. Consistent with the process used for pesticide re-registration, registrants will have the option of citing to existing data to meet testing requirements set forth in the Test Orders in addition to the option of conducting testing to meet the requirements."

EPA Response: See response #1 in Section I of this document.

2) **OMB Comment:** Page 1, Response 1: Please cite the OSRI guidance document—this will help ease some concerns. The comment is linked to the following highlighted/underlined text in the Response: "For those that choose to rely on citations to existing data, EPA will evaluate the industry submissions and eliminate unnecessary testing to the extent that available functionally equivalent and other scientifically relevant information adequately address the objectives of the Tier 1 screening."

EPA Response: See response #3 in Section I of this document.

3) **OMB Comment:** Page 2, Response 2, second response: Whats missing here is some kind of final conclusion by OECD. Did OCED say anything more to refute the ECVAM and ICCVAM statements? Its not clear that "good correlation" is sufficient. The comment is linked to the following highlighted/underlined text in the Response: "OECD addressed all of the significant issues raised by The Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) and the European Center for the Validation of Alternative Methods (ECVAM). In response to ICCVAM's concern about phytoestrogens, data from the validation program showed that phytoestrogens in feed were not a concern for rats if phytoestrogens were kept below 350 µg genestein equivalents per gram of feed. In response to questions that negative chemicals had not been demonstrated, OECD conducted an in depth analysis of a negative chemical, styrene, and also compared the results of the ER binding, transcriptional activation and uterotrophic assays for 60 compounds. This comparison showed good correlation; perfect correlation was not expected due to factors such as absorption and metabolism in *in vivo* systems."

EPA Response: This is the OECD's final conclusion. To clarify that, EPA will revise this sentence as follows:

Based on this in depth analysis, OECD concluded that the ~~This~~ comparison showed good correlation~~;~~ OECD did not expect perfect correlation ~~was not expected~~ due to factors such as absorption and metabolism in *in vivo* systems. More specifically, OECD concluded that "The qualitative and semi-quantitative comparison of Uterotrophic

Bioassay data with those from two screening assays demonstrate that the Uterotrophic Bioassay can well differentiate between chemicals with strong/weak estrogen receptor binding and agonist activity... Thereby it has to be taken into account that the in vitro tests belong to a lower level of the "OECD Conceptual Framework" and more weight has to be given to the results of the in vivo Uterotrophic Bioassay. In addition to the negative result obtained in the international validation program with dibutyl phthalate (the negative reference chemical tested), these data give strong evidence for good specificity of the Uterotrophic Bioassay..."

4) **OMB Comment:** Page 2, Response 2, third response: Please clarify when in 2009. Can EPA say that the castrate portion has gone through all the OECD hoops without concern (as EPA wishes to say to support AMA validation)? The comment is linked to the following highlighted/underlined text in the Response: "Although it is true that the Hershberger test guideline will not be accepted *by OECD* as final until 2009, that is a separate question from whether the Hershberger castrate test procedure (which is what will be required as part of EPA's EDSP battery) has been validated. The Hershberger castrate test procedure has been peer reviewed and the reviewers (including the FIFRA SAP) concluded that draft test guideline covering that procedure is validated and can be used in its current form."

EPA Response: EPA will revise this to read "will not be accepted *by OECD's National Coordinators of the Test Guideline Programme* as final until its March 31-April 1, 2009 meeting."

5) **OMB Comment:** Page 2, Response 2, third response: If it is correct to say that the weanling portion is not part of Tier1 it would be useful to clarify this. The comment is linked to the following highlighted/underlined text in the Response: "OECD has not yet adopted the test guideline as final because OECD intends to include both the weanling and castrate versions of the assay in a single test guideline. The weanling procedure validation report is undergoing peer review at the current time. While the current draft test guideline can serve the EDSP in an interim basis, we would shift to the OECD adopted guideline once it is available. None of the provisions of the draft test guideline regarding the castrate adult is expected to change."

EPA Response: Actually, given the significant delay in finalizing these Response documents, this response needs to be updated to reflect the completion of peer review and the presentation of final guidelines to OECD. As such, this will be replaced with the following text:

"OECD has not adopted the Hershberger test guideline as final because several member countries wanted to await the completion of validation and peer review of the test using a weanling version to see if it could be included as a substitute for the castrate adult version. The validation and peer review were completed in January 2009 and this issue will be discussed and decided by the National Coordinators of Test Guidelines, who meet in April. Thus, a final version of this test guideline will be available by the time EPA begins issuing Test Orders."

6) **OMB Comment:** Page 3, Response 2, fourth response: This is a bit misleading as the Mar 2008 SAP was set up to presume complete validation, not to question it. Thus it's a

bit disingenuous to mix the concept of the need for the assay endpoint and the validation of the assay. Suggested edit (blue text) should help with this. The comment is linked to the following highlighted/underlined text in the Response: "EPA responded in detail to all of the comments raised in each of the peer reviews in response-to-comment documents posted on the OSCP website, as well as those raised by public commenters. With respect to the concern raised by the peer review panel that EPA had failed to show specificity of the male and female pubertal assays, EPA has laid out its evidence for believing that these assays are specific. Although a similar concern was also noted by the SAP, both the majority of the peer review panels and the entire SAP ultimately recommended that these assays be included in the battery, notwithstanding their concerns on this issue which were being addressed through a separate process. Estrogen was negative in the frog metamorphosis assay using the data interpretation guidance. Three separate negatives were used in the validation of the fish screen including potassium permanganate, octanol, and sodium perchlorate."

EPA Response: OK on insert.

7) **OMB Comment:** Page 3, Response 2, fifth response: Delete "that" in this sentence from the first paragraph of this response: "Despite its concern about the use of high doses, the SAP recommended ~~that~~ the use of the assays but with appropriate caution in interpreting endocrine effects only at high doses."

EPA Response: OK.

8) **OMB Comment:** Page 3, Response 2, fifth response, 2nd paragraph of this response: Suggest adding sentence and footnote to describe the validation process. The comment is linked to the following suggested text in the Response: "The SAP did not conclude that validation of the pubertal assays is incomplete without refinement of the body weight analysis to account for reduction in body weight gain due to reduced feed consumption. SAP was not asked to comment on validation as this was conducted through a separate process. EPA regards the SAP discussion of body weight analysis as an important suggestion for improvement of the assay, not notification of a fatal flaw. In EPA's judgment, it would not be appropriate to delay implementation of the testing phase of the EDSP for this improvement since the appropriate analysis method has not been fully worked out and the effect of the correction is likely to be small."

EPA Response: EPA will add the following footnote at the end of the preceding sentence:

> The SAP was not asked to comment on the specific assay validation as this was conducted through a separate process. Additional information about the Agency's EDSP validation effort can be found at http://www.epa.gov/scipoly/oscpendo/pubs/assayvalidation/.

9) **OMB Comment:** Page 3, Response 2, 7th response: Delete added emphasis: "The SAP did not question, as purported, the reproducibility of the fish assay *per se*, but acknowledged that they heard public comment regarding the reliability of the assay. The specific quote is: "However, the Panel did hear some concern from public comment on the reliability of the fish short-term reproduction assay. This concern addressed the

standardization of reproductive success by measurement of fecundity. **However, it was noted that this component of the assay was an essential part of apical analysis of hypothalamic/pituitary/gonadal (HPG) activity."** ~~(emphasis added)~~ The SAP did raise a concern that a false positive result could be obtained in the fish assay based on fecundity due to mechanisms other than those involving EAT activities. The Panel recommended that EPA be alert to non-endocrine mediated refinements of the fish assay to ensure fecundity effects are truly representative of EAT mechanisms and not generalized toxicity. The Panel went further to emphasize: 'It should be recognized that the role of the fecundity assay is paramount for evaluations of the HPG axis.'"

EPA Response: OK.

XI. Response to CLA Comments/Petition Document:

1) **OMB Comment:** Page 4, Section II.B.1., 3rd paragraph: Paragraph presents really one way: an assay by assay basis. Please clarify. The comment is linked to the following highlighted/underlined text in the Response: "Test Order recipients can respond to Test Orders in a number of different ways."

EPA Response: This refers to the various different response options, each of which may be used by a recipient to respond to one or more of the assays. The recipients are NOT limited to responding only one way to the Order. EPA believes that this concept is described in sufficient detail in the final Policy & Procedures document, ICR, Order Templates, and is reflected in the structure of the response forms them selves. To clarify this here, EPA will revise this paragraph response as follows:

"Test Order recipients can respond to Test Orders in a number of different ways, as specified within the order itself and including the following options:
Option 1: Generate New Data;
Option 2: Submit or Cite Existing Data (including other scientifically relevant information);
Option 3: Form a Task Force or Offer to Join a Task Force
Option 4: Claim Not Subject To the Order
Option 5: Voluntarily Cancel the Pesticide Registration(s)
Option 6: Reformulate the Product(s) to Exclude this Chemical from the Formulation
Option 7: Claim a *Formulators' Exemption*
Option 8: Other Response Options, such as asking EPA to reconsider some or all of the testing specified in this Order if:

a) You can demonstrate (supported by appropriate data) that the chemical is an endocrine disruptor and that EDSP screening is unnecessary.

b) You can demonstrate (supported by appropriate data) that the chemical meets the standard for an exemption under FFDCA section 408(p)(4) (*i.e.*, "that the substance is not anticipated to produce any effect in humans similar to an effect produced by a naturally occurring estrogen").

c) Your chemical was used by EPA as a ‘‘positive control’’ to validate one or more of the screening assays. EPA will only accept these data in satisfaction of that part of the test order related to those assays for which the chemical was used to complete the testing as part of the validation effort.

An Order recipient may elect any of these options for one or more of the assays in the Order, and is not limited to electing a single response for all assays, nor are they required to elect different options for each assay. For simplicity, however, the Response Form is structured so that recipients indicate their responses on an assay-by-assay basis – even if the response is the same for more than one of the assays.

~~On an assay by assay basis~~Under one of the response options provided, a Test Order recipient can elect to cite or submit existing data that the recipient believes meets one or more of the data requirements of the order. Existing data may be of several types. ….”

2) **OMB Comment:** Page 4, Section II.B.1., 3rd paragraph: As per above this still seems to be responding to how to respond on an assay by assay basis. The comment is linked to the following highlighted/underlined text in the Response: “But more generally, it will be scientifically relevant information. Scientifically relevant information can include data from studies other than the EDSP Tier 1 assays, e.g., studies conducted to satisfy a 40 CFR part 158 data requirement, data from other studies conducted to address an identified issue, or data from studies found in the scientific literature.”

EPA Response: This is addressed by the previous response.

3) **OMB Comment:** Page 4, Section II.B.1., 3rd paragraph: Please cite the OSRI document and provide a link to it letting petitioner know that more guidance exists. The comment is linked to the following highlighted/underlined text in the Response: “In all cases a scientifically sound rationale must be submitted that explains how the submitted or cited data provides the information needed to satisfy the data need identified by each listed assay in the Order.”

EPA Response: See response #3 in Section I of this document.

4) **OMB Comment:** Page 4, Section II.B.1., 4th paragraph: Please revise as indicated: “The recipient’s response to Test Orders for Tier 1 assays will be evaluated by EPA to determine whether the Agency can conclude that the submitted or cited data fulfills the objectives of the test~~ing~~ order (to provide reasonable assurance that a chemical does or does not have the potential to interact with on the estrogen, androgen, or thyroid systems). This will require a case-by-case determination by the Agency whether the information submitted ~~is comparable and~~ achieves the objective of Tier 1 assays to provide reasonable assurance that a chemical does or does not have the potential to interact with on the estrogen, androgen, or thyroid systems. This approach is consistent with ensuring effective and efficient use of societal and governmental resources in generating and reviewing data, as well as minimizing the use of animals in regulatory testing.”

EPA Response: See response #1 in Section I of this document.

5) **OMB Comment:** Page 4, Section II.B.1., 5th paragraph: Suggest deleting this as it does not flow logically and its relation to the previous sentence—which has to do about determining adequacy of data BEFORE issuing a test order. The comment is linked to the following highlighted/underlined text in the Response: "Furthermore, EPA disagrees with the view, implicit in CropLife America's argument, that EPA should bear the responsibility for making a determination of whether existing data are adequate for the EDSP prior to issuing an order. ~~Both FIFRA and the FFDCA clearly indicate that it is the responsibility of the manufacturer and/or registrant to demonstrate that their chemical and/or product can be used safely. Moreover,~~ EPA believes that manufacturers/registrants are better placed to identify data specific to their chemical/product that addresses the chemical's potential to interact with the endocrine system."

EPA Response: No. EPA disagrees. This sentence is directly responsive to the comment described in the preceding sentence. The statutes clearly and unambiguously place the burden on industry – not on EPA as the petitioner suggested.

6) **OMB Comment:** Page 4, Section II.B.1., 5th paragraph: Suggest inserting this sentence in this paragraph, after the language above. "Once the full set of data are identified in response to the test orders, EPA will then be able to make a determination about the adequacy of the data. EPA believes that it is in the interest of both the Agency and industry that orders be issued and responses documented so that all parties can clearly demonstrate that the obligations imposed by FFDCA § 408 have been met."

EPA Response: The suggested edit appears to limit when EPA can make the determination because it is unclear what is intended by "full data set" – does this mean the Battery; and "in response to the test orders" – which appears to eliminate the consideration of OSRI available other than in response to the order. Instead, EPA will insert the following revised sentence:

"Once ~~the full set of~~ all the data to be considered are identified ~~in response to the test orders~~, EPA will then be able to make a determination about the adequacy of the data."

7) **OMB Comment:** Page 4, Section II.B.1., 6th paragraph: Deletion suggested because this is again setting a high standard—EPA is best to stay away from what is validated and what is not-plus the statute includes OSRI which EPA is not defining as validated. The comment is linked to the following highlighted/underlined text in the Response: "The CropLife America Petition also criticized the Agency for failing to consider "that ToxCast may provide valuable data to inform chemical screening." The mandate to develop the EDSP (FFDCA §408(p)(1)) clearly states that EDSP is to use the "appropriate validated test systems and other scientifically relevant information." ~~At this time, ToxCast does not qualify as a "validated" test system.~~ EPA is currently reviewing ToxCast and will consider its use ~~in the future~~ as "other scientifically relevant information" on a case by case basis. ~~In short~~However, in general, ToxCast is not yet sufficiently vetted as a tool to be used under the EDSP in lieu of the Tier 1 screening data without a case by case evaluation."

EPA Response: OK, with minor revisions. ToxCast is a tool, and what EPA may consider is the data used to populate ToxCast. EPA will revise this as follows:

> "~~At this time, ToxCast does not qualify as a "validated" test system.~~ EPA is currently reviewing ToxCast data and ~~will~~may consider ~~its~~their use ~~in the future~~ as "other scientifically relevant information" on a case-by-case basis. ~~In short~~However, in general, ToxCast is not yet sufficiently vetted ~~as a tool~~ to be used under the EDSP in lieu of the currently validated assays for developing Tier 1 screening data ~~without a case by case evaluation~~."

8) **OMB Comment:** Page 5, Section II.B.2.b., 1st paragraph: Insert the following at the end of this paragraph: "Again, the FIFRA SAP Meeting Minutes on the proposed EDSP Tier 1 Screening Battery recommended using the battery as proposed. EPA acknowledges that the SAP March 2008 panel was not charged with commenting on the validation of the assays which occurred through an extensive validation process, separate from the SAP meeting. SAP members presumed that validation was complete through this separate process."

EPA Response: OK on the first sentence, but we will not insert the second sentence because it implies that the Agency knows the personal presumptions of each SAP member.

9) **OMB Comment:** Page 6, Section II.B.2.c., 2nd paragraph, last sentence: Perhaps deleted because EPA should be ready to commit to a process- peer review and public comment seems appropriate. Below EPA couches that this may or may not be an SAP process—this is fine. Although other than SAP, what options is EPA considering? The comment is linked to the following highlighted/underlined text in the Response: "EPA intends to provide an opportunity for public review of the SEPs ~~perhaps~~ as part of a peer review and public comment process."

EPA Response: OK on deleting "perhaps" but the other insert is redundant and not necessary.

10) **OMB Comment:** Page 7, Section II.B.2.c., 7th paragraph: Really? This does not seem consistent with other documents which talk about releasing Tier 1 results as soon as they are available—which will likely be before all of Tier 2 is ready. Please clarify as consistency among documents is needed. The comment is linked to the following highlighted/underlined text in the Response: "In addition, Tier 2 assays are expected to be available for use before the Agency announces any Tier 1 screening results, along with the information used for making those determinations."

EPA Response: See response #4 under Section V. of this document.

11) **OMB Comment:** Page 7, Section II.B.2.c., 7th paragraph: This seems odd as this is using Tier 1 assays outside the ESDP program to talk about endocrine effects. Its unclear how this relates to concerns about the SEP and WOE approach for Tier 1 information. The comment is linked to the following highlighted/underlined text in the Response: "Thus, the Agency has already established a precedent of using the Tier 1 screening data in combination with other existing test data when they contribute to our understanding of

the potential effects of a chemical, even though final SEP and WOE information are not available."

EPA Response: See also response #5 under Section IV. of this document. As discussed, in addition to being used to determine whether Tier 2 data are needed for the particular chemical, Tier 1 data will assist EPA in determining which Tier 2 data are needed, and may be used in combination with other information available to help identify the potential mode of action when analyzing adverse effects. In particular, in the context of pesticide registration decisions where EPA is required to consider such adverse effects in decision making related to registration. This aspect of the response specifically addresses the petitioner's concern that a delay in the written SEP or WOE documents might somehow prevent the Agency from using the data.

12) **OMB Comment of 3/17/09:** Page 8, Section II.B.3.: We do have one other issue, not previously mentioned, that comes up in the croplife response: the question of what these documents are and whether they are subject to economic analysis requirements. We'll be looking at this further, but we do have a quibble with a response that states that the Policy and Procedures document, currently under EO 12866 review, is not subject to EO 12866 review.

EPA Response: The Agency's response does not say that it is not subject to EO 12886 review. It says that EPA is not obligated to conduct a Regulatory Impact Analysis under EO 12866 because those provisions do not apply unless the Agency's action "promulgates or is expected to lead to the promulgation of a final regulation." Neither the List FR document or the Policy and Procedure FR document impose any requirements or otherwise attempt to promulgate or are expected to lead to the promulgation of a final regulation.