Docket ID No. EPA-HQ-OPPT-2007-1081

Response to Comments on the Public Review Draft of the Information Collection Request (ICR) entitled: "Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP)"

EPA ICR No. 2249.01, OMB Control No. 2070–new
(72 FR 70839, December 13, 2007)

April 10, 2009

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Introduction

On December 13, 2007, EPA issued two Federal Register (FR) notices seeking public comment on the Endocrine Disruptor Screening Program (EDSP). The first FR notice sought public comment on the draft policies and procedures that the Agency intends to use for the initial screening of pesticide chemicals under the Agency's EDSP (73 FR 70842, docket ID No. EPA-HQ-OPPT-2007-1080). The other sought public comment on the draft Information Collection Request (ICR) that describes the information collection activities associated with Tier 1 screening of the first group of chemicals under the EDSP and provides EPA's estimates for the related paperwork burden and costs (72 FR 70839, docket ID No. EPA-HQ-OPPT-2007-1081).

This document provides a summary of the comments received on the draft ICR, and the Agency's responses to those comments applicable to the ICR document. For information about the Agency's responses to the comments received about the proposed policy and procedures, please go to docket ID No. EPA-HQ-OPPT-2007-1080. To view the comments received, please go to the docket for these documents at www.regulations.gov.

Commenters

The following 11 entities filed substantive comments on the draft ICR (does not include any commenters that simply asked for an extension of the comment period):

Ref (1)	**Document ID #** (2)	**Commenter** (3)
04	EPA- HQ-OPPT-2007-1081-0004	B. Sachau
05	EPA- HQ-OPPT-2007-1081-0005	Carla J. Mattingly, National Engineering Regulatory Compliance Coordinator, Centennial Communications
06	EPA- HQ-OPPT-2007-1081-0006	Michael C. White, Director of Regulatory Affairs, Chemical Producers and Distributors Association (CPDA)
07	EPA- HQ-OPPT-2007-1081-0007	Dee Ann Staats, Environmental Science Policy Leader, CropLife America
09	EPA- HQ-OPPT-2007-1081-0009	Larry E. Hammond, Chairman, Technical Committee, Industry Task Force II on 2,4-D Research Data
10	EPA- HQ-OPPT-2007-1081-0010	Michael P. Walls, Managing Director, Regulatory and Technical Affairs, American Chemistry Council (ACC)
11	EPA- HQ-OPPT-2007-1081-0011	Kimberly S. Gilbert, Regulatory Leader, Dow AgroSciences
12	EPA- HQ-OPPT-2007-1081-0012	Scott Slaughter, Center for Regulatory Effectiveness (CRE)
13	EPA- HQ-OPPT-2007-1081-0013	Dee Ann Staats, Environmental Science Policy Leader, CropLife America (2nd Comments)
14	EPA- HQ-OPPT-2007-1081-0014	Susan Ferenc, President, Chemical Producers and Distributors Association (CPDA)
15	EPA- HQ-OPPT-2007-1081-0015	Beth L. Law, Assistant General Counsel, Consumer Specialty Products Association (CSPA)

KEY:

(1) This is the number that is used in this document to refer to this particular commenter.
(2) This is the number that is used to identify this comment in the docket at www.regulations.gov
(3) This is the name of the individual or entity that submitted the comments, along with their affiliation, if provided.

These 11 commenters provided similar comments that can be grouped into specific topic or subject categories. This document is organized according to the topic or subject categories.

Comments and Responses

1. Validation of Tier 1 and 2 Assays is a Prerequisite

Comment: Commenter #12 stated that the record does not demonstrate this ICR's consistency with the Paperwork Reduction Act (PRA) requirements, 44 U.S.C. §§ 3506(4)(b)(i)(c),(d); 44 U.S.C. § 3507(a). Specifically, the commenter asserted that EPA cannot satisfy the PRA requirements until EPA has validated and published all of the tier 1 and tier 2 assays being considered for the EDSP. Only then can the public comment on-- and only then can the Office of Management and Budget (OMB) determine-- the practical utility, accuracy and reliability, cost and burden of the EDSP. They believe that this cannot be separated for the purpose of public comment and compliance with the PRA. To explain their comment, they provided this example:

> "[I]f a compound elicits a positive outcome in the tier 1 screening assays, then it will have to perform tier 2 assays. The cost and burden of the tier 2 assays flow from the tier 1 assay results, and the tier 1 assays are useless without the tier 2 assays, because as EPA stated, "the ultimate purpose of the EDSP is to provide information to the agency that will allow the agency to evaluate the risks associated with the use of a chemical and take appropriate steps to mitigate any risks." 72 Fed. Reg. 70842, 70844 (Dec. 13, 2007). Consequently, the cost, burden and usefulness of the tier 1 assays depend on the tier 2 assays. EPA itself has cautioned that the practical utility of the tier 1 assays cannot be determined until their results can be compared to the tier 2 assay results: "while it is of interest to know how well these [tier 1] screens perform in identifying chemicals that are positive in tier ii tests, this can only be done to a limited extent at this time. Examples of this type of assessment have been conducted with the uterotrophic and hershberger in vivo screens against other in vivo data including multi-generational tests. However, the real proof of the performance of the tier I screens will be a retrospective comparison of the performance of the battery with tier II results after sufficient tier II data have been generated in the testing program. This is why EPA is committed to a retrospective analysis of the test data generated on the first 50 to 100 chemicals tested in the EDSP."

Since the EPA record does not show compliance with the PRA's standards, the Commenter states that EPA must withdraw this ICR until the agency believes it has validated both the tier 1 and tier 2 assays. If and when EPA has validated both the tier 1 and tier 2 assays, then EPA should allow another public comment period on a proposed ICR before EPA sends an ICR to OMB for review.

In addition, the Commenter stated that the EPA record doesn't demonstrate this ICR's compliance with EPA's guidelines under the Information Quality Act ("IQA"), 44

U.S.C. § 3516[1], because EPA has not demonstrated that the tests generate accurate and reliable results.

EPA Response: The Agency disagrees with this commenter. The ICR is in compliance with the PRA and EPA's IQGs.

1. The scope of ICR was stated as being the information collection activities related to Tier 1 screening only.

First and foremost, it is important to remember that this ICR only applies to the Tier 1 assays. Any discussion in the ICR of Tier 2 under the EDSP is provided for the sole purpose of describing the overall program, and was not provided for the purposes of obtaining approval for any potential future Tier 2 activities under the PRA. Any activities related to the Tier 2 testing phase of the EDSP will be addressed in a future ICR. Although the Tier 2 assay validation process is underway, the Agency has stated that it will address the paperwork activities related to the as yet undefined procedures for requiring Tier 2 testing in a future ICR. There are NO current Tier 2 related paperwork activities that require approval under the PRA. This was specifically explained in the draft ICR, as well as in the related draft procedures document.

To clarify this further, the Agency has revised the title of the ICR to specifically reflect the "Tier1" focus, and has revised the discussion to make this scope very clear.

2. Completion of the validation process for all of the assays in the final Tier 1 battery is not a prerequisite for compliance with the PRA.

Since FFDCA requires EPA to use validated test methods, as explained in more detail in the procedures document, until the validation process for an assay is complete, EPA will not be able to require any order recipient to perform that assay. Validation is defined as the process by which the reliability and relevance of test methods are evaluated for a specific use. The validation process was established based on recommendations from the advisory committees consulted on EDSP implementation over the years, and, along with the peer review materials and the validation status of each assay, details are available on the Agency's EDSP Web site at: http://www.epa.gov/scipoly/oscpendo/pubs/assayvalidation/index.htm.

Completion of the validation process for all of the Tier 1 assays in the final Tier 1 battery is not a prerequisite for compliance with the PRA. Under the PRA, the Agency is required to provide, among other things, a **functional description** of the information that it anticipates will be collected (e.g., indicating how, by whom, and for what purpose the information is to be used).[2] In implementing guidance, the Office of Management and Budget (OMB) instructs agencies to ensure that the description provided in the ICR is sufficiently complete so as to inform potential respondents of the possible activities they may need to engage in and any related information to be collected. For example,

[1] Page 12 of OMB IQA guidance available online at http://www.whitehouse.gov/omb/inforeg/iqg comments.pdf, states that every ICR must meet IQA guidelines. EPA's IQA guidelines are available online at http://www.epa.gov/quality/informationguidelines/documents/epa_infoqualityguidelines.pdf.
[2] 44 U.S.C. 3506(c)(1)(A)(ii); 5 CFR 1320.8(a)(2).

where the specific data elements of a particular collection are expected to vary across respondents or are otherwise uncertain at the time that the ICR is submitted, agencies are instructed to provide sufficient information to identify the full scope of potential information to be collected for consideration and comment by the respondents and the public.

Under the PRA [5 CFR 1320.8(d)(1)(i)-(iv)], the agency is to seek public comment to permit the agency to:

i. Evaluate whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information will have practical utility.
ii. Evaluate the accuracy of the agency's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used.
iii. Enhance the quality, utility, and clarity of the information to be collected.
iv. Minimize the burden of the collection of information on those who are to respond, including through the use of appropriate automated, electronic, mechanical, or other technological collection techniques or other forms of information technology, e.g., permitting electronic submission of responses.

These issues are also those about which the public may have personal experience, perspectives and concerns that would help inform the agency while it carries out its evaluation, and help permit the agency to make the certification required by the PRA. This public comment opportunity is designed to help the agency in its ongoing development of the new collection or evaluation of an existing collection.

An agency should provide the proposed collection of information in the form to which it has been developed at that point; if the agency, for example, is at that point considering alternative approaches to collect the information, a range of possible questions, or different kinds of disclosure, the agency should be prepared to provide the public with these alternative approaches. However, the agency does not have to have completed the development of the collection of information at the point of the 60-day advance notice. The interested public will have a second opportunity to submit comments at the time the agency has refined the collection of information and is submitting the information clearance package to OMB for review. [5 CFR 1320.5(a)(1)(iv).]

When the draft ICR was issued for public review and comment starting in December 2007 and ending in March 2008, the Agency specifically identified **all** of the assays that were being considered for inclusion in the final Tier 1 battery, and also indicated that the battery was not yet finalized, and that the information collection would be limited to the final battery – once it was established. In fact, the majority of the assays under consideration for inclusion in the Tier 1 battery had indeed completed the validation process, with the remaining few assays in the final stages of the EDSP validation process. For each assay under consideration for the Tier 1 battery, the draft ICR provided a description of the assay, its intended function in the context of the Tier 1 battery and in terms of the information being collected, and the estimated costs and burden related to the assay. As such, the draft ICR provided the necessary information

to ensure that the public and potential respondents could consider the details of the proposed information collection activities and provide informed comment.

The public comment process for the draft ICR is not intended to serve as a substitute for the public comment opportunities provided during the development of the assays or related peer reviews, it is intended to provide an opportunity for the public to comment on the Agency's practical utility justification for the collection activities and its related burden and cost estimates as presented in the ICR. Since the Tier 1 battery had yet to be decided upon, the ICR identified all of the Tier 1 assays under consideration, and clearly stated that the Tier 1 battery may consist of fewer assays, but would not include additional assays not listed. The ICR explained the utility of the data generated by each assay and its intended use in decision-making, as well as the estimated cost and burden for each assay.

3. Available documentation demonstrates that the assays in the final Tier 1 battery generate accurate and reliable results for the intended purpose.

As indicated in its July 2007 document addressing validation, EPA has implemented the validation process for EDSP in several phases:

- Preparing detailed review papers (DRPs) that involve a search of the relevant scientific literature and development of a document that discusses the scientific basis of each assay and critically evaluates candidate protocols.
- Conducting pre-validation studies that demonstrate and optimize the assay, with the end result being a standardized protocol for use in the multi-laboratory validation phase.
- Conducting validation studies in multiple laboratories. The purpose of this phase is to demonstrate the transferability of the protocol, measure lab-to-lab variability, and help establish final performance characteristics for the assay.
- Peer reviewing the data to determine strengths and weaknesses of the assays. Peer review is the critical evaluation of scientific and technical work products by independent experts. Its purpose is to improve the quality, credibility, and acceptability of regulatory decisions.

The documentation associated with all of these phases for each assay formed the basis for the Agency's determination that a particular assay generates accurate and reliable results for the intended purpose identified for that assay, and that the assay successfully completed the validation process.

To clarify that this documentation is available, the ICR has been amended to clearly point the reader of the ICR to the validation documentation on the Agency's Website. The Agency is otherwise not required to repeat this information in the ICR.

2. Duplication of Data

Comment: Commenter #12 asserted that the EDSP draft policies and procedures will cause unnecessary duplication of data collection, but indicated that EPA could reduce unnecessary duplication by exempting companies from the EDSP if they meet either

one of two alternative conditions. First, the company submits current information for a chemical that indicate that the number of potential exposure pathways and the potential for exposure are below the threshold for including the chemical on the tier 1 testing list. Second, and in the alternative, the company submits information that is functionally equivalent to all or some of the tier 1 assay information. Under this alternative, EPA should only require tier 1 assays for that information for which there is no functionally equivalent information. This recommendation is similar to the approach advised by the endocrine disruptor screening and testing advisory committee.

EPA Response: 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).

In the context of the first suggestion, companies were provided with an opportunity to submit information about the exposure of the chemicals on the draft list, including information regarding potential exposure pathways. The Agency considered information and comments submitted in determining the final list. As such, see also the Response to Comment documents prepared for the List and the Policy and Procedures document.

With regard to allowing for the submission of "functionally equivalent" information in lieu of some or all of the Tier 1 assay data, the Agency specifically addresses this more clearly in the final Policy and Procedures document. Specifically, 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 part or all of the Tier 1 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). Other scientifically relevant information 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. Some "other scientifically relevant information" may be sufficient to satisfy part or all the Tier 1 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.

In addition, the Agency has written a paper entitled "EPA's Approach for Considering Other Scientifically Relevant Information (OSRI) under the Endocrine Disruptor Screening Program." 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 Docket ID number EPA–HQ–OPPT–2007–1080.

Implicit in the comment is the idea that EPA should bear the responsibility for making a determination of whether existing data are adequate for the EDSP prior to issuing an order. However, both FIFRA and 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.

Comment: Commenter #12 indicated that EPA acknowledges that minimizing duplicative testing in the EDSP is a "complex issue... The agency recognizes that, if EPA sends test orders under the EDSP screening program to multiple companies that produce the same substance and then each recipient of the test order conducts the required studies, there could be a great deal of duplicative testing." 72 FR 70848 (Dec. 13, 2007). As far as we can tell, EPA's proposed solution to the duplication problem is to send everyone who makes the same product the same testing order, and hope that they work something out among themselves to minimize duplication. EPA's extensive discussion of whether competitors will share what is often CBI suggests that the EDSP violates the PRA's mandate to eliminate unnecessary duplication. See 72 FR 70848-70852 (Dec. 13, 2007).

EPA Response: Based on nearly thirty years' experience with issuing data call-in (DCI) notices for pesticide active ingredients, EPA believes that companies have adequate incentives to join together to develop data jointly. Joint data development minimizes the costs for each participant and EPA has almost never seen instances of duplicative testing for pesticides. Since the EDSP procedures closely follow the procedures used in the DCI process, EPA believes that there is no reason to expect different results under the EDSP.

Finally, 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.

Comment: Commenter #14 indicated that the ICR does not account for the significant likelihood that ambiguous test results will necessitate repeating one or more of the assays in any battery for a particular chemical. If assays must be repeated, the costs of even a single battery will increase dramatically. In addition, Commenter #15 stated that the agency failed to account for the significant likelihood that ambiguous results will necessitate repeating one or more screens for a particular substance. This is especially likely given the lack of historical use of these assays in regulatory programs and the

lack of guidance provided by the agency regarding interpretation of results. Although it may be difficult to project the percentage of screens that might need to be repeated, 10% would be a very conservative estimate based on industry's preliminary experience with these assays.

EPA Response: As already indicated publicly, EPA believes that the development of tools for EPA staff, such as a Weight of the Evidence Approach (WOE) and Standard Evaluation Procedures (SEPs), will help to provide consistency in Agency decision-making, as well as provide additional transparency to order recipients and the public.

With respect to the interpretation of the results from individual assays or other data submitted or cited in response to an order, EPA is working on developing SEPs for the initial screening, and intends to consider lessons learned in any early case-by-case determinations. EPA intends to provide an opportunity for public review of the SEPs as part of a peer review process.

Although the SEPs will not be publicly available in final form before EPA begins issuing the orders, EPA expects the SEPs to become publicly available in final form before any Tier 1 related decisions are announced to the public. EPA also expects the SEPs to be available in draft form for public comment.

The WOE approach makes explicit the assumption that results of some assays, in some taxa, at some level of severity, are intrinsically “worth” more than others and should, therefore, carry more weight in decisions following Tier 1 screening. EPA will develop reference document for interpretation of the results of the Tier 1 screening battery which will be made public.

The SAP may also review such reference documents. This would provide the opportunity for both written and oral public comment, but the exact process for developing and vetting such documents has not yet been determined by the Agency.

EPA disagrees, however, that issuing test orders for Tier 1 screening cannot occur until after such information is available in final form, or that the availability of such information is necessary for order recipients to determine how they will respond to the order. The information is not used to determine whether or not a chemical is on the initial list, or to determine who should receive an order for that chemical. In terms of responding to an order, an order recipient can certainly determine how they want to respond to the order without considering such information.

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 has explained publicly that the hazard and risk assessments of a chemical will consider all available, scientifically relevant information. The current availability of final SEPs and WOEs for EDSP related determinations does not preclude the Agency from evaluating the potential interaction of a chemical with the endocrine system.

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. Practical Utility

Comment: Commenter #12 asserted that the practical utility of this ICR cannot be determined until EPA has validated and published both the tier 1 battery of assays and the tier 2 assays.

EPA Response: As indicated previously, this ICR only applies to the Tier 1 battery - NOT Tier 2. In addition, the Agency has indicated that the individual assays in the final Tier 1 battery will have all completed validation before the final Tier 1 battery is announced and before any Orders are issued under the EDSP. In fact, at this time, all but one of the assays in the proposed Tier 1 battery have completed the validation process, and the last assay is in the final stages of the validation process. The ICR discussions have been revised to ensure that this is clear.

Comment: Commenter #12 stated that EPA should also emphasize in the record for both the ICR and the substantive EDSP policies and procedures that tier 1 assays have no value unless properly validated, and that even validated tier 1 assays are useful only as a trigger for tier 2 assays and have no other value. Consequently, EPA should unambiguously state in the record that tier 1 assay tests should never be used for risk assessment purposes except to trigger other assays which may be useful for risk assessments.

EPA Response: EPA has revised the ICR to clarify the uses of the Tier 1 data received, which are not limited in the way suggested by the Commenter. The primary purpose of Tier 1 screening is to identify substances that have the potential to interact with the estrogen, androgen, or thyroid hormone systems using a battery of assays. Based on an weight-of-evidence evaluation of the available information, including the Tier 1 data and other scientifically relevant information, the chemical will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary.

EPA has extensive experience in using data from multiple sources to develop integrated assessments of hazard, modes of action / mechanisms of toxicity, and overall potential for risk. EPA scientists will continue to use such experience, together with insights from the validation process for Tier 1 assays, to address the potential of chemicals to cause adverse effects as a consequence of interaction with the endocrine system. In fact, EPA has considered the potential interaction of a chemical with the endocrine system in making certain pesticide registration decisions. For example, EPA considered data from prototypes of the assays included in the current EDSP Tier 1

screen, along with other existing data, in preparing the risk assessments of procymidone[3] and vinclozolin[4].

4. Methodology for Estimating Burden and Costs

Comment: Commenter #12 stated that the cost and burden of this ICR cannot be determined until EPA has validated and published both the tier 1 battery of assays and the tier 2 assays.

EPA Response: As indicated previously, this ICR only applies to the Tier 1 battery - NOT Tier 2. In addition, whether an assay has completed the EDSP validation process does not preclude the Agency from estimating the potential burden or related costs for the assay. Since the tests that will be used in the EDSP are not yet offered by the laboratories, market costs for these tests are not available. The Agency therefore used estimated costs for 2 assays that were based on estimates provided by the EPA scientist overseeing the validation effort for those 2 assays. Since EPA is funding the assay validation effort, we believe that these estimates are reasonable surrogates for actual market prices at this time and for the purposes of this ICR. For the other assays, the Agency used the Cost Estimate Survey of commercial laboratories and other information provided by industry representatives. Once these tests are available on the market, these costs will be adjusted as appropriate.

Comment: Commenter #14 commented on the ICR's calculation of the paperwork burden for the data generation as 35% of the test costs. This percent-based estimate of paperwork associated with conducting a test was initially established in consultation with OMB in the 1980's.[5] In this collection, the agency therefore estimates the data generation paperwork burden to be $131,090 per battery, per chemical. The agency will need to adjust this estimate if more accurate and current assay costs figures are collected. If the agency maintains a paperwork burden estimate of 35%, it can readily be seen that this burden may more accurately total $305,440. When carried through the calculations of table 9 of the draft supporting statement, the total burden of the paperwork to generate the data is $22,297,120 rather than the $9,569,574 estimated by the agency, bringing the total respondent burden to $33,389,800, rather than the $20,662,254 estimated by the agency.

EPA Response: Once these tests are available on the market, the Agency's estimated costs will be adjusted as appropriate. EPA has revised the ICR to reiterate this.

Comment: Commenter #15 stated that, although it is not possible to accurately estimate the degree to which the agency has underestimated costs without undertaking a formal assessment, the agency's projected expenditures for the tests alone appear to comprise less than one-half the actual costs that respondents would incur. Given the probable financial impact of this new program, EPA should have conducted formal

[3] To access the documents related to the procymidone decision, go to http://www.epa.gov/pesticides/reregistration/procymidone/.
[4] To access the documents related to the vinclozolin decision, go to http://www.epa.gov/pesticides/reregistration/vinclozolin/.
[5] From draft ICR supporting statement edspicr-draft-2007-12-05, page 27.

assessments to collect actual cost data and should have conducted those cost assessments not only for the candidate assays alone, as APT did previously, but also for the various associated costs that were not and could not have been evaluated previously without knowledge of EPA's implementation plans. Only in this way would it be possible to determine whether it is reasonable to continue to assume that as much as 35% of the test costs represent the paperwork burden.

EPA Response: Until the tests are readily available on the market, conducting a survey about the tests would not be productive. Laboratories did not yet have any experience with these tests upon which to they could have provided information. Although not possible for this ICR, the Agency does intend to consult with the recipients of these first Tier 1 Orders about their experiences, costs and burdens. This consultation will be used to revise the estimates presented in this ICR for the ICR renewal or future ICRs related to the EDSP.

Comment: Commenter #14 stated that the agency also assumes that 367 companies will be required to provide tier 1 data on the initial list of chemicals and that all will participate in a consortium but provides no rationale for these assumptions. If only 5% of the affected entities (18) choose not to enter into a consortium, another $21,000,000 burden may be incurred.

EPA Response: This commenter incorrectly assumes that each company that chooses not to enter into a consortium will generate the data on their own. The Policy and Procedures document states that the Agency expects to only receive one submission of data for each chemical. As indicated previously, EPA believes that companies have adequate incentives to join together to develop data jointly because they routinely do so now and have done so for the past 30 years. Companies have demonstrated in the past that they are able and willing to join forces to minimize their costs and experience other benefits from collaborating on the development of data for submission to EPA. There is no evidence to indicate that companies are no longer able or willing to continue such collaboration.

Comment: Commenter #10 believes that there are serious shortcomings with the accuracy of the draft ICR for the following reasons, all of which are developed in more details in the enclosed report (see EPA-HQ-OPPT-2007-1081-0010.2, APT REPORT):

- The number and complexity of tier 1 assays has increased since 2003, but EPA did not account for this in the current ICR. Also, the agency has not made a final determination on the design and procedures of any of the tier 1 assays.
- APT's 2003 report did not include the costs associated with the tier 1 amphibian metamorphosis assay or the tier 1 fish reproduction screening assay, and it did not evaluate the potentially significant costs of analytical chemistry requirements under good laboratory practices standards, which will be required under the EDSP. The current ICR does not address these costs.
- There is no assurance that respondents will be expected to conduct less than the entire battery of assays. In the absence of clarification from EPA, there is no scientific rationale for assuming that less than the entire battery would be required for each substance and, consequently, no foundation for a meaningful ICR until such time as the agency provides such clarification.

- The agency has failed to account for the likelihood that ambiguous results will necessitate repeating one or more screening tests for a particular substance. This is especially likely given the lack of experience with these assays in regulatory programs and the absence of agency guidance regarding interpretation of results.
- EPA's outsourcing assumption does not overestimate the burden associated with the EDSP as the agency claims. In fact, for the reasons APT explains, many respondents will have to rely on contract labs and thus incur the associated burden in terms of actual costs and paperwork.
- EPA's draft ICR does not address the significant issue of laboratory capacity. Some of the screening assays are sufficiently new and specialized that only one or a very few laboratories are able to perform them. Although it is certain that supply will rise to meet demand, it is also certain that the cost of expanding contract laboratory capacity will be borne by respondents.

Some of these comments were also reflected in comments #14 & 15.

EPA Response: The Agency accepts that the 2003 survey previously provided by industry is not perfect or complete. It does, however, provide a reasonable estimate for the burden and costs of these new tests. As indicated previously, the Agency did not believe that a survey would provide more valuable information at this time because these tests are not currently available on the market. At best, a survey might have provided different estimates, but without a clear indication that could describe the basis for those differences.

The ICR is not required to account for a respondent's mistakes or inability to follow the final protocol or test guidelines to conduct the assay. Nor is it required to assess the capacity of commercial laboratories. An ICR is required to evaluate the potential paperwork burden associated with information collection activities.

The Agency has made some adjustments to the ICR discussion and the test costs that formed the basis for the data generation burden estimates. Assertions regarding the potential for the total ICR burden and costs to be an over estimate have been removed, and the Agency has added analytical chemistry costs to the estimate. Please note, however, that these costs are not expected to be significant because none of the chemicals on the List are new – such that they would not already have an established methodology.

5. Estimated Test Costs

Comment: Commenter #10 estimates that the performing a tier 1 battery of tests may cost $ 500,000 per substance. The acc estimates that performing tier 2 tests could exceed $1,000,000 per substance. These cost estimates significantly exceed EPA's estimates for tier 1 assays.

EPA Response: There is no support for this estimate.

Comment: Commenter #14 indicated that the ICR does not account for the analytical costs associated with each of the assays in the battery. These costs may add 100-

300% of the agency estimated test costs to each assay within the battery significantly increasing the total test burden. Industry representatives with experience in conducting the assays report analytical chemistry costs in excess of those included in the updated assay costs reported by APT. For example, for the *in vivo* uterotrophic assay, APT estimates current assay costs, including a portion of the analytical chemistry costs missing from the ICR estimates, to range from $38,000- $47,000. Industry experience indicates the analytical chemistry costs alone can add $45,000 to this assay. Adding this $45,000 to the ICR-estimated assay cost of $20,068 provides an estimated minimum cost for this assay well above the $47,000 reported by APT. For the *in vivo* hershberger and prepubertal assays, experience indicates the analytical chemistry costs add $45,000-$90,000 to the cost of the assays, doubling or tripling the estimates used in the ICR for these assays. For the *in vitro* steroidogensis, and estrogen/androgen binding assays, analytical chemistry costs generally add $23,000 to the assay costs. This quadruples the ICR estimates of the binding assays and triples the costs of the steroidogenesis assay.

EPA Response: The Agency has added analytical chemistry costs to the ICR. The estimates provided by APT, however, are not applicable to this ICR because they represent costs associated with conducting analytical chemistry tests for the first time for a particular substance, which includes initial costs to determine appropriate methodologies. Specifically, the cost for analytical chemistry that was added to the ICR is based on that used in other EPA ICRs that contain this test. It is important to note that the chemicals on the initial list are all already well established existing pesticides, which means there will not be a need to create any new analytical methods to identify the substance for testing purposes. As such, the analytical costs included here represent the application of the existing methods to identify the substance being tested.

Comment: Commenter #14 indicated that they believe the agency's analysis grossly underestimates the costs of conducting the assays in the tier 1 screening battery. In the appended supporting document produced by APT, a review of only four of the assays expected to be included in the final screening battery suggests that average current test cost are 2.33 (range 1.45-3.13) times greater than those estimated by the agency. If these increases are extrapolated over the cost of the full battery by simple calculation, the cost of a single battery may easily reach $872,685, well in excess of the $374,543 estimated by the agency (please see the appended APT report for a discussion of various underestimated figures used by the agency).

EPA Response: There is insufficient support for the estimates provided. For example, because the final testing protocols were not used, the estimated costs are too high. As indicated in the final reports for the assays, many of the protocols were revised to minimize the use of animals or to streamline the procedures. These changes have the effect of reducing the overall costs related to the assay using that final protocol.

Comment: Commenter #15 suggested that EPA recalculate the projected costs of the tier 1 assays using a more formal method to account for unseen costs such as good laboratory practices (GLP) chemical analysis for identity and purity, GLP analysis of test concentrations, outside contractors, and in- house resources must be added to the cost estimates to reflect the actual burden to registrants. Additionally, there will be a great deal of registrant confusion during this "pilot phase" of the program, requiring outside

guidance on optional test groups and endpoints, optional controls, studies needed, and interpretation of the findings. Based on industry experience, consortia establishment costs are generally in the $15k to $20k range, with ongoing costs of several thousand dollars incurred during and after the data development phase. EPA should also consider adding factors to account for inflation and the potential rise in laboratory costs due to competition for approved laboratories.

EPA Response: To the extent that costs were related to paperwork burden, EPA has increased its estimates for consortia formation and initial familiarization, as well as added base costs for analytical chemistry. EPA will evaluate these estimates prior to seeking renewal of this ICR.

6. Estimated Burden and Costs

Comment: Commenter #14 believes that there are several improvements that should be made before reporting the results of the ICR to OMB for review. In both the Federal Register ICR notice and it's draft supporting statement, the agency states that the estimated total annual burden for this ICR is to include, among others, "conducting tests" however, the agency does not include the burden of conducting the tier 1 batteries in their analyses. The commenter believes that by using currently-available test cost survey results and appropriately including this burden in the ICR, the actual total burden of this information collection will readily approach $100,000,000. At this time, the agency estimates the total burden for this collection to be just $20,662,254.

EPA Response: There is no basis for the $100 million estimate provided. The ICR does include the paperwork burden for conducting the tests. In this case, the activities are spread over the 3 year period of the ICR because there is no clear way of dividing the activities by year. As a result, the total burden is divided by 3 to annualize it.

Comment: Commenter #14 suggests that the ancillary burdens such as those associated with analytical chemistry, repeated assays and batteries, and transaction and opportunity costs were not factored into the total burden.

EPA Response: These activities are not associated with the paperwork burden such that they would ever be accounted for in the ICR. An ICR does not consider overall impacts in the same way that an Economic Analysis would.

7. Small Entity Burdens

Comment: Commenter #14 suggested that the agency should better characterize the burden and potential impacts on small entities to ensure that they are not unduly affected and an appropriate mechanism is in place to address these concerns. EPA dismisses the potential impact on small businesses by assuming that few small entities will be covered under the EDSP and that those companies which do receive a test order will likely join a consortium to generate the required data. However, the agency does not adequately identify the potential data collection burden expected to be incurred by a company that chooses to fulfill its testing obligations as part of a larger consortium nor does EPA provide a comprehensive assessment of the burden that would likely be

incurred by a company choosing to generate the data on its own. The burden to a small entity, even if participating as a member of a large consortium, could be significant and have a major impact on that company's decision to remain in production.

EPA Response: There are no separate estimates for small businesses because the burden for a small business is not expected to be different. There is no information available to indicate that a small business participating in a consortium would experience a greater burden. In fact, information available on small businesses participating in testing consortiums formed under the TSCA program indicates that these businesses experience less burden on average. EPA will attempt to identify which Tier 1 Order recipients might qualify as a small business so as to consult specifically with them about potentially disproportionate burdens that they experienced. Upon renewal of this ICR or for the subsequent ICR, EPA will use revise the ICR to reflect this consultation.

8. Other Topics

Comment: Conduct a formal evaluation. Several commenters (#13, 14, 15) recommended that EPA conduct a formal evaluation of the test costs. Commenter #13 expressed concern that EPA has significantly underestimated the probable costs associated with the initial phase of its EDSP, and that a formal evaluation was necessary. Commenter #14 suggested that he agency should conduct a formal survey of present-day, actual costs of conducting the validated assays so as to develop a more accurate and refined assessment of "burden" (as it is defined under the PRA) that reflects currently available data. Commenter #15 believes that a formal evaluation is necessary because the agency has not yet issued formal protocols, test guidelines, or other recommendations that would indicate an ultimate decision on final study designs and procedures for any of the EDSP tier 1 assays, which directly influence costs.

EPA Response: EPA intends to conduct a formal evaluation of the test costs in consultation with the recipients of the Tier 1 Orders.

Comment: Clarify the assays. Commenter #15 suggested that the agency should also survey potential respondents to determine the level of detail at which assays will actually be conducted. With the known variability inherent in some of the required and suggested endpoints, respondents will likely feel compelled to include these optional endpoints to hedge against what might ultimately be necessary to interpret the results. The agency has yet to provide guidance on how results of the individual assays will be interpreted and whether results from individual assays will be considered in isolation or within the context of other screening studies. Furthermore, the assays are relatively new and their stable performance unexplored. Hence, many respondents feel compelled to include additional positive controls to better explain uncertain assay performance. The increased costs associated with these full-featured protocols are a practical cautionary approach against much greater costs, in both resources and animals, for repeating the assays to obtain more complete and interpretable data. A good example of opting for a more full-featured assay protocol involves the uterotrophic assay. According to the current draft OECD test guideline, this screening study may be run at a limit dose or

with an as yet to be determined number of test doses (2 or 3). In addition, it may include optional endpoints, such as histopathology, as well as additional positive controls, such as a lower potency estrogen like genistein, and additional dose groups to probe antiestrogenic potential. In the absence of guidance from the agency on interpreting the results, and lacking a history of reliable test performance, it is a practical reality that the assays will include more dose groups than the minimum required by current protocols. Hence, the costs will be much higher than projected in the draft ICR. The agency should first conduct a formal survey to understand at what level of detail the assays are likely to be conducted in order to develop a formal cost estimate survey based on more realistic versions of the protocols than were available in 2003.

EPA Response: As already indicated publicly, EPA believes that the development of tools for EPA staff, such as a Weight of the Evidence Approach (WOE) and Standard Evaluation Procedures (SEPs), will help to provide consistency in Agency decision-making, as well as provide additional transparency to Order recipients and the public because EPA intends to provide an opportunity for public review of the SEPs as part of a peer review process.

EPA disagrees, however, that issuing test orders for Tier 1 screening cannot occur until after such information is available in final form, or that the availability of such information is necessary for Order recipients to determine how they will respond to the order. The information is not used to determine whether or not a chemical is on the initial list, nor is it used to determine who should receive an order for that chemical. In terms of responding to an order, an Order recipient can certainly determine how they want to respond to the order without considering such information.

The current availability of final SEPs and WOEs for EDSP related determinations does not preclude the Agency from evaluating the potential interaction of a chemical with the endocrine system. As indicated previously, EPA has extensive experience in using data from multiple sources to develop integrated assessments of hazard, modes of action / mechanisms of toxicity, and overall potential for risk. EPA scientists will continue to use such experience, together with insights from the validation process for Tier 1 assays, to address the potential of chemicals to cause adverse effects as a consequence of interaction with the endocrine system.

Comment: Resolve Data Compensation & Protection Uncertainties. Commenter #15 requested that EPA identify how and where submitted data will be maintained and confirm if a recent suggestion that the special review and re-registration division would be the repository of the data is correct. Another pressing question is whether the “data” required includes inerts. Data compensation under FIFRA would be the most preferable option, since a proven method already is in place. The FIFRA process should be replicated for inerts that are not subject to FIFRA. EPA also needs to ensure a level playing field at all times and establish a fair and equitable data compensation scheme for both active and inert ingredients. One set of issues involves handling compensation if a registrant does not support an ingredient and a group of formulators step up to take over the testing to ensure the ingredient remains available for their product lines. Additionally, more clarity should be provided to registrants with monitoring use products (MUPs). EPA may choose to proceed with its proposed data compensation scheme in

its initial screening. EPA must, however, revisit this issue in future implementation notices and should gather more public and stakeholder input.

EPA Response: These issues are addressed in the Policy and Procedures document, and are not established in the ICR.

Comment: Animal Welfare. Commenter #12 asserted that the EDSP draft policies and procedures will cause unnecessary and useless animal death and suffering, in violation of the regulatory acceptance criteria established by the Interagency Coordinating Committee for the Validation of Analytical Methods ("ICCVAM"). The commenter further "sharply criticizes EPA for allowing environmental groups like NRDC to coerce the agency into killing many animals during tests with no demonstrated value." The EDSP assays must meet ICCVAM's validation and regulatory acceptance criteria.[6] These criteria require "adequate animal welfare considerations (3rs). [7] In ICCVAM's own words, the EDSP assays "must provide adequate consideration for the reduction, refinement, and replacement of animal use."[8] We find no place in the record where EPA explains specifically how it is working in the EDSP "to reduce animal use, refine procedures involving animals to make them less stressful, and replace animals where scientifically appropriate."

EPA Response: This issue is related to the selection of the assays and the final Tier 1 battery. As explained in the ICR, the selection of the final Tier 1 battery is happening in a separate but parallel process - a process that involved extensive public participation from the very beginning in 1996. These issues are therefore more appropriately addressed in that process, and not as part of the ICR, whose focus is solely on the paperwork activities related to the issuance of Tier 1 Orders for the 67 chemicals identified.

Comment: Stop allowing endocrine disruptors in the market. Commenter #04 asserted that EPA has been very negligent in allowing endless endocrine disruptors to be bought, sold and produced in this country, when they should have been denied any approval at all. This agency is so under the thumb of chemical profiteers that it is disgusting. They meet constantly and this agency forgets that its biggest stakeholders are american citizens, who provide the tax dollars for this agency to even be in existence. All tests should be twenty years long. All tests should be on people. All tests should show all combinant testing with every other chemical in use in the country. EPA has allowed endless lax administration and has not been protecting the people, and life in this country for the last 30 years. That is disgusting.

EPA Response: Although this comment is not related to the paperwork activities or estimated burden in the ICR, EPA appreciates the concern expressed by this comment but strongly disagrees that it has been lacking in meeting its statutory mandate to

[6] Validation And Regulatory Acceptance of Toxicological Test Methods, Interagency Coordinating Committee on the Validation of Alternative Methods, Executive Summary (March 1997). Available online at http://iccvam.niehs.nih.gov/docs/about_docs/validate.pdf.
[7] Who's Who in the Validation of Assays for the EDSP, Briefing for New EDMVAC Members, March 2, 2005. Available online at http://www.epa.gov/oscpmont/oscpendo/pubs/edmvac/validation_briefing_edmvac_030205.pdf.
[8] Id., section 3.5.

protect public health and the environment from unreasonable risks from exposure to pesticides.

Comment: **Consider sensitive sub-populations.** Commenter #05 expressed concern about those individuals who may have allergic reactions from exposure to pesticides. In particular, to pesticide treatments in the office, where they felt that residual residues existed for 2-3 days after treatment that caused them severe reactions: including headaches, becoming lethargic, experience breathing difficulties and sometimes develop skin irritations including hives. The following list of common names of pesticides have been reported by scientists to be sensitizers in certain susceptible individuals: allidochlor, anilazine, antu, barban, benomyl, captafol, captan, dazomet, dichloropropane, dichloropropene, lindane, maneb, nitrofen, propachlor, pyrethrum/pyrethroids, rotenone, thiram, zineb. Pesticides may be encountered as residues in food, air and water. People may also be exposed to pesticides used in agriculture, applications for pest control at home or at work, applications to roadside right-of-ways to control weeds and applications of pesticides for public health vector control programs.

EPA Response: Although this comment is not related to the paperwork activities or estimated burden in the ICR, it is important to point out that the Agency does consider potential disproportionate risks to sensitive sub-populations in the risk assessments that form the basis of EPA's pesticide registration decisions.