Center for Regulatory Effectiveness' ("CRE") Comments on Environmental Protection Agency's ("EPA") Proposed Information Collection Request ("ICR") for Tier 2 Data Collection for Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP); *ICR number:* EPA ICR No. 2479.01; *OMB control number:* 2070-New; http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2013-0171-0001.
Comments filed with EPA on August 23, 2013, at www.regulations.gov, EPA-HQ-OPPT-2013-0171.

Executive Summary

This proposed ICR addresses the information collection activities for those chemicals that were screened under Tier 1 of the EDSP and are now proceeding to testing under Tier 2 of the EDSP. This ICR covers the full range of information collection activities associated with Tier 2 of the EDSP, including the paperwork activities associated with the issuance of Tier 2 orders, initial responses from order recipients, paperwork activities associated with generating the data requested, and submitting the data to EPA pursuant to the order.

EPA should not submit, and OMB/OIRA should not approve, this ICR because EPA has not demonstrated that the EDSP Tier 2 tests meet Information Quality Act ("IQA") Guidelines and Paperwork Reduction Act ("PRA") requirements. For example, EPA has not demonstrated that the EDSP Tier 2 tests are reliable, reproducible, and useful. EPA has also not demonstrated that the EDSP Tier 2 tests are the least burdensome necessary, and that they are necessary for the proper performance of EPA's functions.

The SAP Concluded that the EDSP Tier 2 Tests are Not Useful, Reliable or Reproducible

The SAP which recently reviewed EPA's Tier 2 tests concluded that the tests are not yet ready to be used in the EDSP. This SAP recommended further evaluation before the tests are used.

For example, one SAP member concluded that

> " the problems with experimental design, validation, experimental execution by some of the contract labs…suggest that maybe we're not ready -- some of these assays are not quite ready for primetime and there should be some further evaluations of the assays….the whole invertebrate section seems like that there seems to be little

rationale for including it in a Tier 2 assay since we didn't even consider these kinds or compounds or consider doing this in the Tier 1 or in the pre-assay evaluations….So these concerns have me a little leery that we really not ready for Tier 2."[1]

Another SAP member told EPA that some of the Tier 2 tests cannot identify adverse endocrine effects:

"The good news is I think people want these assays to move forward. I think that's definitely what I've heard at least in conversations is that we do want them to move forward, but we also want them to be correct in terms of linking the responses to an endocrine-based response. At least the consistent theme I hear, at least through most of the assays is that it's just not there….The point here is that you want to link it to an endocrine response to an AOP and EAT particularly. I think that's where, at least as I hear this, this is the common sort of negative component that I hear throughout this whether it's the inverts not even having a Tier 1 or even some of the bird and amphibian things. It's really difficult to link those apical endpoints to that EAT AOP, and I think that's at least the challenge that I see most people sort of presenting in this particular Panel."[2]

Some other SAP criticisms of the EDSP Tier 2 tests follow:

"I'm concerned that some combination of poor contractor lab performance or low statistical power is going to result in production of nothing but negative results that We don't know if they are false negatives or real negatives. And if those are accepted for regulatory purposes and they're false negatives, then we've wasted all the money."[3]

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"The high variability in some aspects of this assay makes it difficult to interpret transferability across labs. For example, because of the strain difference issue and because of the lack of use of positive controls." [4]

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"Members of the group express concern that the inter-lab tests presented may not characterize the potential for adverse effects to be exhibited in the F2. If the lack of a difference are driven by the low statistical power that we've discussed, or protocol issues then the lack of effects in the F2 may prove to be misleading for risk assessment purposes."[5]

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[1] SAP Meeting Transcript ("SAP Trans."), page 728, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .
[2] SAP Trans., pages 729-30, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .
[3] SAP Trans., pages 374-75, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .
[4] SAP Trans., pages 422, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .
[5] SAP Trans., page 436, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .

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"The results were still inconsistent between laboratories, or at least that's how the data appeared to us."[6]

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"For practical purposes, the Panel feels that the reliability and the robustness of the assay have not been fully demonstrated for this assay."[7]

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"With respect to test method reproducibility,…there are clearly some unresolved issues with test method repeatability…."[8]

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"So onto the interlab tests that were conducted to assess basically the AOP of AR antagonism with the Vinclozolin study, I think as addressed in Question 5, the Panel really found that this ring test was highly variable and suffered from a lack of consistency and assay performance….So I guess in conclusion, the Panel felt that based on the Vinclozolin study that the data at this time suggests that the assay is not 100 percent transferable."[9]

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"Consequently, the Panel found that the protocol should be reevaluated to determine if clarity could be improved."[10]

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"So while there have certainly been a significant amount of work evaluating the MMT, additional confirmatory studies, using the specific and more detailed guidelines are necessary before the MRT can be adopted as a Tier 2 assay. Overall, it appears that global validation of both the MMT and MRT is rather subjective. So on a global scale, there is little statistical indication of performance parameters needed to establish assay reproducibility and reliability. Additional validation tests would address this issue, and additional interlaboratory studies are needed to demonstrate transferability, reliability and reproducibility."[11]

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"So while the potential exists for the LAGDA to be a powerful diagnostic for thyroid disruption that can impact animal development. No data from the interlaboratory analysis

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[6] SAP Trans., page 498, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .
[7] SAP Trans., page 500, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .
[8] SAP Trans., page 504, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .
[9] SAP Trans., page 510, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .
[10] SAP Trans, page 516, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .
[11] SAP Trans., page 537, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .

support that it has been validated for this purpose."[12]

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"From a statistical point of view, the [LAGDA] protocol is incomplete until we see a power analysis that would help us identify biologically important differences for endpoints."[13]

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"A better method, or better guidelines are needed for histopathological analyses, and that more comprehensive guidelines are needed for animal husbandry….In validating a method that will be applied in different settings it is important to demonstrate that it performs similarly across laboratories. To assess the validity of the assay, it is important that several histopathologists score the same sets of slides and that the results be compared. So given the uncertainty in the reason for the anomalies, it is not currently possible to determine if the liver histopathology is sufficiently robust and repeatable to be used in the Tier 2 assay."[14]

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"So overall, the Panel feels that the reliability and robustness of the [LAGDA] assay, for practical purposes, has not been fully demonstrated for this assay."[15]

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"In summary, once the protocols are clear and the QA/QC parameters are stringently outlined and met by the contract companies running the assays, the LAGDA assay will function towards the stated purpose of a Tier 2 assay. It has potential for understanding the risk of adverse outcomes, however, the variation across laboratories shows that the validation to date has not demonstrated the capacity for consistent dose outcomes leading to clear LOECs at this time."[16]

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"The Panel endorses the use of an invertebrate assay, but as prescribed in the protocols. But feels that without some Tier 1 invertebrate assay that focuses on a chemical's potential to interact with the hormone system in invertebrates or other appropriate invertebrate hormone metrics, either ecdysone or what-have-you, that this Tier 2 test, in some ways, is out of place without having some way to define the potential to effect endocrine systems; otherwise, we're left with testing all compounds with A, E, and T to be tested for an invertebrate endocrine effects."[17]

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[12] SAP Trans., page 551, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .
[13] SAP Trans., page 555 at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .
[14] SAP Trans., pages 562-63, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .
[15] SAP Trans., page 605, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf.
[16] SAP trans., page 614, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .
[17] SAP Trans., pages 622-23, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .

> "We also in public comment had similar concerns about this expressed in some of the comments by the Endocrine Policy Forum. This lack of consistency in response between labs and between F1 and F2 generations and interlab testing undermines not only the complexity of these assays to be able to maybe move a spore as a test-to-test in a multigenerational aspect, but also on the ability to define dose response effectively….The use of the Tier 2 mysid test, without a representative Tier 1 or Tier 2 prescreen to determine endocrine disruptive dose response effects on estrogen, androgen, thyroid controlling processes in human and wildlife has questionable validity and is counterintuitive, considering the current EDSTAC framework."[18]

These and other SAP criticisms of the EDSP Tier 2 tests are also discussed in public comments on the tests. These comments note that the tests do not consistently detect adverse affects; that the tests cannot be performed by some labs; and that the tests' results are not reproducible across various labs.[19]

This ICR Should Not be Submitted or Approved because EPA has Not Demonstrated that the Tier 2 Tests have Practical Utility or that they Meet IQA Guideline Requirements

In order for OMB/OIRA to approve this ICR, EPA must demonstrate that all the EDSP Tier 2 tests will generate information which meets the IQA quality standards of accuracy, reliability, reproducibility, and utility. EPA cannot make this demonstration for tests that have not been demonstrated to generate accurate, reliable, reproducible and useful information. OMB/OIRA's IQA guidance is unambiguous and unequivocal on this requirement:

> "...we note that each agency is already required to demonstrate the 'practical utility' of a proposed collection of information in its PRA submission, i.e., for draft information collections designed to gather information that the agency plans to disseminate. Thus, we think it important that each agency should declare in its guidelines that it will demonstrate in its PRA clearance packages that each such draft information collection will result in information that will be collected, maintained, and used in a way consistent with the OMB and agency information quality standards. It is important that we make use of the PRA clearance process to help improve the quality of information that agencies collect and disseminate. Thus, OMB will approve only those information collections that are likely to obtain data that will comply with the OMB and agency information quality guidelines."[20]

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[18] SAP Trans., pages 624-25, at http://www.epa.gov/scipoly/sap/meetings/2013/june/062513transcript.pdf .

[19] *E.g.*, Endocrine Policy Forum comments, at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2013-0182-0081 .

[20] Page 12 of OMB IQA Guidance at http://www.whitehouse.gov/sites/default/files/omb/inforeg/iqg_comments.pdf .

EPA's own IQA guidelines require that EPA demonstrate to OMB/OIRA and the public that the EDSP Tier 2 tests will generate information that complies with the IQA quality standards:

> "For all proposed collections of information that will be disseminated to the public, EPA intends to demonstrate in our Paperwork Reduction Act clearance submissions that the proposed collection of information will result in information that will be collected, maintained and used in ways consistent with the OMB [IQA] guidelines and these EPA [IQA] Guidelines." [21]

Consequently, before OMB/OIRA can approve an ICR for any EDSP Tier 2 test, EPA has to demonstrate that the test will generate accurate, reliable, reproducible and useful information. [22]

For the reasons stated above, EPA has not made this required demonstration for this ICR. For example, EPA has not demonstrated that these Tier 2 test will consistently detect adverse endpoints. Consequently, EPA has not demonstrated that the tests are useful. As another example, EPA has not demonstrated that the Tier 2 tests meet the IQA Guidelines' reproducibility and reliability requirements.

Independent of the IQA/PRA interface, OMB/OIRA's ICR rules under the PRA require that EPA demonstrate that the EDSP Tier 2 tests will generate accurate, reliable, reproducible and useful information. OMB/OIRA's ICR rules define the term practical utility as "the actual, not merely the theoretical or potential, usefulness of information to or for an agency, taking into account its accuracy, validity, adequacy, and reliability...."[23]

With regard to EPA's duties, the ICR rules state that "[t]o obtain OMB approval of a collection of information, an agency shall demonstrate that it has taken every reasonable step to ensure that the proposed collection of information...has practical utility." [24]

The PRA itself states:

> "Before approving a proposed collection of information, the Director shall determine whether the collection of information by the agency is necessary for the proper performance of the functions of the agency, including whether the information shall have practical utility."[25]

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[21] *E.g.*, EPA IQA Guidelines, Section 6.5, available online at http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf .
[22] *Id.*, Sections V and Appendix A.3.5, at http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf .
[23] 5 CFR §1320.3(l), at http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=ee3022a406e4b99581354a4cd083f29e&rgn=div8&view=text&node=5:3.0.2.3.9.0.48.3&idno=5 .
[24] 5 CFR 1320.5(d)(1)(iii), at http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&SID=ee3022a406e4b99581354a4cd083f29e&rgn=div8&view=text&node=5:3.0.2.3.9.0.48.3&idno=5 .
[25] 44 U.S.C. 3508, at http://www.law.cornell.edu/uscode/text/44/3508 .

With regard to OMB/OIRA's's duties, the ICR rules require that

> "OMB shall determine whether the collection of information, as submitted by the agency, is necessary for the proper performance of the agency's functions. In making this determination, OMB will take into account the criteria set forth in paragraph (d) of this section, and will consider whether the burden of the collection of information is justified by its practical utility."[26]

In other words, OMB/OIRA has an independent, mandatory duty under its own PRA ICR rules to determine whether EPA has produced a public record demonstrating that the EDSP Tier 2 tests covered by this ICR will generate valid, accurate, useful, and reproducible information.

For the reasons stated above, EPA has not produced this required record for the Agency's proposed EDSP Tier 2 ICR.

EPA is Abandoning the EDSP Tier 2 Tests Covered by this ICR for Faster and More Cost Effective Test Methods

EPA plans to abandon the current Tier 1 tests and proposed Tier 2 tests, and EPA plans to replace them with very different tests. EPA told Congress:

> "In FY2012 EPA will begin a multi-year transition from the [EDSP] to validate and more efficiently use computational toxicology methods and high-throughput assays that will allow the Agency to more quickly and cost- effectively assess potential chemical toxicity."[27]

At EPA's request, another SAP recently reviewed and reported favorably on EPA's development of CompTox methods.[28]

EPA should not submit, and OMB/OIRA should not approve, this ICR for an EDSP Tier 2 tests which EPA is abandoning for other tests "that will allow the Agency to more quickly and cost-effectively assess potential chemical toxicity." Clearly, EPA has not taken every reasonable step

[26] 5 CFR § 1320.5(e).

[27] 27 See, *e.g.*, Environmental Protection Agency Endocrine Disruptor Screening Program Comprehensive Management Plan Comprehensive Management Plan (June 2012), page 6, http://www.epa.gov/endo/pubs/EDSP-comprehensive-management-plan.pdf ; and in Endocrine Disruptor Screening Program for the 21st Century: (EDSP21 Work Plan), page 2, available online at http://www.epa.gov/endo/pubs/edsp21_work_plan_summary%20_overview_final.pdf .

[28] The CompTox SAP's report is available as Document EPA-HQ-OPP-2012-0818-0037 at http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0818-0037 .

to ensure that the EDSP Tier 2 tests covered by this ICR are the least burdensome necessary, and these tests are not necessary for the proper performance of the functions of the agency.[29]

We thank you for the opportunity to submit these comments.

The Center for Regulatory Effectiveness
www.thecre.com

[29] See 44 U.S.C. 3508, at http://www.law.cornell.edu/uscode/text/44/3508 ; 5 CFR 1320.5(d), at http://www.law.cornell.edu/cfr/text/5/1320.5 .