Dear Ms. Robbins:

RE: Information Collection Request Submitted to OMB for Review and Approval; Comment Request; ICR Request for List 1 Chemicals; Tier 2 Data Collection for Certain Chemicals Under the Endocrine Disruptor Screening Program; Docket ID EPA-HQ-OPPT-2013-0171.

These comments are submitted on behalf of People for the Ethical Treatment of Animals (PETA), Physicians Committee for Responsible Medicine (PCRM), and The Humane Society of the United States (HSUS), national animal protection and scientific advocacy organizations, which together represent more than thirteen million members and supporters who share the common goal of promoting reliable and relevant regulatory testing methods and strategies that protect human health and the environment while reducing, and ultimately eliminating, the use of animals.

This is a new Information Collection Request (ICR) from the Environmental Protection Agency (EPA) to issue Tier 2 test orders for List 1 chemicals (OMB Control No. 2070-New; EPA ICR No. 2479.01) and, thus, represents the next phase for those chemicals that were screened under Tier 1 of the current Endocrine Disruptor Screening Program (EDSP). We previously commented on this new ICR in August 2013 when it was first submitted to the Office of Management and Budget (OMB)\(^1\). At that time we considered the ICR request by the EPA to be premature for several reasons. First, a number of significant modifications to the Tier 2 ecotoxicity test protocols – intended to enhance performance and relevance – had been recommended by the FIFRA Science Advisory Panel (SAP) during a meeting held in June 2013 to review the inter-laboratory validation studies for these tests. Second, the EPA’s 2011 weight of evidence (WoE) guidance document\(^2\) lacked transparency and could not be used in a standardized manner to evaluate results of Tier 1 testing, along with any Other Scientifically Relevant Information (OSRI) submitted by the test order recipients, to determine which chemicals would require further testing under Tier 2. Recommendations for improving the EPA’s WoE approach had been provided by the FIFRA SAP during its July-August 2013 meeting and had not yet been incorporated into the guidance. Finally, the practical utility\(^3\) of the

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1 78 FR 37803, June 24, 2013.
2 Available: [http://www.regulations.gov/#/documentDetail;D=EPA-HQ-OPPT-2010-0877-0021](http://www.regulations.gov/#/documentDetail;D=EPA-HQ-OPPT-2010-0877-0021)
3 Practical utility (along with burden imposed by the information collection on the public) are the two main areas that OMB/OIRA is responsible for reviewing to ensure that the information to be collected is necessary and not duplicative of other government actions and that the cost of draft regulations (and ICRs) do not exceed the benefits.
Tier 2 methods was in question due to their apparent inability to provide reliable and relevant information that could be used confidently in future risk assessment and regulatory decision-making. The excessive complexity and duration of the proposed Tier 2 assays, as well as the failure of the lab ring testing to deliver consistently reproducible results suggested that it would be extremely difficult for any but the most experienced laboratories to meet the rigorous standards required to properly conduct them.

In its Response to Public Comments on the Public Review Draft of the Information Collection Request (ICR) entitled: "Tier 2 Testing of Certain Chemicals under the Endocrine Disruptor Screening Program (EDSP)"\(^4\), the EPA addresses the issues raised in the comments on the initial ICR in 2013. With respect to the modifications to the Tier 2 protocols recommended by the FIFRA SAP, we acknowledge that many of these were made. Notably, the Medaka Multigeneration (2 ½ generations) study was revised and is now an extended one-generation study using a somewhat smaller number of fish than the original study design.

The Japanese quail two-generation reproduction test was modified to include fewer endpoints, resulting in a small reduction of animals used. We are pleased to see that language was added to the guidance that clarifies the termination point of the study at measurement of the 14-day survival of the F2 generation, effectively turning this test into an extended one-generation test, as we had recommended, with the decision to extend breeding to the F2 generation being optional\(^5\). The number of birds used, while reduced, still remains quite large, however.

The larval amphibian growth and development assay (LAGDA) was recently adopted at OECD as Test Guideline (TG) 241 and is described as enabling “…measurement of a suite of other endpoints that allows for diagnostic evaluation of suspected endocrine disrupting chemicals”\(^6\). However, the TG states: “Due to the limited number of chemicals tested and laboratories involved in the validation of this rather complex assay, especially inter-laboratory reproducibility is not documented with experimental data so far, it is anticipated that when a sufficient number of studies is available to ascertain the impact of this new study design, the Test guideline will be reviewed and if necessary revised in light of experience gained.” We still feel that the LAGDA assay is not sufficiently tested or reliable enough to be used in Tier 2 testing, and therefore the practical utility of any results generated by it remains suspect. This creates a situation that risks the use of large numbers of animals to collect information of uncertain utility. The List 1 chemicals that are slated to be tested using the LAGDA, in our opinion, will be part of an ongoing validation of this method and may pose the unreasonable burden on test order recipients of determining whether or not this assay is, in fact, fit for the purpose for which it is intended. Efforts should be made to avoid the EPA having to revisit a final test guideline to improve it, as

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this imposes a cost and burden on an already resource-strained agency as well as necessitates yet another public comment period.

This ICR does not appear to cover testing using the comparative thyroid assay (CTA), which was recommended for four List 1 chemicals in the Tier 1 WoE reports\(^7\). This test is not one of the four tests listed in the Tier 2 ICR. It does not have a formal test guideline, nor has it been validated for EDSP through typical processes of peer-review, ring-testing or meeting performance standards. As the EPA has not included any discussion of the CTA in the Tier 2 ICR, we believe the Agency should clarify how it intends to handle a data request using this assay. Similarly, the Tier 1 WoE report for one List 1 chemical recommends a special study on the male reproductive system be conducted, but again, we question how this will relate to the Tier 2 testing ICR and cost/burden calculations. Alternatively, while the ICR does not mention the CTA, it does includes cost estimates for the rat extended one-generation study (EOGRTS) (listed as Reproduction and Fertility Effects in Attachment D), which none of the Tier 1 WoE reports recommends be conducted.

We are pleased to note that in its Response to Public Comments, the EPA agreed with our suggestion that the agency consider OSRI submissions in Tier 2 testing and that OSRI submissions have been included in EDSP ICR burden calculations. However, we are not aware of a revised EDSP WoE guidance document for evaluating Tier 1 data and submitted OSRI placed in the public docket EPA HQ OPPT 2010 0877, as the Response to Public Comments indicates. As far as we could tell, the document that is there is the same version (September 14, 2011) we reviewed and had issues with previously.

The ICR continues to estimate an upper limit of 26 chemicals that might proceed to Tier 2 testing. With the release of Tier 1 WoE reports from the 52 List 1 chemicals\(^7\), the actual number of chemicals identified for Tier 2 testing is only 18. We question why the ICR continues to use an estimated number of chemicals rather than the actual number when calculating burden.

As we have mentioned before, application of fit-for-purpose Integrated Approaches to Testing and Assessment (IATA) encourages the maximal use of existing information by organizing it into a “mode of action” framework (such as the Adverse Outcome Pathway approach) and identifying what key events along the causal pathway lead to some adverse regulatory outcome of concern. Assays measuring discrete responses at the cellular or organ/tissue level may be able to satisfy the needs of EDSP Tier 2, rather than conducting generational studies using animals. If additional data are still needed, we would continue to encourage the EPA to consider the use of other, shorter term, more specific and less animal-intensive tests in lieu of proposed Tier 2 assays. In particular, we have been made aware of a test proposed by Dow Chemical that provides comparable data to the CTA but uses far fewer animals. We would welcome the opportunity to follow-up with you and our colleagues in industry to discuss specific, more appropriate approaches that may be able to satisfy the data needs of EDSP Tier 2.

Thank you for the opportunity to comment.

\(^7\) Available: [http://www2.epa.gov/ingredients-used-pesticide-products/endocrine-disruptor-screening-program-tier-1-assessments](http://www2.epa.gov/ingredients-used-pesticide-products/endocrine-disruptor-screening-program-tier-1-assessments)
Sincerely,

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