August 23, 2013

Teresa Green
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Environmental Protection Agency
1200 Pennsylvania Ave., N.W.
Washington, DC 20460–0001

Dear Dr. Green:

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.

General Comments

This is a new ICR for Tier 2 testing of List 1 chemicals (OMB Control No. 2070-New; EPA ICR No. 2479.01) and represents the next phase for those chemicals that were screened under Tier 1 of the existing Endocrine Disruptor Screening Program (EDSP). Submission of this new ICR to the Office of Management and Budget (OMB) by EPA is premature for a number of reasons as described below.

Tier 2 tests are expensive, long-term, animal intensive studies that must be conducted by experienced laboratories capable of meeting high quality standards. Recent validation efforts have shown that the current proposed Tier 2 ecotoxicity tests are not reproducible; these studies have also not demonstrated sensitivity or specificity with regard to endocrine effects. In addition, preliminary inter-laboratory studies identified many opportunities to introduce error into the tests that can lead to confounding results, demonstrating that the protocols and perhaps the methods themselves require further modification and refinement. A FIFRA Science Advisory Panel (SAP) meeting held in June 2013 to review the inter-laboratory validation studies for the Tier 2 ecotoxicity tests revealed serious issues with these assays, and numerous recommendations were made by the SAP to modify and improve these tests before test order recipients are required to conduct them, which have yet to be acted upon by EPA. In addition, EPA has not yet clearly and transparently demonstrated how it will use weight-of-evidence (WoE) to select chemicals for further testing; such information has been requested from OMB in the Terms of Clearance for
the previous ICR for Tier 1 testing,\(^1\) from EPA’s Office of the Inspector General (OIG),\(^2\) and from Congress.\(^3\).

**Comments in Response to Specific Requests for Information in the Federal Register Notice: 78 FR 37803-804**

Our primary concern is the practical utility of this program: information generated should be done in the most efficient manner possible and used in risk assessment for protecting human and environmental health. Our comments are therefore directed to information requests 1 and 3, which are related:

1. 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.
2. Enhance the quality, utility, and clarity of the information to be collected.

**Need for additional Tier 2 information on List 1 chemicals: maximal use of existing information**

Of the 52 List 1 chemicals that were tested in Tier 1 assays, 50 of them are pesticides. For registration, pesticides currently are often subject to dozens of separate animal tests, including reproductive and chronic/lifecycle studies in rodents, fish and birds, as well as metabolism and pharmacokinetics studies.\(^4\) These tests kill thousands of animals and include many of the same endpoints addressed in the proposed EDSP Tier 2 tests.

For example, Reproduction and Fertility effects (OPPTS 870.3880) and Prenatal Developmental Toxicity (OPPTS 870.3700) tests are required for both food-use and non-food-use pesticide Technical Grade of the Active Ingredients (TGAI). In addition, reproductive effects in other species are available for many List 1 chemicals. Proposed EDSP Tier 2 screens would appear to provide little or no value-added for pesticide chemicals.

As part of the submission of Tier 1 information, EPA was instructed by OMB to review and “accept…to the greatest extent possible,” Other Scientifically Relevant Information (OSRI),\(^5\) EPA agreed to consider OSRI, which it defined to be “…information that informs the determination as to whether the substance may have an effect that is similar to an effect produced by another substance.”

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3 House of Representatives Report No. 111-180 at 105 (2009). “engage in a timely re-evaluation of the battery of screening, replacing outdated ones with updated, more efficient screens that have been validated (for example, a recombinant receptor assay to replace the cytosolic receptor assay for estrogen receptor binding)” and “develop and publish criteria for evaluating the results of Tier I screening and determining whether a chemical should undergo Tier II analysis within one year of enactment.”
4 72 FR 60934, October 26, 2007: EPA 40 CFR Parts 9 and 158: Pesticides; Data Requirements for Conventional Chemicals.
5 In the above mentioned Terms of Clearance OMB stated: “EPA should promote and encourage test order recipients to submit Other Scientifically Relevant Information (OSRI) in lieu of performing all or some of the Tier I assays, and EPA should accept OSRI as sufficient to satisfy the test orders to the greatest extent possible.”
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.” EPA’s 2009 guidance on consideration of OSRI
specifically mentions that guideline tests conducted under 40 CFR Part 158 data requirements to
support pesticide registration may be considered by EPA.7

The acceptance of OSRI by EPA during the Tier 1 information request was minimal, primarily
limited to data that was identical or nearly identical to that which would have been obtained by
performing one of the 11 Tier 1 assays. EPA did not in its review apply a true weight-of-
evidence approach in considering all of the available information. A series of publications that
discuss this issue are in preparation, 8 and it is hoped that EPA will revise and expand its
application of WoE, and therefore its use of existing data, in future evaluations. In addition, the
use of OSRI should not be limited to fulfilling Tier 1 data requirements, but should be
considered in the overall purpose of the EDSP, which is to regulate chemicals based on their
potential to cause endocrine-related adverse effects. Much of the information submitted to EPA
was from Part 158 studies; this information should be taken into account on a chemical-by-
chemical basis before requesting additional information, Tier 2 or otherwise.

Practical utility: agency decisions based on EDSP information

OMB’s Terms of Clearance for the 2009 ICR for Tier 1 information mentioned above also states,
“…in order to ensure that EPA has maximized the practical utility of the Tier I assays as the
program moves forward, EPA should ensure sufficient opportunity prior to submission of any
revision to this collection for public comment and peer review of the EPA tools to be developed
to guide agency decisions on whether a chemical must proceed to Tier II, including the Weight
of the Evidence Approach and Standard Evaluation Procedures.” In addition, the House
Appropriations Committee for the Interior and Environment FY 2010 report that directed EPA
to: “develop and publish criteria for evaluating the results of Tier 1 screening and determining
whether a chemical should undergo Tier 2 analysis within one year of enactment. The process
should allow for public input.”9

EPA–HQ–OPPT–2007–1080; Endocrine Disruptor Screening Program; Policies and Procedures for Initial
Screening.
7 USEPA. 2009f. EPA’s approach for considering Other Scientifically Relevant Information (OSRI) under the
8 For example, proceedings from the TERA-sponsored workshop: Lessons Learned, Challenges, and
Opportunities: The US Endocrine Disruptor Screening Program, April 23 – 25, 2013; Bishop and Willett, The
Use of Other Scientifically Relevant Information in the US EPA Endocrine Disruptor Screening Program,
submitted.
EPA has issued guidance on WoE and convened an SAP meeting July 30 – August 1, 2013 to review EPA’s WoE approach to determining if a chemical had the potential to interact with the endocrine system; however, this discussion explicitly excluded discussion of decision-making, including whether to move to Tier 2 testing. Five List 1 chemical case studies were presented: four used a combination of Tier 1 assay results and other scientifically relevant information (OSRI), such as data from Part 158 guideline studies for pesticide registration, and one case study relied exclusively on OSRI. The primary charge for the SAP at that meeting was to comment on how EPA was interpreting the various results and using them in a WoE approach to make evaluate a chemical’s ability to interact with the endocrine system.

These case studies offered the potential opportunity to illustrate how EPA proposes to use WoE to justify the need for additional testing and demonstrate how the additional testing would be used: e.g., to better characterize chemicals that displayed strong positive results, or to further investigate equivocal cases, or both. However, EPA specifically excluded this essential discussion.

Once EPA’s WoE analysis of the remaining 47 chemicals is complete, EPA should be in a better position to evaluate its WoE process and indicate to stakeholders how it intends to select chemicals for further testing. In addition, the recommendations of the SAP for the WoE approach will be available in October and should be fully considered by EPA and incorporated into its process before moving ahead to Tier 2.

In the meantime, there is currently no guidance or explanation as to how EPA will decide when to proceed to Tier 2, and if so, which Tier 2 information might be requested. Based on recommendation from several SAP attendees as well as OMB and Congress, this critical missing process must be addressed before Tier 2 information is requested.

Ability of proposed Tier 2 assays to provide useful information

In the support materials provided and reviewed at the SAP meeting on proposed EDSP Tier 2 Ecotoxicity Tests held on June 25-28, 2013, it was apparent that the ability of the Tier 2 ecotoxicity tests to demonstrate reliability and relevance is suspect. The results of the inter-laboratory validation studies clearly demonstrated that, due to the complexity and duration of these tests, their reliability is questionable. Numerous opportunities exist for introduction of error and variability that could confound the interpretation of findings. Accordingly, there is a high potential for inexperienced laboratories to generate poor quality data, resulting in the repeating of tests that will kill many more animals. One of the most obvious issues noted in all of the inter-laboratory comparisons was the lack of consistency across labs in identifying effects. The avian Tier 2 inter-laboratory study used a single reference chemical test substance, the AR antagonist vinclozolin that demonstrated few treatment-related effects. However, there were several potential sources of variation in results noted, such as the strain of the bird, which could lead to serious problems with interpretation of results. The fish inter-laboratory comparison also used vinclozolin as the single reference substance for the inter-lab study and the only significant conclusion regarding effects across labs seemed to be that all three labs did not see decreased reproduction, making evaluation of the test’s reproducibility, sensitivity and/or specificity impossible. In the case of the amphibian inter-lab comparison where two different reference
chemicals were used, there also were few instances where all labs consistently reported the same significant finding. Because these assays have not been demonstrated to provide consistent or reliable information, they should not be used in assessing chemicals at this time. Furthermore, the absence of effects in tests of known endocrine-active substances calls into question the ability of these assays to provide information that can be used in risk assessment of other potential endocrine-active substances.

Finally, in light of the extensive information available for most of the List 1 chemicals, it is not clear that requiring additional Tier 2 testing would enhance the regulation of any of the chemicals. It is unlikely, given their performance, that the currently proposed Tier 2 tests will provide more useful information than what is already available from Part 158 guideline studies for pesticide registration.

**Modification of EDSP Tier 2 Ecotoxicity Tests based on FIFRA Science Advisory Panel (SAP) Reviews**

The role of the SAP includes providing advice to EPA on the appropriateness of the science used to make regulatory decisions. This feedback is critical at this stage of the EDSP since Tier 1 data are now available for the first 52 chemicals, registrants and contract labs have had some experience with these assays, and EPA has had the opportunity to refine its policies and guidance with respect to the use of this information in regulating chemicals. EPA convened SAP reviews four times this year, covering topics related to the EDSP including: a computational toxicology/in vitro assay expert system for prioritizing chemicals that may interact with the estrogen system (January); a review of the performance and relevance of the Tier 1 assays (May); a review of the validation studies for Tier 2 ecotoxicity (June), and; a review of EPA’s method for using WoE to evaluate the results of Tier 1 screening and determine whether or not a chemical has the potential to interact with the endocrine system (July). The substantial feedback from the SAP meeting on performance and validation of the Tier 2 ecotoxicity assays is integral to modifying these tests. The final SAP report of this review will not be issued until late September at the earliest. If EPA intends to use those recommendations to improve its Tier 2 approach and modify the assays accordingly, as it must do if its request for peer review by the SAP is to be considered something more than just lip service, more time will be needed to accomplish this. We question, then, why EPA is submitting a Tier 2 ICR to OMB now when this important task has yet to be completed.

**Consideration of other, shorter term, more specific tests in lieu of proposed Tier 2 assays**

At the June SAP meeting and elsewhere, there has been discussion by EPA and others of possibly using intermediate, shorter-term tests – a “Tier 1.5” – to better determine if a chemical was truly displaying an endocrine effect, before deciding if full multi-generation tests will be required. Further exploration of this possibility is warranted before issuing full Tier 2 testing orders for the List 1 chemicals.

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10 For example see Presentations given at the previously mentioned workshop, Lessons Learned, Challenges, and Opportunities: The US Endocrine Disruptor Screening Program, April 23 – 25, 2013: [http://www.tera.org/peer/edsp](http://www.tera.org/peer/edsp) (accessed 23 August 2013).
Summary

Several critical pieces of the EDSP program are still missing or need to be improved, including:

1) Full consideration of existing data to fulfill information needs (including Tier 2);
2) Explanation and weight-of-evidence guidance on how Tier 1 (or any other) information will be used to determine which chemicals proceed to Tier 2, and which Tier 2 information may be requested;
3) The availability of reliable, reproducible, endocrine-sensitive and relevant tests for further evaluation (whether these are the proposed Tier 2 tests or other relevant tests).

Until all these considerations have been made and pieces put in place, submission of a List 1 Tier 2 ICR is premature.

Thank you for the opportunity to comment.

Sincerely,

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