

Petition to Demonstrate Paperwork Reduction Act Compliance of the Endocrine Disruptor Screening Program

SUBMITTED TO

U.S. Environmental Protection Agency

SUBMITTED BY

*Chemical Producers & Distributors Association
Halogenated Solvents Industry Alliance, Inc.
People for the Ethical Treatment of Animals*

December 7, 2011

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Cc: Louise Wise, Acting Deputy Assistant Administrator, OCSPP, EPA

Dear Dr. Bradbury, Ms. Cleland-Hamnett and Mr. Sanders:

The Chemical Producers & Distributors Association, the Halogenated Solvents Industry Alliance, Inc. and People for the Ethical Treatment of Animals ("the Petitioners") submit this petition to ask the Environmental Protection Agency (EPA or Agency) to fully comply with the Paperwork Reduction Act

(PRA)¹ as specified in the Office of Management and Budget's (OMB) Terms of Clearance (TOC)² for the Information Collection Request (ICR) associated with 67 pesticide chemicals under the Endocrine Disruptor Screening Program (EDSP) before issuing test orders for Tier 1 screening of additional chemicals.

I) Introduction

In October 2009, EPA began issuing test orders for Tier 1 screening of 67 pesticide chemicals (List 1) under the Federal Food, Drug and Cosmetic Act (FFDCA).³ EPA indicated that all screening results must be submitted within two years from the date a test order was issued or, for the List 1 chemicals, by February 2012. Under the PRA information collection regulations ("Information Collection Rule"), EPA is required to demonstrate that any proposed collection of information "is not duplicative of information otherwise accessible to the agency" and that it "has practical utility."⁴ In approving the ICR for Tier 1 screening of List 1 chemicals, the OMB, under authority of the PRA, attached a notice of TOC directing the Agency to demonstrate the maximum practical utility of the information collection and evaluate the sufficiency of other scientifically relevant information (OSRI) on these chemicals prior to requiring the public to screen additional chemicals.

The Agency has not complied with these requirements and, by extension, cannot meet its FFDCA obligation to rely on science.

Assertions:

EPA has failed to comply with the PRA under Tier 1 screening of the EDSP:

- The Agency has not demonstrated that the information collection is non-duplicative of information to which it may already have access.
- The Agency has not demonstrated that the Tier 1 assays have practical utility by providing the scientific support on which to make the necessary distinction that a chemical "may" or "may not" have the potential to interact with the endocrine system.⁵

Resolution:

To ensure compliance with the mandates of the PRA, EPA must demonstrate that any proposed collection of information is not duplicative of information otherwise accessible to the agency, and demonstrate the practical utility of EDSP Tier 1 screening by reviewing and revising the Tier 1 Battery before requiring screening of additional chemicals.

¹ 44 U.S.C. §§ 3501 *et seq.*

² Office of Management and Budget. 2009. *Notice of Office of Management and Budget Action, ICR Reference Number 200904-2070-001; New ICR 2070-0176.*

³ 21 U.S.C. § 346(p)(3); FDCA § 408(p)(3).

⁴ 5 C.F.R. § 1320.5(d)(ii) and (iii).

⁵ Comments submitted by the Chemical Producers & Distributors Association *et al.*, available in Docket ID Number EPA-HQ-OPP-2007-1081-0020.

II) EPA must demonstrate that the information collected during Tier 1 screening of the EDSP is not duplicative of already existing information.

To obtain OMB approval, EPA must “demonstrate that it has taken every reasonable step to ensure that the proposed collection of information ... [i]s not duplicative of information otherwise accessible to the agency.”⁶ EPA incorrectly interprets the prohibition on duplication in FFDCA as being the same “duplicative” prohibition in the PRA. The FFDCA provision restricts EPA from collecting newly duplicative information,^{7,8} whereas the PRA requires EPA to avoid duplication of existing data. The latter prohibition is considerably broader.

Under the PRA, duplication exists if the need for the proposed collection can be served by information “otherwise reasonably accessible to the agency.”⁹ At a minimum, this includes vast quantities of test data that EPA already possesses, much of which has been provided by chemical manufacturers under the Toxic Substances Control Act¹⁰ and pesticide registrants under the Federal Insecticide, Fungicide and Rodenticide Act.¹¹ However, it appears that EPA did not thoroughly evaluate the feasibility of using existing information, whether held by the Agency or by other federal agencies, prior to sending Tier 1 test orders to List 1 chemical recipients.

OMB directed consideration of OSRI under the ICR Terms of Clearance.

1) EPA should accept OSRI as sufficient to satisfy the test orders to the greatest extent possible.

The OMB Information Collection Rule states 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...”¹² and that OMB has the sole authority to determine “whether the burden of the collection of information is justified by its practical utility.”¹³ Therefore, OMB has oversight authority for interpreting the adequacy of federal agencies’ compliance with the PRA’s provisions and the ICRs they submit.

OMB attempted to address the PRA compliance issues via conditional TOC on the 2009 EDSP List 1 ICR approval.¹⁴ The text implicitly and undeniably recognizes that EPA did not adequately demonstrate the information to be collected in Tier 1 screening of List 1 chemicals would not be duplicative of existing information or demonstrate that it would have practical utility, and directed EPA to use the information collected and evaluated on

⁶ 5 C.F.R. § 1320.5. The responsible agency official must certify this “and provide a record supporting such certification” (21 C.F.R. § 1320.9).

⁷ 21 U.S.C. § 346a(p)(5)(B).

⁸ Similarly, the Agency improperly uses a narrow definition of duplicative testing for the screening of List 1 chemicals: “the term ‘duplicative testing’ applies when more than one company conducts the exact same assay on the exact same substance.” EPA Response to CroLife Petition available in Docket ID Number EPA-HQ-OPP-2007-1080.

⁹ 44 U.S.C. § 3506(c)(3)(B).

¹⁰ 15 U.S.C. §§ 2601 *et seq.*; TSCA §§ 2 *et seq.*

¹¹ 7 U.S.C. §§ 136 *et seq.*; FIFRA §§ 2 *et seq.*

¹² 5 CFR § 1320.5(e).

¹³ *Id.*

¹⁴ *Supra* note 2.

the List 1 chemicals before expanding the program to include screening of additional chemicals. The TOC specifically states that:

“OMB appreciates the continuing dialog with respect to the practical utility of the Tier 1 battery of EDSP assays and the role that the results from these first 67 chemicals will play in ensuring practical utility for subsequent groups of chemicals. Nonetheless, ***under the principles of the PRA, 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 1 assays, and EPA should accept OSRI as sufficient to satisfy the test orders to the greatest extent possible.***”

For this reason, and to further validate EPA’s burden estimates, OMB requests that EPA provide a report re-estimating the burden of this information collection based on the responses to the Tier 1 test orders, including the use of cost-sharing and data compensation, ***the submission and acceptance of existing data and OSRI, and description of any instances in which submission of OSRI was deemed insufficient to satisfy the testing order.*** OMB requests this report prior to or at the same time of submission of revision of this information collection to cover additional chemicals.”
[emphasis added]

2) EPA rejected the majority of the OSRI submitted on List 1 chemicals.

Although EPA provided List 1 test order recipients with the required opportunity to submit existing data or OSRI in lieu of conducting some or all of Tier 1 Battery screening assays,¹⁵ the Agency did not clearly articulate its basis for evaluating OSRI submissions for the List 1 chemicals and did not clearly outline its policy goals concerning OSRI. In November 2010, EPA stated that it would review submitted existing data or OSRI “to determine whether a submission provides sufficient information to allow EPA to identify substances that have the potential to interact with the estrogen, androgen, or thyroid systems. In making this judgment, EPA compares the ability of OSRI to answer the question with the types of information we would get from the assays in the Tier 1 battery.”¹⁶ The Agency also noted that it would use a “weight-of-the-evidence approach in review of OSRI.”

The Agency published its final Weight-of-Evidence (WoE) Guidance (“Guidance”) in September 2011. The Guidance does not set forth, in a transparent, reproducible, and consistent way, how EPA plans to determine whether existing data or OSRI satisfy EPA’s stated purpose for the information: to enable it to discriminate scientifically between substances that “may” or “may not” have the potential to interact with the endocrine system. Contrary to the OMB TOC, EPA discourages the submission of valid scientific data in the Guidance and categorically dismisses such information by asserting that “to comply with the test orders, recipients must submit the results of EDSP Tier 1 screening.”

¹⁵ OMB stated in the Terms of Clearance: “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 1 assays, and EPA should accept OSRI as sufficient to satisfy the test orders to the greatest extent possible.”

¹⁶ EPA Response to Croplife America et al., Nov 17, 2010 available in Docket Number EPA-HQ-OPP-2009-0634-0233.

All initial List 1 chemical test order responses, including OSRI, were due to the Agency by spring of 2010, well before the Guidance was published. The OSRI submitted with responses to these test orders was apparently accepted or rejected without the benefit of review under the Agency's Guidance and as of August 2011, the Agency had rejected 323 of the 412 (78%) OSRI submissions reviewed.¹⁷ Without having published the Guidance prior to its review of OSRI submitted in response to List 1 chemical test orders, the Agency cannot justify the OSRI determinations it made at that time. It is obvious from EPA's dismissive treatment of OSRI for List 1 chemicals that the body of knowledge for a particular chemical had not been fully considered in a WoE approach, nor had a consistent weighting scheme been applied to assess the quality of the studies and results submitted.

3) Non-duplication must be demonstrated in order to justify animal testing in EDSP screening.

EPA, as a charter member of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), is committed to "eliminate unnecessary duplicative efforts" and "reduce, refine, or replace the use of animals in testing, where feasible."^{18,19} Consistent with Congress' directive in the PRA to avoid collecting duplicative information,²⁰ the OMB directive to promote and encourage the use of OSRI, the statutory mandates to reduce animal testing,²¹ and the requirements of the PRA, EPA must ensure through transparent and reproducible review of existing data that the information collection is not duplicative of information "otherwise reasonably accessible to the agency." Therefore, the Agency must demonstrate that its "may" and "may not" administrative decisions on the Tier 1 information: (1) cannot be made without the use of animal testing, and (2) cannot be made based on OSRI.

III) EPA must demonstrate the practical utility of the information collected in Tier 1 screening of the EDSP.

The Information Collection Rule defines 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, and the agency's ability to process the information it collects"²² FFDCA § 408(p) directs EPA to establish the EDSP relying on science (*i.e.*, based on "appropriate and validated test systems") to discern substances that "may" have the potential to interact with one or more components of the endocrine system from substances that "may not" have this potential. Each transparent and reproducible "may" and "may not" administrative decision made by EPA must be based on a solid scientific foundation to have practical utility.

¹⁷ Willett CE, Bishop PL, Sullivan KM. 2011. A Strategy for Reducing Animal Use in the U.S. EPA's Endocrine Disruption Screening Program. 8th World Congress on Alternatives & Animal Use in the Life Sciences, August 21 – 25, Montreal, Canada.

¹⁸ 42 U.S.C. § 2851 *et seq.*; ICCVAM Authorization Act of 2000.

¹⁹ *Id.* at § 2851-4(b). According to the Act, as a Federal Agency, EPA "shall promote and encourage the development and use of alternatives to animal test methods (including batteries of tests and test screens), where appropriate, for the purpose of complying with Federal statutes, regulations, guidelines, or recommendations (in each instance, and for each chemical class) if such test methods are found to be effective for generating data, in an amount and of a scientific value that is at least equivalent to the data generated from existing tests, for hazard identification, dose-response assessment, or risk assessment purposes."

²⁰ 21 U.S.C. § 3506(c)(3)(B).

²¹ 42 U.S.C § 2851-4(e); NIH Revitalization Act of 1993 (P.L. 103-43).

²² 5 C.F.R. § 1320.3(1).

To demonstrate practical utility under the PRA, the information collected through the EDSP Tier 1 Battery assays must provide a sufficient scientific basis on which to make administrative decisions.

During the development and implementation process for Tier 1 screening under the EDSP, serious scientific concerns were raised regarding the appropriateness, suitability and validation status of the assays included in the EDSP Tier 1 Battery²³ and the practical utility of the information provided by the collection.²⁴ In addition, Congress and EPA's own Office of the Inspector General (OIG) have instructed EPA to improve the EDSP by reviewing and revising the Tier 1 assays to ensure maximal practical utility of the information derived from EDSP-mandated testing. For instance, the OIG specifically recommended in its May 2011 review report²⁵ that EPA: (1) develop and publish a standardized methodology for prioritizing the universe of chemicals for screening and testing, (2) finalize specific Tier 1 and Tier 2 criteria to evaluate testing data, (3) develop performance measures, (4) develop a comprehensive management plan, and (5) hold annual program reviews.

Congress has also expressed its concern regarding the adequacy of the Tier 1 screening battery by providing guidance to EPA in both 2010 and 2011 House Appropriations Committee Reports. The report language for Fiscal Year (FY) 2010²⁶ instructed EPA to re-evaluate and revise, as needed, the Tier 1 battery. Additionally, the report language for FY 2012²⁷ recognized that technical advances have occurred since the Tier 1 Battery was developed and need to be considered. The report instructed EPA to: (1) take steps to ensure EDSP testing minimizes the use of animals and considers existing knowledge and targeted testing, and justifies use with appropriate statistical considerations; (2) evaluate the Tier 1 test chemicals in ToxCast assays and determine their performance in endocrine relevant estrogenic, androgenic, and thyroid assays to refine toxicological prediction models; and (3) utilize high throughput *in vitro* screening assay results to prioritize Tier 1 chemical testing and to inform future endocrine disruptor investigations. These instructions are consistent with a general policy shift at EPA toward predictive human health and environmental protection.²⁸

²³ Comments submitted by People for the Ethical Treatment of Animals *et al.*, Crop Life America, the American Chemistry Council, the Center for Regulatory Effectiveness, available in Docket ID no. EPA-HQ-OPP-2008-0012.

²⁴ Comments submitted by the Chemical Producers & Distributors Association *et al.*, available in Docket ID Number EPA-HQ-OPP-2007-1081-0020.

²⁵ OIG Report, available at <http://www.epa.gov/oig/reports/2011/20110503-11-P-0215.pdf>.

²⁶ H.R. Report No. 111-180 at 105 (2009), directing EPA to "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."

²⁷ H.R. Report No. 112-151 (2011), "Recognizing ToxCast has great promise to streamline and significantly increase the throughput of the Endocrine Disruptor Screening Program (EDSP), the Committee directs EPA to accelerate the evaluation, validation and implementation of the endocrine-relevant ToxCast assays. The Agency shall (1) in future EDSP Test Orders, use a targeted approach and adjust individual Test Orders in response to scientifically credible requests by taking existing data into account, and using information from valid *in vitro* assays or computer models, including ToxCast, as appropriate; and (2) use a peer consultation process to revise the EDSP weight of the evidence guidance to assure a systematic and consistent approach for evaluating other scientifically relevant information and EDSP results. These two activities shall include public comment and publication of Agency responses."

²⁸ This approach has been articulated in a 2007 report from the National Research Council (Toxicity Testing in the 21st Century: a Vision and a Strategy. National Academies Press, Washington, DC.), has been adopted by EPA in their 2009 Strategic Plan for Evaluating the Toxicity of Chemicals, and is in a large part the impetus for a recent departmental reorganization of EPA's Office

1) EPA has not demonstrated the scientific reliability and appropriateness of the current Tier 1 Battery assays.

It has been repeatedly pointed out to EPA that the Tier 1 assays are not reproducible or sufficiently specific to adequately identify chemicals that are capable of interacting with estrogen, androgen or thyroid hormone receptors or systems.^{29,30,31} EPA has responded to some of these concerns;³² however, several of the responses highlight, rather than mitigate, many of the concerns. For example, in response to concerns about inter-laboratory variability (reproducibility) of the amphibian metamorphosis assay and the male and female pubertal assays, EPA acknowledged that, while different labs did indeed obtain different results, “the overall trend was consistent among laboratories.” This admission is disconcerting since a single chemical will be screened in Tier 1 assays in a single lab and there will be no “overall trends” available for comparison.

Likewise, in response to concerns about specificity (*i.e.*, the ability to distinguish true negatives from true positives) of several of the assays, EPA argued that, “[b]ecause the Tier 1 assays will operate in a battery and will only identify a chemical’s potential to interact with the endocrine system, rather than to predict actual effects, the rate of false positives and negatives for individual assays in the battery is not an essential part of validation.” This reasoning is deeply flawed. Logically, if a battery consists of multiple assays of low specificity, the combined results will be heavily skewed toward false positives. For several of the assays, all chemicals tested in the validation studies gave some positive response, including some of the negative controls. This calls into question the ability of this testing battery to distinguish positives from negatives, and thus the overall practical utility of the battery.

2) Practical utility of the List 1 information cannot be demonstrated without the use of a scientifically sound weight of evidence approach that is applied to all information collected.

OMB, OIG and Congress collectively instructed EPA to provide decision criteria and guidance for Tier 1 testing and decision-making. On September 28, 2011, EPA published the Guidance that contractors and Agency reviewers are to use to consider all screening information collected on the List 1 chemicals. While this 47-page document is certainly an improvement over the 8-page draft issued for public comment in November 2010,³³ it remains a self-described “general” guidance document that lacks the rigor and specificity required to provide a transparent, consistent review of data. The Guidance addresses assays and

of Research and Development (<http://www.epa.gov/ord/priorities/chemicalsafety.htm>) as well as a collaboration between EPA, the National Institutes of Health, and the Food and Drug Administration to address the technical aspects of this shift in policy (Collins *et al.* 2008. *Science* 319:906; M.A. Hamburg. 2011. *Science* 331: 987).

²⁹ *Supra* note 25.

³⁰ Comment document entitled: EPA Response to the Center for Regulatory Effectiveness (CRE) Information Quality Act Request for Correction Regarding the Amphibian Metamorphosis Assay, available in Docket ID no. EPA-HQ-OPPT-2007-1080.

³¹ Physicians Committee for Responsible Medicine (PCRM) Comments to OMB on the Endocrine Disruptor Screening Program (EDSP), available in Docket ID Number EPA-HQ-OPPT-2007-1080.

³² Draft Response to Comment document entitled: “Physicians Committee for Responsible Medicine’s Comments to OMB and EPA’s Responses,” available in Docket ID Number EPA-HQ-OPPT-2007-1080.

³³ Endocrine Disruptor Screening Program (EDSP); Announcing the Availability of a Draft for Weight-of-Evidence Guidance Document: Evaluating Results of EDSP Tier 1 Screening To Identify Candidate Chemicals for Tier 2 Testing, 75 Fed. Reg. 67,963 (Nov. 4, 2010); EPA-HQ-OPPT-2010-0877-0002.

endpoints applicable to each endocrine pathway and does not lend clarity to WoE evaluations of several or all assay results combined. The Guidance also provides only a general overview of how data might be used to decide whether any Tier 2 testing is indicated.

The Guidance includes general considerations in evaluating the quality of scientific information and lists general factors to consider when evaluating data (*e.g.*, soundness, applicability and utility, clarity and completeness, uncertainty and variability, and evaluation and review), but does not describe how data from the Tier 1 assays will be evaluated according to these criteria. Although the Guidance correctly points out that specificity, sensitivity, and rigor of validation are important considerations in evaluating assay results, it then ignores these critical considerations by giving only one general illustration of a simple, straightforward hypothesis-driven evaluation description of how data might be tabulated without any explanation of how such data would be evaluated according to a WoE approach.

For the EDSP Tier 1 assays, many of the elements necessary for a transparent and reproducible WoE approach could be informed by the validation studies. Moreover, the wealth of existing information for the List 1 chemicals could be used to revise and improve the comprehensiveness and utility of the Guidance.³⁴ In addition, there are several alternative WoE approaches to evaluating endocrine testing data in the published literature, including guidance for evaluating EDSP data that is more appropriate in terms of rigor and completeness.^{35,36,37,38}

IV) Conclusions:

We acknowledge EPA's obligation to screen chemicals for endocrine effects pursuant to the FFDC and recognize the Agency's significant efforts to implement the program at this time. Nevertheless, it appears that EPA has abandoned its initial intention to implement the phased approach to the EDSP recommended by its Scientific Advisory Board (SAB).³⁹ The SAB recommended that EPA initially screen 50 to 100 substances and that once the Agency collects data from those substances, it should review all endocrine screening battery data and test methods to revise the program "with an eye towards revising the process and eliminating those methods that don't work."⁴⁰ However, EPA has instead initiated actions to issue a second round of test orders for an additional group of chemicals.⁴¹ These actions

³⁴ This is especially important for several of the assays for which validation studies indicated insufficient specificity or reproducibility (*i.e.*, the pubertal assays, the amphibian metamorphosis and fish short-term assays).

³⁵ Willett CE, Bishop PL, Sullivan KM. 2011. Application of an integrated testing strategy to the U.S. EPA Endocrine Disruptor Screening Program. *Toxicol. Sci.* 123(1):15-25.

³⁶ Bars R, Broeckaert F, Fegert I, *et al.* 2011. Science based guidance for the assessment of endocrine disrupting properties of chemicals. *Regul. Toxicol. Pharmacol.* 59(1):37-46.

³⁷ Borgert CJ, Mihaich EM, Quill TF, *et al.* 2011. Evaluation of EPA's Tier 1 Endocrine Screening Battery and recommendations for improving the interpretation of screening results. *Regul. Toxicol. Pharmacol.* 59: 397-411.

³⁸ Borgert CJ, Mihaich EM, Ortego LS, *et al.* 2011. Hypothesis-driven weight of evidence framework for evaluating data within the US EPA's Endocrine Disruptor Screening Program. *Regul. Toxicol. Pharmacol.* In press: doi:10.1016/j.yrtph.2011.07.007.

³⁹ Consistent with the SAB recommendation, EPA confirmed in the EDSP List 1 policies and procedures document, that the Agency intended use the results from the first phase of EDSP screening to review and revise as necessary its Tier 1 battery prior to issuing new testing orders.

⁴⁰ *Review of the EPA's Proposed Environmental Disruptor Screening Program; Review of the Endocrine Disruptor Screening Program by a Joint Subcommittee of the Science Advisory Board and Scientific Advisory Panel.* EPA-SAB-EC-99-013, July 1999.

⁴¹ Draft documents and comments submitted available in Docket ID Numbers EPA-HQ-OPPT-2007-1080-9, EPA-HQ-OPPT-2009-0477, and EPA-HQ-OPPT-2007-1081.

clearly are not in accordance with OMB's TOC admonition to not order additional endocrine screening until the EDSP Tier 1 screening of List 1 chemicals was completed; until EPA had assessed the performance of its screening assays and battery and made necessary changes to the assays and battery; and until EPA had evaluated the sufficiency of other scientifically relevant information to satisfy test orders and avoid unnecessary testing. We believe the Agency has the obligation and opportunity to consider recommendations by the SAB, OMB, OIG, Congress and stakeholders to demonstrate non-duplicativeness and practical utility of the EDSP through careful review of Tier 1 information on List 1 chemicals before requiring the screening of additional chemicals.

V) Recommendations:

EPA should not require the screening of additional chemicals until it has demonstrated the practical utility of the information collected through Tier 1 screening.

- *EPA should review and revise the Tier 1 Battery, including promoting use of OSRI, before requiring the screening of additional chemicals.*
- *EPA should re-evaluate all OSRI submitted on the List 1 chemicals after all assay results have been evaluated, to demonstrate where OSRI would have been sufficient for the "may" or "may not" administrative decision on whether a chemical has the potential to interact with the endocrine system.*
- *EPA should review and revise, as needed, the Tier 1 Battery assays with alternative validated testing methodologies.*

EPA should evaluate the sufficiency of the Guidance to reproducibly and transparently characterize screening assay results across reviewers, chemicals and laboratories for the List 1 chemicals and revise the Guidance appropriately.