May 7, 2013

Dr. David Dix
Acting Director, Office of Science Coordination and Policy
USEPA Headquarters
Ariel Rios Building
1200 Pennsylvania Avenue, N. W.
Washington, District of Columbia 20460

Submitted electronically to regulations.gov

Re: Comments on "Endocrine Disruptor Screening Program (EDSP) Evaluation of Tier 1 Screening Assays and Battery Performance" [Federal Register /Vol. 78, No. 36 / Friday, February 22, 2013 /Notices 12311-12313] EPA-HQ-OPP-2013-0075

Dear Dr. Dix,

The American Chemistry Council (ACC)[1] appreciates the opportunity to submit comments on EPA's Endocrine Disruptor Screening Program: Evaluation of Tier 1 Screening Assays and Battery Performance. The ACC has played a constructive role in the Agency's development of the EDSP and in furthering the goal of implementing the EDSP as quickly and efficiently as possible, in a manner consistent with the law and authoritative scientific policies and practices. To that end, ACC has consistently supported increased funding for the Agency's research and laboratory studies to develop, standardize and validate the screening and testing methods required for the EDSP. ACC has sponsored technical studies to supply needed data for endocrine test development and validation, and has participated with the broader scientific and stakeholder communities on EPA's standardization and validation advisory committees. Additionally, ACC sponsored scientific research on the endocrine hypothesis through its Long-Range Research Initiative. As these actions demonstrate, ACC members take concerns about endocrine disruption seriously, as with any potential chemical risks.

ACC has consistently recommended that, following the conclusion of Tier 1 screening of EDSP List 1 substances, the Agency should critically review the performance of each assay and the

[1] The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $760 billion enterprise and a key element of the nation's economy. It is the largest exporting sector in the U.S., accounting for 12 percent of U.S. exports. Chemistry companies are among the largest investors in research and development. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against any threat to the nation's critical infrastructure.

overall Tier 1 Battery, and we commend EPA for undertaking such a review. In addition to the technical issues that are documented in the comments submitted to EPA by the Endocrine Policy Forum, of which ACC is a member, we offer the following comments, suggestions, and recommendations pertaining to the broader issues of policy and communications.

1. **EPA Should Consistently Describe and Communicate the Purpose and Use of the EDSP Lists**

EPA's Office of Science Coordination and Policy (OSCP) and Office of Pesticide Programs (OPP) have done a commendable job communicating to the public about the EDSP. When EPA published the Tier 1 List 1 pesticide actives and inerts, and when it published the draft Tier 1 List 2 substances, the Agency accurately communicated what the draft list is and is not. ACC urges EPA to continue to carefully communicate accurate information throughout each stage of the EDSP process: listing of substances for screening and later testing, issuance of test orders, results from Tier 1 screening and Tier 2 testing, and hazard and risk characterization. ACC agrees with the Agency's clear caution in the 2010 draft Tier 1 List 2 substances, and requests that EPA continue to communicate the final List 2 in this manner:

> Based on current information, the public should not presume that the listing of a chemical or substance indicates in any way that EPA currently suspects that such chemical or substance interferes with the endocrine systems of humans or other species simply because it has been listed for screening under the EDSP. At the present time, EPA believes that these chemicals or substances should be candidates, at least for screening purposes, under EDSP testing based only on their pesticide registration status and/or because such substances may occur in sources of drinking water to which a substantial population may be exposed.[2]

2. **EPA Should Consistently Describe and Communicate EDSP Related Issues Across the Agency**

ACC urges EPA to accurately communicate EDSP related issues across the Agency. The definition of "endocrine disruptor" is a case in point. EPA did not adequately discuss the purpose of Tier 1 and Tier 2 testing in the 2010 Listing Notice. EPA should be clear as to what the purpose of Tier 1 screening is and what the results of Tier 1 screening mean. As EPA has correctly stated in other Federal Register notices, the purpose of Tier 1 is to identify substances that have the potential to interact with the estrogen, androgen, or thyroid hormone systems, and the purpose of Tier 2 is to identify and establish a dose-response relationship for any adverse effects that might result from the interactions identified through the Tier 1 assays. It is clear from EPA's long-standing policy statements that "endocrine disruptors" are substances that adversely affect the organ systems by interacting with the endocrine system. Therefore, substances that have an adverse impact on the endocrine system as a secondary effect of some other toxicity (e.g., hepatotoxicity) are not endocrine disruptors - they do not exert an adverse effect by a primary mode of action of interaction with the endocrine system. Indeed, any frank toxicity often

[2] EPA (2010). Endocrine Disruptor Screening Program; Second List of Chemicals for Tier 1 Screening, Federal Register Volume 75, Number 221 (Wednesday, November 17, 2010), Pages 70248-70254.

results in some endocrine response, which may be no more than a homeostatic response. It would be illogical to term all substances that may exert a toxic effect at any dose an "endocrine disruptor."

Unfortunately, communications across the Agency with regard to its definition of "endocrine disruptor" have not been consistent with EPA's descriptions of Tier 1 and Tier 2 testing in EPA's EDSP. For example, EPA's Office of Research and Development (ORD) described "endocrine disruptors" in various ways on the ORD website (http://epa.gov/ncer/science/endocrine/#eds):

- Endocrine disruptors are basically chemicals with the potential to interfere with the function of endocrine systems.
- Endocrine disrupting chemicals (EDCs) have been defined as exogenous agents that interfere with the production, release, transport, metabolism, binding, action, or elimination of the natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes.

Absent from ORD's description is the notion that endocrine disruptors cause adverse effects, rather than simply interfering with the endocrine system. Any definition of endocrine disruption that does not include both the requirement for the direct interaction with the endocrine system and adverse effects is irrational. Not only is the ORD description inconsistent with EPA's described purpose of Tier 1 and Tier 2 testing, it is inconsistent with EPA's definition of "endocrine disruptor" in its EDSP Policy Statements:

> The purpose of Tier 1 is to identify substances that have the potential to interact with the endocrine system. The purpose of Tier 2 is to determine whether the substance causes adverse effects, identify the adverse effects caused by the substance, and establish a quantitative relationship between the dose and the adverse effect. At this stage of the science, only after completion of Tier 2 tests will EPA be able to determine whether a particular substance may have an effect in humans that is similar to an effect produced by a naturally occurring EAT, that is, that the substance is an endocrine disruptor.[3]
>
> The purpose of Tier 1 screening (referred to as ''screening'') is to identify substances that have the potential to interact with the estrogen, androgen, or thyroid hormone systems using a battery of assays. The fact that a substance may interact with a hormone system, however, does not mean that when the substance is used, it will cause adverse effects in humans or ecological systems. The purpose of Tier 2 testing (referred to as ''testing''), is to identify and establish a dose-response relationship for any adverse effects that might result from the interactions identified.[4]

ACC requests that the management of the EDSP program take appropriate actions to ensure that all EPA programs, including program offices and ORD, correct any and all incorrect statements regarding endocrine disruption, and assure the definitions, descriptors, public web sites etcetera

[3] Federal Register / Vol. 63, No. 248 / Monday, December 28, 1998, page 71545.
[4] Federal Register / Vol. 74, No. 71 / Wednesday, April 15, 2009, page 17561.

are aligned with the EDSP. The EDSP sets the policy on endocrine disruptors for all of EPA, not simply OPP, OSCP and the Office of Pollution Prevention and Toxics (OPPT).

3. EPA Should Consistently Describe and Communicate EDSP Related Issues to the Public

Now that EDSP List 1 Tier 1 screening results have been completed, EPA will need to assure that the results put forward by OPP, OSCP and OPPT are accurately and appropriately characterized and communicated to all EPA programs, including ORD and the Regions, and to the public. There is considerable concern that without proper characterization and communication, some may inappropriately misuse Tier 1 results to incorrectly conclude that substances with some positive activities in one or more Tier 1 assays are endocrine disruptors.

Furthermore, EPA has an obligation, when communicating Tier 1 results, to explicitly describe how these results should be used in hazard evaluation and risk assessment, particularly since some of the EDSP Tier 1 assays include apical endpoints. EPA should be explicit and indicate the limitations on the interpretation of the results.

- Specifically, for the in vitro assays, ACC requests that EPA explicitly include a statement to the effect that "EPA cannot conclude that the results of these in vitro assays translate into an understanding of particular health or environmental hazards and risks in vivo."[5]
- For the in vivo assays, ACC requests that EPA include a statement along the lines of: the in vivo Tier 1 assays individually and Tier 1 Battery collectively do not provide, indication of impending hazards or risks to human or ecological species, followed by the aforementioned quotes above from EPA's Policy Statements.[6]

4. EPA Should Revise Certain EDSP Tier 1 Test Guidelines as Appropriate before Issuing New List 2 Screening Orders

The experiences from the contract research organizations and the test order recipients clearly show that there is a need to closely evaluate the EDSP test method procedures and endpoints. Certain methods need to be upgraded and their corresponding test guidelines revised before EPA proceeds with issuing additional Tier 1 test orders for List 2 substances. The specifics are described in the analyses of the *in vitro* assays, the *in vivo* mammalian assays and *in vivo* ecotoxicity assays in the comments submitted by the Endocrine Policy Forum and in the presentations from the April 23-24 workshop "EDSP: Lessons Learned."[7]

---

[5] 1999 Policy Statement.
[6] Op. Cit. references 3 and 4.
[7] Session I - Performance of the EDSP Tier I Screening Assays; Insights from Conducting Assays for List 1 Chemicals; Introduction to Session I - Dr. Susan Borghoff, Session Chair (http://www.tera.org/peer/edsp/presentations/Borghoff_Session_I_intro.pdf); Review of in vitro Assays - Validation Results and Methods for Improving in vitro Tier 1 Endocrine Disruption Screening Assays - – Dr. Colleen Toole, Ceetox (http://www.tera.org/peer/edsp/presentations/Toole_Session_I_in_vitro.pdf); Review of in vivo Mammalian Assays - Challenges and Considerations for Conducting and Interpreting These Screening Assays - Dr. Leah Zorrilla, ILS, (http://www.tera.org/peer/edsp/presentations/ZorrillaTERA_EDSPfinal.pdf); Review of Non-mammalian Assays - Challenges and Potential Solutions for the Conduct and Interpretation of the Amphibian

It is imperative that EPA deliberately evaluate the Tier 1 screening results, alongside the Tier 1 assays, "functionally equivalent data," and "other scientifically relevant information" to identify the most effective and efficient path forward to improve certain EDSP test guidelines as appropriate. To that end, ACC requests that the Agency undertake the following procedures for revising the EDSP test guidelines:

- Release the proposed changes to the test guidelines for a 60-day public review and comment period. The documents released by EPA should include a strike-through / replace edited version of the test guideline along with a statement documenting EPA's rationale for each significant proposed change.
- The Agency should then evaluate the public comments received, finalize revisions to the test guidelines and publish the revised test guidelines. This should be accompanied by a "response to comment" document including EPA's disposition of comments and the rationale for EPA's decisions.

5. Thoughts on Possible Modifications to the EDSP Tier 1 Battery

a. Uterotrophic, Hershberger and Pubertal Assays

ACC fully supports efforts to reduce, refine, and replace animal methods when other methods can be used reliably and with adequate scientific confidence to support a product stewardship or regulatory decision. However, EPA's request to consider dropping the uterotrophic assay and the Hershberger assay would leave only the male and female pubertal assays and the fish short term reproduction assay to confirm estrogen, anti-estrogen, androgen, and anti-androgen activities. This could be very challenging because the uterotrophic and Hershberger assays use mechanistic endpoints, and are very sensitive and specific, whereas the pubertal assays and fish assay rely heavily on apical endpoints, and it is well-known (and was documented in the validation studies) that these apical endpoints are responsive not only to endocrine active substances, but are readily influenced by systemic toxicity.[8,9] Furthermore, the dose setting requirements for the pubertal assays have proven so onerous that almost all test order recipients appear to have had to run range finding studies with age matched animals. This has resulted in a considerable use of additional laboratory animals to comply with EPA's test guideline requirement to meet the specific level of body weight reduction required of the high dose group in order to have an acceptable study. ACC therefore, requests that EPA fully address the strengths and limitations of all the in vivo assays, including the pubertal assays and not just modify or eliminate the Hershberger or uterotrophic assays.

Metamorphosis Assay and the Fish Short Term Reproduction Assay - – Dr. Katherine Coady, The Dow Chemical Company (http://www.tera.org/peer/edsp/presentations/Coady_Session_I_Assays.pdf).

[8] S. C. Laws et al. (2006) Chapter 11: The US EPA EDSP: In Vitro and In Vivo Mammalian Assays, in Developmental and Reproductive Toxicology: A Practical Approach, Second Edition, edited by Ronald D. Hood. CRC Press, Boca Raton, Florida. Page 509.

[9] P. Matthiessen (2013), Chapter 7: Using Fish to Detect Endocrine Disrupters and Assess Their Potential Environmental Hazards in Endocrine Disrupters: Hazard Testing and Assessment Methods. John Wiley and Sons, Hoboken, New Jersey.

b. ToxCast Assays and Prediction Models

EPA also needs to recognize that it takes up to 3 years to generate EDSP Tier 1 data, at a cost of approximately $1,000,000 per substance. This cost estimate does not include Agency transaction or review time and effort. EPA should consider whether at this point, it would be better to accelerate the necessary determinations of relevance, reliability, sensitivity and specificity of the very promising ToxCast advanced high through-put and high-content endocrine screening techniques with the goal of substituting these in the EDSP, rather than to simply move ahead with additional Tier 1 screening of List 2 substances. The ToxCast methods hold great promise to increase the efficiency of EDSP Tier 1 screening, provide greater sensitivity and specificity at a lower cost and use fewer lab animals. But before they can be used in the EDSP, they must be shown to be scientifically valid for their intended purpose. Accelerating the development and validation of the ToxCast prediction models over the course of the next 2-3 years may be a better use of Agency resources and ultimately lead to more efficient use of private sector resources. Our publication[10] on approaches to developing the required scientific confidence in such assays provides a useful approach that should be considered by the ToxCast program. In addition, the comments of EPF and ACC[11] submitted to EPA and presented at the January 2013 FIFRA SAP highlight concerns with the performance of the ToxCast endocrine assays. These concerns should be expeditiously addressed as EPA proceeds with improving the ToxCast assays and prediction models.

****

The American Chemistry Council appreciates the opportunity to comment on EPA's evaluation of the EDSP Tier 1 assays and Tier 1 Battery. If you have questions regarding these comments, please contact one of us 202-249-7000 or by e-mail at Rick_Becker@americanchemistry.com or Emily_Tipaldo@americanchemistry.com.

Sincerely,

Richard A. Becker, Ph.D., DABT
Senior Toxicologist and Senior Director

Emily V. Tipaldo, MA
Manager

[10] Use and validation of HT/HC assays to support 21st century toxicity evaluations. Patlewicz G, Simon T, Goyak K, Phillips RD, Rowlands JC, Seidel SD, Becker RA. Regul Toxicol Pharmacol. 2013 Mar;65(2):259-68. doi: 10.1016/j.yrtph.2012.12.008. Open Access.

[11] Comments are posted in Regulations.gov, Docket ID: EPA-HQ-OPP-2012-0818 at http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2012-0818.