Comments of the American Chemistry Council
On EPA's Endocrine Disruptor Screening Program
Filed on January 18, 2011

1. ACC Comments on Second List of Chemicals for Tier 1 Screening" [75 FR 70248; 11/17/2010; EPA-HQ-OPPT-2009-0477; FRL-8848-7]

2. ACC Comments on Draft Policies and Procedures for Screening Safe Drinking Water Act Chemicals 75 Fed. Reg. 70558, Nov. 17, 2010 [EPA-HQ-OPPT-2007-1080; FLR-8848-9]

3. ACC Comments on EPA Information Collection Activities; Proposed Collection; Addendum for the Second List of Chemicals; Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP); EPA ICR No. 2249.02, OMB Control No. 2070-0176

4. ACC Comments on EPA's EDSP Draft Weight-of-Evidence Guidance Document, 75 Fed. Reg. 67963 (Nov. 4, 2010) (Docket ID: EPA-HQ-OPPT-2010-0877)

January 18, 2011

OPPT Document Control Office (DCO)
EPA East Building, Room 6428
1201 Constitution Avenue, N.W.
Washington, DC. 20460
Attention: Docket ID Number EPA-HQ-OPPT-2009-0477
Submitted via Federal eRulemaking Portal: http://www.regulations.gov

Re: Comments on "Endocrine Disruptor Screening Program: Second List of Chemicals for Tier 1 Screening" [75 FR 70248; 11/17/2010; EPA-HQ-OPPT-2009-0477; FRL-8848-7]

Dear Sir or Madam:

The American Chemistry Council (ACC)[1] appreciates the opportunity to submit comments on EPA's Endocrine Disruptor Screening Program: Second List of Chemicals for Tier 1 Screening (the "Draft EDSP List 2"). Pursuant to EPA's request for comments on the Draft EDSP List 2, 75 Fed. Reg. 70248; 11/17/2010, (the "Listing Notice"), ACC provides a number of general comments related to the Draft EDSP List 2 and the Agency's chemical prioritization approach. These comments do not address specific substances the Agency has chosen as candidates for the initial list. ACC panels and/or member companies will submit separate comments concerning some of those specific substances.

The American Chemistry Council (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 also 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 has sponsored scientific research on the endocrine hypothesis

[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 $674 billion enterprise and a key element of the nation's economy. It is one of the nation's largest exporters, accounting for ten cents out of every dollar in 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.

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 commends EPA on its care in accurately communicating what the draft list is and is not in its notice announcing the Draft EDSP List 2. We urge EPA to continue to carefully communicate accurate information at each stage of the EDSP process: listing of substances for screening/testing, issuance of test orders, results from Tier 1 screening and Tier 2 testing, and in hazard and risk characterization.

With respect to the Agency's efforts to implement all of the necessary components of the EDSP, considerable additional effort is needed to ensure scientifically reliable data is generated. EPA must build upon existing data sources to distinguish "data needs" from "data gaps" in a cost efficient manner that fully considers animal welfare issues. EPA must also follow clear and consistent approaches for interpreting the data within a weight of evidence construct and for applying the test results in risk assessments. The EDSP Tier 1 screening is an ambitious testing program that is being implemented under new policies and procedures. It will utilize a suite of newly validated – and expensive -- test methods. For the reasons discussed in more detail in our comments, we believe EPA should, consistent with the recommendations of the Agency's independent scientific experts, the Science Advisory Board and Scientific Advisory Panel (SAB/SAP)[2], pause after EDSP Phase 1 to first conduct a review of the Tier 1 assays before requiring screening of additional chemicals using these assays. Such a pause would allow the Agency to modify and replace Tier 1 assays as necessary based on the Agency's Phase 1 experience.

ACC is disappointed in EPA's statement that "[t]he Agency does not plan to respond formally to information or comments that may be submitted…" on the draft list. We think the rationale for this plan is flawed as well as inconsistent with open and transparent regulatory practices. For the reasons discussed below, ACC urges EPA to formally respond to comments received on the Draft EDSP List 2.

Furthermore, ACC believes that the Agency's criteria for evaluating substances, for both initial inclusion on the Draft EDSP List 2 and for subsequent exclusion from the Draft EDSP List 2 (due to such scientific criteria as " not likely to be biologically active" or "incompatible with testing assays for various reasons due to one or more of their physiochemical properties"), and the final EDSP List 2 itself, should undergo scientific peer review, in accordance with the requirements of EPA's Peer Review Handbook, Peer Review Policy and the Agency's Information Quality Guidelines.

[2] EPA (1999). Review of the Endocrine Disruptor Screening Program by a Joint Subcommittee of the Science Advisory Board and Scientific Advisory Panel. http://www.epa.gov/scipoly/sap/meetings/1999/finalrpt.pdf. "There was broad support among the Subcommittee for the concept that the Agency should convene a panel of independent scientists to review all the screening data for 50-100 compounds, with an eye towards revising the process and eliminating those methods that don't work." Page 2.

ACC has several additional comments about the selection processes for substances included in the Draft EDSP List 2 EDSP as well as issues related to screening and implementation of the EDSP. We urge the Agency to consider these concerns, and suggestions as it implements the second phase of its EDSP. These are contained in ACC's detailed comments, which are attached.

ACC appreciates the opportunity to provide comments to the Agency on implementation of the EDSP. Please do not hesitate to contact us should you require additional information/clarification on any of the provided comments. I can be reached by phone at 202-249-6405 or by e-mail at Rick_Becker@americanchemistry.com.

Sincerely,

Richard A. Becker, Ph.D., DABT
Senior Toxicologist and Senior Director
Regulatory and Technical Affairs Department
American Chemistry Council

Attachment: Comments of the American Chemistry Council on "Endocrine Disruptor Screening Program: Second List of Chemicals for Tier 1 Screening" [75 FR 70248; 11/17/2010; EPA-HQ-OPPT-2009-0477; FRL-8848-7]

Comments of the American Chemistry Council

"Endocrine Disruptor Screening Program; Second List of Chemicals for Tier 1 Screening"
[75 FR 70248; 11/17/2010; EPA-HQ-OPPT-2009-0477; FRL-8848-7]

January 18, 2011

The American Chemistry Council (ACC) is pleased to have this opportunity to submit comments on EPA's *Endocrine Disruptor Screening Program; Second List of Chemicals for Tier 1 Screening* (the "Listing Notice") 75 Fed. Reg. 70248, Nov. 17, 2010. Pursuant to EPA's request for comments, ACC provides the following general comments related to EPA's Endocrine Disruptor Screening Program Second List of Chemicals for Tier 1 Screening (the "Draft EDSP List 2") and chemical prioritization approach. These comments do not address specific substances the Agency has chosen as candidates for the initial list. ACC panels and/or member companies will submit separate comments concerning some of those specific substances.

I. Introduction

ACC commends EPA on its care in accurately describing the draft list in its Listing Notice. ACC encourages EPA to continue to frame its activities under the EDSP in the proper context. ACC agrees with EPA's decision to focus solely on exposure potential when selecting substances for EDSP screening. If EPA had included other factors, such as evidence of potential endocrine activity or toxicity, it would have created uncertainty concerning the significance of the list and may have lead the public to misinterpret the list as a list of endocrine disruptors or a list of hazardous substances, thereby creating significant communication challenges for the Agency and harming the regulated community.

Although ACC agrees with the Agency's approach to focus on exposure potential in compiling the Draft EDSP List 2, EPA must also improve its process for determining exposure potential. Specifically, EPA should more critically consider the scientific robustness of the exposure data sources it relies on. As discussed below, ACC believes EPA should undertake a critical review of its exposure databases prior to further prioritization efforts.

Finally, we think it would be inappropriate if EPA were to issue screening orders for these new substances before EPA has reviewed the results of the screening battery being applied in Phase 1 of the EDSP. We believe EPA should follow the advice of the Agency's Science Advisory Board and Scientific Advisory Panel (SAB/SAP)[3] by completing EDSP Phase 1, and conducting the SAB/SAP-recommended review of the performance of the Tier 1 assays and the Tier 1 battery prior to requiring screening for additional substances.

[3] Ibid.

II. EPA Should Continue to Ensure Accurate, Complete and Consistent Communications Concerning the EDSP to the Public and Across the Agency

ACC believes EPA has done an excellent job thus far in communicating the meaning of its draft candidate list in the Listing Notice. ACC agrees with the Agency's clear caution in its notice that "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."[4]

The Agency must continue to communicate accurate and complete information about the substances on the list, however, even after the list is finalized. For example, when it issues the final EDSP List 2, EPA should also clarify that from a human health risk assessment perspective, the current lack of endocrine mechanistic information for any particular substance does not mean that the substance poses significant risks, even at environmentally relevant levels of exposure.

Further, while ACC agrees that it makes sense to base EDSP prioritization on exposure potential, ACC also believes that EPA should emphasize in all of its EDSP communications that, for many if not all of the substances on the EDSP List 2, the Agency already has data and information on relevant apical tests that are used for risk assessment purposes, including tests for reproduction and developmental toxicity (potential effects which are mediated by endocrine pathways). EPA already has a large amount of toxicity data on all pesticide chemicals. Furthermore, many of the commodity chemicals identified on the draft EDSP List 2 have had health risk assessments developed as part of the Agency's drinking water regulatory program and a majority have been assessed in the Agency's Integrated Risk Information System. Even if specific endocrine screening has not yet been conducted on certain compounds, hazard identification based on observable outcomes from apical toxicity tests (e.g., outcomes such as pathologic states indicative of disease conditions) covers all modes of action, including endocrine pathways.

II.A. Communication about Data Already Available to the Agency

As EPA is well aware, endocrine activity, as determined by Tier 1 screening, is not a distinct toxicological hazard *per se*, but rather a measure of a compound's ability to interact with

[4] 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.

components of the endocrine system. Interaction with or modulation of endocrine processes may or may not give rise to adverse effects. It is the apical tests, the EDSP Tier 2 tests or similar toxicology tests that determine adverse effects and dose response that are to be used for hazard identification and risk assessment. As EPA has stated:

> EPA developed a two-tiered approach to implement the statutory testing requirements. 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 through the Tier 1 assays.[5] (Emphasis added.)

In the Agency's EDSP Policy Statement EPA clearly indicates that toxicity testing – evaluation of apical endpoints for adverse effects -- is central to determining "whether a particular substance may have an effect in humans that is similar to an effect produced by a naturally occurring EAT [estrogen, androgen thyroid], that is, that the substance is an endocrine disruptor."[6] Existing toxicity test results that have evaluated established apical adverse effect endpoints, primarily reproductive and developmental toxicity endpoints, are relevant to the EDSP. In this regard, the toxicity information on apical endpoints developed by ACC members as part of product stewardship and regulatory programs is directly pertinent to evaluating hazards and risks, including potential effects mediated by endocrine pathways, to health of individuals, including children. Such data typically includes: 1) identification and definition of possible hazards upon all major organ systems from both acute and repeated exposures; 2) detection of potential hazards arising from *in utero* exposures; 3) evaluation of potential of a substance to affect reproduction; and 4) evaluation of the potential of a substance to damage DNA. The acute toxicity studies, while critical to ensure correct packaging, labeling and handling to prevent poisoning incidents, are not directly relevant for determining endocrine disruption. The developmental and reproductive toxicity studies, however, are relevant for determining endocrine disruption because they assess risks that could affect normal prenatal and postnatal growth, development and maturation.

Hazard information from apical toxicity tests are available for many of the commodity chemicals included in the draft EDSP List 2. Such hazard evaluation studies (i.e., outcomes such

[5] EPA (2009). Endocrine Disruptor Screening Program; Policies and Procedures for Initial Screening. Federal Register Volume 74, Number 71 (Wednesday, April 15, 2009) Pages 70248-70254. http://www.epa.gov/endo/pubs/revised_pandp_frn_041509.pdf

[6] EPA (1998). Endocrine Disruptor Screening Program: Statement of Policy. Federal Register Volume 63, Number 248 (Monday, December 28, 1998) page 71542.

as pathologic states indicative of disease conditions) cover all modes of action, including endocrine pathways. When toxicity test results are available that provide information on apical endpoints (e.g., identify dose levels that cause adverse effects, irrespective of a substance's mode of action), the Agency has the data needed for understanding the dose-response relationship between exposure and adverse health effects for risk assessment purposes. Of the commodity chemicals included in the Draft EDSP List 2, for every substance that is a regulated drinking water contaminant EPA has conducted a hazard evaluation based on apical toxicity data to set a Maximum Contaminant Level Goal (MCLG). The MCLG is "the maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on the health of persons would occur, and which allows an adequate margin of safety."[7] In addition, approximately 70% are included in the OECD HPV chemical list,[8] and available hazard information for these substances can be accessed on the e-ChemPortal.[9] What's more, greater than 75% of these chemicals have been assessed by EPA and included in the Agency's Integrated Risk Information System (IRIS http://www.epa.gov/IRIS/). IRIS assessments include evaluation of apical toxicity tests, and, IRIS establishes Oral Reference Doses which are an "estimate of a daily oral exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime."[10] For chemicals with potential carcinogenic activity, IRIS establishes Oral Slope Factors for use in deriving estimates of upper bound lifetime cancer risks. The Agency relies on IRIS assessments in a number of programs, including the Drinking Water Office, for assessing and for determining risk management options.[11] Therefore, because Agency decisions on these substances are based on adverse effects in the toxicology studies that cover all modes of action, and the Agency already has the results of such studies in hand for a majority of the commodity chemicals included in the draft EDSP List 2, there should be little concern that potential significant risks have not been accounted for.

ACC believes that it is important for the public to understand the extent of toxicity data that is relevant to endocrine disruption that is already available for the commodity chemicals included in the EDSP. By not referencing existing, publicly available sources of hazard and risk information, such as Drinking Water Standards and Health Advisories,[12] IRIS and the e-ChemPortal, the Agency has missed an opportunity to inform the public and policy makers of the extent of existing toxicity information already in the public domain concerning the EDSP Draft List 2 candidates. This oversight should be corrected when the Agency publishes the final EDSP List 2, by including references and links to relevant Agency hazard and risk information data sources.

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[7] http://water.epa.gov/lawsregs/rulesregs/regulatingcontaminants/basicinformation.cfm
[8] OECD (2004). The 2004 OECD List of High Production Volume Chemicals. http://www.oecd.org/dataoecd/55/38/33883530.pdf
[9] http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en
[10] http://www.epa.gov/IRIS/
[11] http://water.epa.gov/action/advisories/drinking/upload/dwstandards2009.pdf
[12] Ibid.

II.B. Ensuring Consistent Communications about Endocrine Disruptors and the EDSP 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 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 places, 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 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 policy statement on the EDSP. For example, EPA's Office of Research and Development (ORD) has 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.
- EDCs can include man-made chemicals such as pesticides and plasticizers, natural chemicals found in plants (phytoestrogens), pharmaceuticals, or hormones that are excreted in animal or human waste.

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 Statement:

> 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.[13]

In addition to ORD, it now appears that EPA's Design for Environment (DfE) program is completely ignoring the Office of Chemical Safety and Pollution Prevention's (OCSPP) EDSP and its definition of "endocrine disruptor" by proposing to apply results of EDSP Tier 1 screening for product risk management actions. In the DfE proposed standard, which is now being circulated for review and comment, the Agency proposes action based solely on "interaction" or "perturbation" of the endocrine system:

> 4.5.5 Potential endocrine effects. Chemicals that are candidates for endocrine screening will be part of the review. **Chemicals found to interact with or perturb the endocrine system**—potentially leading to reproductive, developmental, carcinogenic, systemic, hormonal or other effects—will not be allowed based on the toxicological hazards they pose.[14] (Emphasis added.)

The DfE proposed risk management action is wholly inappropriate and inconsistent with EPA's EDSP policy. In the two-tiered EDSP, Tier 1 is specifically designed to maximize the sensitivity to detect any interaction with components of the estrogen, androgen and thyroid systems. The EDSP Tier 2 is designed to identify adverse effects and dose response and it is the Tier 2 results that are to be used for risk assessment and risk management. The EDSP Tier 1 assays, which determine the potential of a chemical to interact with components of the endocrine system, are not intended to signal a concern for health risks that would lead to bans or substitutions. EPA OCSPP is very clear on this point.

EPA developed a two-tiered approach to implement the statutory testing requirements. The

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[13] EPA (1998). Endocrine Disruptor Screening Program: Statement of Policy. Federal Register Volume 63, Number 248 (Monday, December 28, 1998) page 71542.

[14] EPA, OCSPP, Design for the Environment (2010). Proposed Enhancements to the Design for the Environment (DfE) Standard for Safer Products. EPA's DfE Standard for Safer Cleaning Products (SSCP) http://www.epa.gov/dfe/proposed_enhancements_to_dfe_standard_for_safer_products.html and http://www.epa.gov/dfe/standard_for_safer_cleaning_products_revisions_updated_oct_26_2010.pdf

> 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 through the Tier 1 assays.[15] (Emphasis added.)

The description and proposed actions regarding endocrine in the draft DfE Standard, as currently written, would base action on Tier 1 EDSP screening results, and would promote regulation based merely on the potential of interactions rather than on adverse effects and risk, thus shifting the Agency's well established, scientifically grounded, risk-based chemical management paradigm. This is inappropriate. Even the NRC panel which used the term "perturbation" is clear that it did not envision regulatory actions would be triggered by any finding of a perturbation. The National Research Council's (NRC) experts stated in "Toxicity Testing in the 21st Century: A Vision and a Strategy":

> Biological responses viewed as the result of an intersection of exposures with biological functions. The intersection leads to perturbations of biological pathways. **When perturbations are sufficiently large or when host is unable to adapt** because of underlying nutritional, genetic, disease or life-stage status, biological function is compromised (Emphasis added.).[16]

The point is an adverse effect (an effect that warrants use as an endpoint for risk assessment and the basis for determining product stewardship or risk management or consideration for possible substitution of a chemical in a product), is not merely any known biochemical or chemical change, or even any known or measureable precursor along the pathway that could lead to some degree of perturbation. The NRC Committee clearly indicated that consideration of adversity occurs when perturbations are sufficiently large.

EPA OCSPP has an obligation to ensure that other EPA programs follow the Agency's policies in describing what EDSP Tier 1 screening results are and are not, and that they use the information generated in the Tier 1 EDSP appropriately. ACC urges EPA to ensure accurate, complete and consistent communications about the list of substances to be screened – both to external audiences and across the agency as EPA moves forward to implement the EDSP. The OCSPP must work to improve its communications about endocrine disruption and the EDSP and work to ensure that the policies set within the EDSP, including the policies for the use of

[15] EPA (2009). Endocrine Disruptor Screening Program; Policies and Procedures for Initial Screening. Federal Register Volume 74, Number 71 (Wednesday, April 15, 2009) Pages 70248-70254. http://www.epa.gov/endo/pubs/revised_pandp_frn_041509.pdf

[16] Toxicity Testing in the 21st Century: A Vision and a Strategy (2007). The National Academies Press, Washington, DC, 20001. Page 49.

screening data and the interpretation and communication of screening results, are followed by all EPA programs and offices.

II.C. EPA Should Consistently Describe EDSP Tier 1 And Tier 2 in Agency Policy Documents, Including the EDSP Notices Issued in The Federal Register.

As EPA moves forward with the EDSP, it is important that the Agency use consistent descriptions of the purpose of Tier 1 and Tier 2. In the Listing Notice EPA describes the EDSP Tier 1 and Tier 2 as:

> Tier I test assays are used to screen the chemicals for interaction with the estrogen (E), androgen (A) or thyroid (T) hormonal systems. Tier II test assays are intended to test for more specific chemical effects on the endocrine system, and are currently in the process of being developed and validated. Further information regarding EDSP and requirements for Tier I and Tier II can be found on the Agency's EDSP.[17]

ACC requests that in each future EDSP notice, EPA consistently use the definitions of EDSP, Tier 1 and Tier 2 adopted by the Agency in its Policy Statement, to wit,

> 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. Therefore, both Tier 1 and Tier 2 are essential elements of the screening program mandated by the FQPA.[18]
>
> EPA believes that the results from the entire battery of tests required in the Tier 1 screening and Tier 2 testing stages (or their equivalents) are necessary to make the statutory determination of whether a particular substance ‘‘may have an effect in humans that is similar to an effect produced by a naturally occurring [hormone]’’(21 U.S.C. 346a(p)). In other words, a positive result in the Tier 1 screening assays would not be adequate to make the determination ‘‘whether a substance may have an effect in humans that is similar to an effect produced by a naturally occurring [hormone].’’ Id. Conversely, a negative result in all Tier 1 screening tests will be adequate to determine that a particular substance is not likely to have an effect on the estrogen, androgen, and thyroid hormone systems (EAT) and, therefore, is not a priority for testing in Tier 2. The confirmatory tests in the Tier 2 testing stage are necessary to determine whether a

[17] EPA (2010). Endocrine Disruptor Screening Program: Second List of Chemicals for Tier 1 Screening (2010). Federal Register Volume 75, Number 221 (Wednesday, November 17, 2010), Pages 70248-70254.
[18] Endocrine Disruptor Screening Program; Policies and Procedures for Initial Screening (1999). Federal Register / Vol. 63, No. 248 / Monday, December 28, 1998, page 71545.

substance may have an effect similar to that of a naturally occurring hormone.[19]

III. EPA Should Complete Screening of its First List of Chemicals before Ordering Additional EDSP Screening

While ACC does not object to EPA's prioritizing additional substances for EDSP Tier 1 screening, ACC believes that EPA should not issue screening orders for these new substances before the Agency has collected and analyzed data from the initial set of EDSP substances. The Tier1 screening component of the EDSP is an ambitious testing program that is being implemented under new policies and procedures. It utilizes a suite of newly validated test methods with which the Agency and industry have little experience. Tier 1 screening costs alone may run as high as $500,000 to $1,000,000 per substance and utilize a significant number of lab animals; Tier 2 testing costs could reach several million dollars per substance. Given the lack of experience with the EDSP screening and testing assays and the Tier 1 battery, it is imperative that the Agency proceed to collect and analyze data from the initial set of EDSP substances before proceeding to additional substances. That approach would allow EPA to examine and revise its Tier 1 assays, the Tier 1 battery and EDSP procedures, such as use of "functionally equivalent data" and "other scientifically relevant information" before undertaking additional testing that could result in the unnecessary use of resources and test animals.

We believe this approach is also consistent with the SAB/SAP's recommendation to "pilot" the first round of EDSP screening with a limited number of chemicals. EPA's initial selection of 67 pesticide chemicals for Phase 1 of EDSP screening was consistent with the SAB/SAP guidance set forth in the July 1999 SAB/SAP *Review of the EPA's Proposed Environmental Endocrine Disruptor Screening Program*[20] which recommended that the Agency consider piloting the EDSP with a set of 50 to 100 chemicals. The SAB/SAP also recommended that EPA convene an external panel of independent scientists to review the initial screening data for the purpose of evaluating whether the Tier 1 screening program could be improved or optimized. ACC agrees with EPA's initial use of a manageable number of pesticide chemicals and with the SAB/SAP recommendation to convene an external panel to review the initial screening data.[21] EPA's reference to this SAB/SAP recommendation is contained in the Agency's description of the EDSP in both the "Response to Comments on the DRAFT Endocrine Disruptor Screening Program (EDSP): Policies &

[19] Ibid.

[20] EPA (1999). Review of the Endocrine Disruptor Screening Program by a Joint Subcommittee of the Science Advisory Board and Scientific Advisory Panel. http://www.epa.gov/scipoly/sap/meetings/1999/finalrpt.pdf. "There was broad support among the Subcommittee for the concept that the Agency should convene a panel of independent scientists to review all the screening data for 50-100 compounds, with an eye towards revising the process and eliminating those methods that don't work."

[21] Ibid

Procedures for Initial Screening and Testing"[22] and the Final "Policies and Procedures for Initial Screening"[23] published in 2009. We have interpreted EPA's reference to the SAB/SAP recommendation as an indication of EPA's intent to comply with this recommendation as it proceeds with the EDSP.

EDSP Phase 1 testing is either still underway or results have not yet been compiled and reviewed by EPA. EPA should follow the SAB/SAP advice and await completion of the EDSP Phase 1 to conduct the SAB/SAP-recommended review prior to requiring screening for additional substances. A staged implementation of EDSP screening (in which new screening orders would be issued only after completion of the first phase of screening) would allow the Agency to modify and/or replace Tier 1 assays as necessary based on the Agency's Phase 1 experience.

In addition, in order to utilize the very promising ToxCast advanced high through-put and high-content endocrine screening techniques within the EDSP, EPA should accelerate the necessary determinations of relevance, reliability, sensitivity and specificity of these methods. A phased approach would allow EPA to complete these determinations. These 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. Indeed, these techniques have already been used by EPA, in lieu of the Agency's own EDSP Tier 1 battery, to compare the dispersants available for use in the Deepwater Horizon oil spill for potential endocrine activity and relative toxicity to living cells. The methods used, EPA's ToxCast™ and the Tox21 NIH Chemical Genomics Center molecular/cellular screening tests, are advanced techniques that have only recently become available. The power of those methods is exemplified by the Agency's full reliance on those test results for purposes of the oil spill evaluation to conclude:

> EPA's results indicated that none of the eight dispersants tested, including the product in use in the Gulf, displayed biologically significant endocrine disrupting activity. The tested dispersants alone had relatively low potential for cytotoxicity, with JD-2000 and SAF-RON GOLD being the least cytotoxic.[24]

As a general matter, EPA can ensure efficient, cost effective generation of scientifically reliable endocrine data by implementation of the EDSP in a manner that builds upon existing

[22] EPA (2009). Docket ID #: EPA-HQ-OPPT-2007-1080 Response to Comments on the DRAFT Endocrine Disruptor Screening Program (EDSP): Policies & Procedures for Initial Screening and Testing. Page 2. http://www.epa.gov/endo/pubs/pandp_r2c_041509.pdf

[23] EPA (2009). Endocrine Disruptor Screening Program; Policies and Procedures for Initial Screening. Federal Register, Volume 74 Number 71 (Wednesday, April 15, 2009) Page 17561

[24] EPA (2010). US EPA's Oil Spill Dispersant Screening Results. Rapid Testing For Potential Endocrine Related Activity & Cytotoxicity. http://www.epa.gov/ncct/download_files/factsheets/Technical%20Fact%20Sheet%20EST%20paper%20In%20Vitro%20Tests%208%20Oil%20Dispersants%207-6-2010.pdf

data sources. In this regard, EPA must distinguish "data needs" from "data gaps." It should focus efforts on filling only data needs, and it should do so in a cost efficient manner taking full consideration of protection of public health, the environment and animal welfare concerns.[25] When needed data are generated, EPA must use clear and consistent objective criteria for determining data quality and study reliability coupled with a structured evaluative framework to provide a systematic approach for assessing the overall weight of the evidence for observed effects and the postulated mode of action.

IV. EPA Should Respond To Comments Submitted on the Draft EDSP List 2

EPA states in its List 2 Notice that "The Agency does not plan to respond formally to information or comments that may be submitted…" on the draft list (75 Fed. Reg. 70248, 70251). Elsewhere in the notice, EPA suggests that because the CCL3 had previously been subject to notice and comment, and EPA response to same, that the Agency wouldn't re-visit those conclusions. This rationale is flawed, however, since the CCL3 was never developed to meet the SDWA §1457 authority for testing substances that "may be found in sources of drinking water" to which a "substantial population" may be exposed. As the Agency is aware, the CCL3 was developed for different purposes of the SDWA. Being on the CCL3 does not necessarily mean the chemical is found in public drinking water sources to which a substantial population may be exposed. The Agency's responses to previous comments on the CCL3 (or the MCLs/MCLGs for that matter), therefore, does not justify the Agency's plans not to respond to comments on the draft EDSP List 2.

Further, when the EDSP List 2 is final and integrated into individual EDSP test orders to manufacturers and importers, new duties and obligations for specific members of the regulated community will be created. These test orders may be challenged (presuming the Agency follows its currently non-binding policies and procedures to treat test orders as final agency action. See ACC's separate comments on Policies and Procedures, Section X), including the Agency's basis for testing a listed substance. But administrative efficiency, consistency with EPA's approach in EDSP Phase 1, and the open and transparent processes and practices envisioned by the Administrative Procedure Act, argue instead for EPA to respond to comment on the draft EDSP List 2 that are submitted to this docket.

[25] Typically, a lab conducting the EDSP Tier 1 battery will use a minimum of 162 rats per chemical for the uterotrophic, Hershberger, male pubertal and female pubertal assays in accordance with the requirements of the EPA EDSP Test Guidelines. However, experience has shown that dose-ranging pilot studies will almost always be necessary, and this will require some 40-50 additional lab animals. Estimates for the frog assay indicate use of 300-400 tadpoles per assay, but in order to get to these numbers (the EPA Test Guideline requires the test tadpoles all be of a precisely defined staging) labs must to start with a total pool of several thousand to select those appropriate for assay. The fish reproduction assay requires approximately 100-120 adults, and typically close to 30,000 embryos.

V. EPA Should Be Fully Transparent in the Procedures Used for Developing the Draft EDSP List 2 of 134 Substances

Although EPA compiled a list of 201 substances as candidates for the EDSP List 2, the Agency has not been fully transparent in its basis for streamlining this candidate list to arrive at the 134 substances included in the Draft EDSP List 2. In the Listing Notice, EPA qualitatively describes the criteria it has employed, but the Agency has not published the actual physiochemical criteria and data it relied on to make the exclusion decisions. For full transparency, ACC requests that EPA publish the specific scientific criteria the Agency employed to determine a substance falls into a category of i) a biological agent or naturally occurring chemical; ii) a chemical for which the manufacturer, importer or registrant cannot be clearly identified; or iii) a chemical not likely to be biologically active or which are incompatible with testing assays for various reasons due to one or more of their physiochemical properties (e.g., gases, strongly acidic or basic, solubility, vapor pressure molecular weight). In this regard, it appears that EPA may not have consistently applied criteria iii) above, in that certain substances contained in the Draft EDSP List 2 appear to be highly reactive and/or highly irritating chemicals.[26] However, because the Agency has not provided the scientific basis for the Agency's determinations for streamlining and removing some substances, independent verification of consistent application of such criteria by EPA is simply not possible at this time.

Furthermore, ACC believes that the Agency's criteria for evaluating substances, both for inclusion and exclusion from the EDSP List 2, must undergo scientific peer review, in accordance with the requirements of EPA's Peer Review Handbook , EPA's Peer Review Policy and Information Quality Guidelines.[27,28] The Agency's policies and guidance on scientific peer review are clear: 1) Agency actions, such as the EDSP List 2, are included in the suite of Agency activities that meet the definition of dissemination of information to the public; 2) EPA's Peer Review Policy states, "[p]eer review of all scientific and technical information that is intended to inform or support Agency decisions is encouraged and expected;" 3) EPA's Peer Review Handbook states, "all influential scientific and technical work products used in decision making will be peer reviewed;" and 4) the EPA EDSP List 2 criteria, both the inclusion criteria and the

[26] Highly reactive and irritating chemicals, like acids and bases, would be expected to react at the point of contact and may not be suitable at certain concentrations for administration by certain routes in some toxicity tests. Some highly reactive chemicals can react exothermically with air or water spontaneously, leading to rapid breakdown of such substances, making dose administration very difficult. In addition, a highly reactive substance would not be expected to persist in the environment as the parent molecule.

[27] EPA (2006). U.S. Environmental Protection Agency Peer Review Handbook, 3rd Edition. http://www.epa.gov/peerreview/pdfs/peer_review_handbook_2006.pdf

[28] EPA (2002). Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency. http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf

exclusion criteria, meet the definition of "influential scientific information" in that use of such criteria will have a clear and substantial impact on important public policies or private sector decisions, since such action will result in Agency determinations that, as proposed, would trigger issuance of EDSP Tier 1 screening test orders.

VI. EPA Must Interpret Key SDWA Provisions Before it Lists Phase 2 Chemicals and Before it Issues Phase 2 Orders

EPA, in the Listing Notice, has described its process for prioritizing chemicals for EDSP List 2. ACC, however, does not agree with EPA's assertion that a chemical on the CCL3 list per se meets the criteria of the 1996 endocrine amendments to the Safe Drinking Water Act (SDWA) that a substance "may be found in sources of drinking water" and to which a "substantial population" may be exposed. The identification of candidates for EDSP List 2 should conform to the Agency's authority specified in the SDWA. We refer EPA to ACC's discussion of this matter in our comments on *EPA's Draft Policies and Procedures For Screening Safe Drinking Water Act Chemicals (75 Fed. Reg. 70558, Nov. 17, 2010),* which have been filed separately.

VII. EDSP Test Order Authority Applies to Current Manufacturers and Importers

The 1996 amendments to the SDWA provide EPA authority to include in the EDSP "substances that may be found in sources of drinking water" to which a "substantial population" may be exposed. The applicable wording in the EDSP Test Order authority section, FFDCA §408(p)(5) "Collection of Information," uses the present tense and thus clearly focuses on current manufacturers and importers, not past:

> "The Administrator shall issue an order to a registrant of a substance for which testing is required under this subsection, or to a person who manufactures or imports a substance for which testing is required under this subsection, to conduct testing in accordance with the screening program . . . ."

Therefore, ACC believes that for chemicals no longer manufactured or imported but which, in some instances, may be found as contaminants of drinking water, are not covered by the 1996 endocrine amendments to the SDWA.

VIII. EPA Should Establish a Transparent Policy to Provide Equitable Resolution of the Question of Who Should be Subject to EDSP Testing of Drinking Water Contaminants

For certain chemicals on the Draft EDSP List 2, occurrence in drinking water sources can result from natural sources, from manufacturing, processing and importing of a specific chemical, and from uses of other products and from other activities. Without addressing any particular chemicals on the Draft EDSP List 2, ACC urges EPA to consider policies that provide

equitable resolution to the question of who should be subject to EDSP testing under EPA's SDWA authority. These policies might address, for example, chemicals which may be found as contaminants in drinking water for which the major sources are from current commercial activities, not from the current manufacture or import of the specific chemical per se. In developing such a policy, EPA should clearly explain its considerations so the regulated community can understand the Agency's rationale.

IX. EPA Should Undertake a Critical Review of its Exposure Databases Prior to Further Prioritization Efforts

Further, with respect to the appropriateness of using the CCL3 list in general, ACC is concerned that EPA has not fully accounted for data quality by relying on certain databases for asserting substances on the CCL3 list automatically satisfy the SDWA endocrine statutory requirements. When utilizing any data source, EPA should undertake a rigorous analysis of data strengths and weaknesses prior to using that data in Agency programs. To ensure its analyses are reproducible, EPA should use only data sources that are publicly available. In evaluating the data sources it relies upon to prioritize substances for EDSP screening, EPA should analyze each database in terms of:

- The extent to which the database represents the current U.S. population (e.g., EPA should consider who was sampled, where samples were collected and sample size).
- Sampling design (including whether sufficient controls were used).
- Quality of the data (e.g., sensitivity and specificity of the chemical analytic techniques; adequacy of the quality assurance/quality control procedures for sample collection, storage, analysis, archiving and record keeping).
- Time frame of sample collection to determine current relevance. EPA should determine whether there have been major changes in production or use patterns, or in regulatory requirements that would impact current exposure circumstances.
- Frequency of occurrence of measured concentrations within the database (e.g., whether the data represent an isolated incident and whether the data are statistically significant).
- Concentration ranges of the samples in the database.
- Identity of a chemical as a parent chemical as opposed to a metabolite of a different chemical.
- Public availability of the data.

Importantly, EPA should not conclude, without adequate written scientific justification, that the information it relies on to assess potential exposure for purposes of prioritization can be extrapolated to the general population and to current, present-day exposure circumstances. EPA has focused considerable attention on information quality issues, and the Agency has adopted a number of policies, procedures and guidelines to guide Agency actions in collecting, evaluating, disseminating and using environmental data, including:

- EPA Quality Manual for Environmental Programs 5360 A1. May 2000. http://www.epa.gov/quality/qs-docs/5360.pdf
- EPA/260R-02-008, December 2002, Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility and Integrity for Information Disseminated by the

Environmental Protection Agency http://www.epa.gov/oei/qualityguidelines/EPA-OEI-IQG-FINAL-10.2.pdf

EPA should ensure all of its actions are consistent with its general policy, procedures and guidelines related to information quality. For the draft EDSP List 2, EPA has not adequately dealt with these data quality issues. For example, the reliance on the National Drinking Water Chemical Occurrence Database (NCOD) is problematic given the following limitations of this database:

- The NCOD is a compilation of data sets developed using different sampling strategies and study design. Therefore, comparison of the data among data sources may not be possible. In addition, the extrapolation of these data nationwide may be limited.
- The extent of QA/QC in the NCOD is not clear from the available data and supporting materials.
- Information to assess the reliability of these data regarding detection limits, sample custody, and sample storage and preservation are lacking.
- Raw-water monitoring data may not be very useful in assessing potential human exposure to drinking water because water treatment methods may affect concentrations of these compounds.
- The age of some of the data compiled in the NCOD may decrease the usefulness and relevance of the data to current potential exposures due to differences in analytical methods and temporal differences in environmental contaminants.

Overall, the process EPA has used to determine that a substance "may be found in sources of drinking water" and that a "substantial population" may be exposed should be revised to rely on more relevant and accurate exposure data sources. Because EPA has asserted that the CCL3 list informs the 1457 Screening program, the reliance on the list involves an action based on science. SDWA Section 1412(b)((3)(A) requires that when, and to the extent such agency action is based on science, EPA must

(i) use the best available peer reviewed science and studies conducted in accordance with sound and objective scientific practices; and

(ii) data collected by accepted methods, or the best available methods, (if the reliability of the method and nature of the decision justifies the use of the data.)

This same standard has been incorporated into EPA's IQA Guidelines. Therefore, the data EPA relies on should meet the Agency's guidelines for data quality, should be publicly available and should be used in a manner that is scientifically justified. The listing criteria contained in the current list proposal fail to meet these basic EPA standards, and are not in accord with the statutory authority for the drinking water program in general.

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The American Chemistry Council appreciates the opportunity to comment on EPA's draft initial list of substances for EDSP screening. If you have questions regarding these comments, please contact Dr. Richard Becker by e-mail at Rick_Becker@americanchemistry.com or by phone at 202-249-6405.

Comments of the American Chemistry Council
On EPA's Endocrine Disruptor Screening Program
Filed on January 18, 2011

2. ACC Comments on Draft Policies and Procedures for Screening Safe Drinking Water Act Chemicals 75 Fed. Reg. 70558, Nov. 17, 2010 [EPA-HQ-OPPT-2007-1080; FLR-8848-9]

Comments of the American Chemistry Council
On EPA's Endocrine Disruptor Screening Program
Draft Policies and Procedures
For Screening Safe Drinking Water Act Chemicals

[75 Fed. Reg. 70558, Nov. 17, 2010]
[EPA-HQ-OPPT-2007-1080; FLR-8848-9]
January 18, 2011

EXECUTIVE SUMMARY

In 1996 Congress adopted amendments to the Federal Food Drug and Cosmetic Act (FFDCA) and the Safe Drinking Water Act (SDWA) calling on EPA to develop a program, using validated assays, to screen and test chemicals for endocrine disrupting effects. Since 1996, EPA and other stakeholders applied significant energy to the scientific validation of endocrine screens and tests and to research on the endocrine disruption hypothesis. ACC played a constructive role in all of those efforts. In addition, ACC continually raised with the Agency the importance of well thought out policies and procedures to implement the Endocrine Disruptor Screening Program (EDSP). All along, ACC's fundamental goal has been to ensure the EDSP is implemented as quickly and efficiently as possible, in a manner consistent with the authorizing laws and authoritative scientific policies and practices.

In 2009, EPA initiated Phase 1 of the EDSP, issuing 750 test orders on some 67 pesticide chemicals. Phase 1 focused on pesticide chemicals first because the FFDCA mandated the testing of all pesticide chemicals – active ingredients and inert ingredients. Phase 2 of the EDSP – the subject of several notices published on Nov. 17, 2010 including this one – proposes the screening of some 134 chemicals under the Safe Drinking Water Act's provisions authorizing the endocrine testing of substances in drinking water to which a substantial population may be exposed.[1]

In these comments on the Phase 2 SDWA policies and procedures, ACC makes the following key points:

- EPA must clearly define the key terms under the SDWA that prescribe the Agency's authority to identify drinking water substances for endocrine screening and must do so before it releases its final list of Phase 2 chemicals and before it issues EDSP Phase 2 orders.

[1] Throughout these comments, Phase 1 will refer to the first phase of the EDSP that focused on pesticide chemicals and Phase 2 will refer to this second phase, which focuses on SDWA chemicals. Congress pressed EPA to give attention to the endocrine screening of chemicals in drinking water in the House Appropriations Committee report for EPA's FY 2010 appropriations.

- Consistent with its FFDCA and SDWA authority, EPA must only issue Phase 2 EDSP orders to current manufacturers, importers and registrants and should allow order recipients to comply with an order by ceasing manufacturing.
- EPA should develop a clear, rational and equitable policy for identifying who shall be subject to EDSP testing under the authority of the SDWA, taking into account those activities that contribute to the occurrence of chemicals in drinking water to which a substantial population may be exposed.
- EPA should continue to ensure accurate, complete and consistent communications concerning the EDSP, including communications about the purpose of the Tier 1 battery and Tier 2 tests, the definition of "endocrine disruptor", the description of the Phase 2 List of Chemicals, and the extent of toxicity data that is relevant to endocrine disruption that is already available for the commodity chemicals included in the EDSP.
- EPA must develop meaningful weight of evidence guidance before it implements EDSP Phase 2 as well as meaningful opportunity for order recipients to rely on existing Other Scientifically Relevant Information in lieu of some or all of Tier 1 screening.
- EPA should not issue EDSP Phase 2 orders until it has received results from Phase 1 screening, assesses those results and, if necessary, modifies its Tier 1 battery and policies and procedures.
- EPA should provide additional guidance on reporting of EDSP Tier 1 results under TSCA 8(e).
- EPA should develop CBI procedures that are specific to the EDSP and that protect industry's legitimate intellectual property interests.
- EPA should develop data compensation provisions that are specific to the requirements of the EDSP and provide for fair and equitable sharing of test costs. These should describe EPA's duties in this area, (e.g., issuance of catch-up orders for late market entrants) and legally bind the Agency to those duties.
- To implement many of these recommendations about its authority and procedures, EPA should promulgate a broad procedural rule for the EDSP.

Comments of the American Chemistry Council On EPA's Endocrine Disruptor Screening Program Draft Policies and Procedures For Screening Safe Drinking Water Act Chemicals

75 Fed. Reg. 70558, Nov. 17, 2010
[EPA-HQ-OPPT-2007-1080; FLR-8848-9]

January 18, 2011

The American Chemistry Council[2] (ACC) is pleased to submit these comments on EPA's draft policies and procedures[3] for requiring Tier 1 screening of substances under the Endocrine Disruptor Screening Program (EDSP) pursuant to Section 1457 of the Safe Drinking Water Act (SDWA) and Section 408(p) of the Federal Food, Drug, and Cosmetic Act (FFDCA) ("Phase 2 screening"). In separate filings, ACC has also submitted comments on EPA's draft list of chemicals for EDSP Phase 2 and on EPA's proposed Information Collection Rule (ICR) for the EDSP. ACC panels and/or member companies have also submitted separate comments on EPA's draft list of chemicals for the EDSP Phase 2.

I. EPA Must Interpret Key SDWA Provisions Before it Issues its Final List of Phase 2 Chemicals and Before it Issues Phase 2 Orders

The scope of the EDSP as it concerns screening of drinking water contaminants turns on EPA's interpretation of the phrases "may be found in sources of drinking water" and "that a substantial population may be exposed." EPA has not yet interpreted those phrases, which limit the Agency's authority to require EDSP screening pursuant to the SDWA. Instead, EPA relies at this time on a number of existing lists of drinking water contaminants. While reliance on those existing lists provide an easy method for EPA to generate a list of potential

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[2] 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 $674 billion enterprise and a key element of the nation's economy. It is one of the nation's largest exporters, accounting for ten cents out of every dollar in 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.

[3] EPA, *Endocrine Disruptor Screening Program; Draft Policies and Procedures for Screening Safe Drinking Water Act Chemicals*, 75 Fed. Reg. 70558, Nov. 17, 2010 ("Draft Phase 2 Policies and Procedures").

substances for EDSP screening, those lists may not identify substances that "may be found in sources of drinking water" and to which "a substantial population may be exposed." Until EPA clearly defines those key phrases, its selection of substances or use of existing lists of substances for Phase 2 screening is arbitrary.

Congress laid out EPA's authority to require EDSP screening pursuant to the SDWA when it stated that EPA may provide for EDSP testing "of any other substance that **may be found** in **sources of drinking water** if the Administrator determines that a **substantial population may be exposed** to such substance." SDWA §300j-17, 42 USC §300j-17 (emphasis added). Congress did not define those key phrases, which clearly delineate the Agency's authority and the scope of the SDWA provision. Rather, Congress left it to the Agency to construe the meaning of the Act. Before it can move forward with selecting substances for Phase 2, the Agency must interpret the Act consistent with procedures provided by the Administrative Procedure Act. EPA's interpretation is subject to judicial review. The Agency is not entitled to grant itself unfettered authority and may not arbitrarily select substances for EDSP screening. The only way for EPA to ensure it acts within the authority granted by Congress is for the Agency to define the phrases "may be found in sources of drinking water" and "that a substantial population may be exposed."

When defining these two phrases EPA should define separately (1) "may be found"; (2) "sources of drinking water"; (3) "substantial population"; and (4) "may be exposed". When defining "may be found" and "may be exposed", EPA should rely on existing SDWA monitoring data and probable scenarios to demonstrate that a substance is found in drinking water to which people are exposed. EPA should also look at how it has defined "substantial population" for other environmental programs.

Further, EPA should define "sources of drinking water" as actual, rather than theoretical, sources of drinking water. Indeed, it might be argued that any water is a potential source of drinking water and any chemical might find its way into some water body or aquifer. But, such a broad interpretation of that phrase would render the express congressionally specified authority meaningless. EPA must assume, consistent with well-established legal principles of statutory construction, that Congress did not intend to include in the 1996 SDWA amendments, the authority of the Agency to apply to all water bodies and aquifers, irrespective of the potential of a water body or an aquifer to be used as a source of potable water.

Section 1457 of the SDWA is the statutory authority for the screening and testing of chemicals in drinking water for endocrine disruption. Basic principles of statutory construction mandate that its language be read as a whole, as well as in the context of the overall purpose of the Act. Thus, the language providing for testing of "any other substance that may be found in sources of drinking water" must be read in light of the subsequent language requiring that the Administrator determine "that a substantial population may

be exposed to such substance." The language on its face and taken as a whole compels the conclusion that EPA is not to test for substances that hypothetically, or by some remote possibility "may be found in sources of drinking water," but rather that it is to test for substances that are (1) likely to be present in sources of drinking water and (2) for which there is an empirical basis for that conclusion based on actual monitoring of finished drinking water or ambient water that is an actual source of water that is delivered to consumers as finished water. As a practical and legal matter under the SDWA, sources of drinking water cannot, in fact, expose substantial populations, absent those two prerequisites being met.

Based on public health considerations and established practices of water treatment and risk management, public water suppliers screen source water supplies as a matter of course to eliminate potential water sources that may present a broad range of potential health concerns (pathogens, regulated contaminants). Rather than drawing from every possible water body in the United States, water professionals select demonstrably pristine waters as drinking water sources, subject to EPA requirements. Drinking water is also drawn from sources where the watershed is managed to prevent runoff of potential contaminants and carefully monitored for the presence of such contaminants at all stages of treatment. Given this carefully managed and highly selective process of identifying water sources that will ultimately provide raw water for treatment, the broad net that EPA is attempting to cast through the use of gross and undifferentiated Toxic Release Inventory (TRI) data to identify candidate chemicals for endocrine screening lacks a rational nexus to the quality of water that is found in actual water sources. This approach is contrary to SDWA regulatory policy.

EPA's drinking water regulations confirm this. Public water systems are required to monitor for a host of regulated and unregulated contaminants, which data are reported and recorded in occurrence databases identified to each individual public water system in each state. In order to ensure that such data are useful from a health risk and management perspective, EPA's regulations expressly require that monitoring be performed on water that is representative of the water that consumers will be drinking. The universe of all ambient waters in the United States simply does not meet that test. Congress was clear that EPA should focus on the narrow and carefully selected subset of that universe, consisting of water that people actually will drink.

Section 1457 screening is authorized by the SDWA, a statute which has an exclusive focus on human health consequences (indeed, it is part of the Public Health Service Act). Accordingly, while other statutory programs such as the Clean Water Act may be concerned with broad based pollutants affecting all waters of the U.S., the SDWA focuses on those sources that ultimately serve as a source of drinking water and which present human health

risks. Given the host of geographic, topographic, water management, source water selection and fate and transport considerations that serve to confound the nexus between TRI emissions and actual source waters, reliance on the TRI database to identify chemicals for source water screening under the SDWA is not sufficiently supported by scientific evidence.

The Contaminant Candidate List 3 (CCL3) is a list of contaminants **not** regulated under the SDWA, but which **may** require a national drinking water regulation in the future. The CCL3 list is used to prioritize research and data collection efforts to help EPA determine whether a specific contaminant should be regulated. Substances can be on the CCL3 list because they may be released into the environment, not necessarily because they have been detected in drinking water sources. For certain substances, the CCL3 process uses TRI information and production data as an indicator of "prevalence" in drinking water. In such cases, EPA clearly acknowledges "[T]he relationship between production or even environmental release data and the actual occurrence in drinking water is complex." The Agency explains that many times the agreement between a CCL3 prevalence score based on actual measurements in potable water samples and a CCL3 prevalence score based on production or TRI data "was not good."[4]

In other words, EPA's analysis showed that in many cases, the scientific basis for using production data or TRI information as a surrogate for presence in drinking water was neither consistent nor accurate. Furthermore, of the commodity chemicals included in the draft EDSP List 2 solely by virtue of TRI information, there are six for which the TRI citations in the CCL3 indicate total releases into water of between 0.2 and 5 pounds total in all of the U.S. (Assuming a density equal to water, this is equivalent to volumes ranging from 3.2 ounces to 80 ounces (or approximately 1/3 a cup (100 ml) to less than 3 quarts (3 liters)). It is difficult to envision how such small volumes could meet the standard "that a substantial population may be exposed" to such substances. Being on the CCL3 list, therefore, does not necessarily mean the chemical is found in public drinking water sources to which a substantial population may be exposed. So being on the list, by itself, does not satisfy the statutory criteria of SDWA 1457. Absent a transparent and comprehensive demonstration of significant correlation, there is no reasoned basis for linking TRI data to potential source water exposure of any drinking water population,

[4] EPA (2009). Final Contaminant Candidate List 3 Chemicals: Classification of the PCCL to CCL EPA-HQ-OW-2007-1189-0187. http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OW-2007-1189-0187. Pages 23-24.

no less a substantial population.

Further, as noted above, public water systems are required by law and regulation to monitor for a host of regulated and unregulated contaminants. EPA concedes that the best available data for determining whether a source may present an issue of exposure to a substantial population is the extensive database of monitoring data that is recorded and reported to them by the nation's thousands of public water systems. Given the extent and accuracy of that database, as well as EPA's reliance upon it to enforce the SDWA, it is not scientifically justified for the Agency to look to surrogate measures, such as national chemical production or TRI data, which do not reliably correlate with prevalence of contaminants in drinking water sources as a means of identifying drinking water chemicals to which substantial human populations may be exposed. EPA has offered no legal or scientific justification for departing from its own accepted regulatory provisions for identifying regulated and unregulated contaminants that pose risks in source waters based on actual data.

EPA establishes drinking water MCLs for regulated contaminants and requires monitoring at or near the limits of detection for both regulated and unregulated contaminants. Significantly, EPA is required to set the MCL through the promulgation of a National Primary Drinking Water Regulation (NPDWR) at a level as close as feasible to the MCLG, which in turn, EPA is required by law to "set at the level at which no known or anticipated effects on the health of persons occur and which allows an adequate margin of safety."

Public water systems regularly monitor these regulated substances and report results for comparison to MCL and MCLG levels as required by the NPDWRs, using testing protocols mandated by the drinking water regulations to ensure the representativeness, accuracy and integrity of the data. Given the fact that that body of data (1) is required of all public water systems, (2) is system specific, and (3)can be traced directly to a water source, it is the only reliable indicator of potential source water contamination other than substantially similar testing of corresponding source water that may be conducted under the USGS or other programs. Testing for contaminants is ordinarily undertaken at or near the levels of detection, which in most instances for chemicals is at the part-per-billion level or less. For example, testing of synthetic organic chemicals in drinking water sources is generally one to two orders of magnitude below a corresponding MCL or MCLG.

In most instances, public water system monitoring does not register a detectable level of a contaminant, no less one that exceeds an MCL. In fact, the drinking water regulations recognize the statistical, practical and legal significance of that fact by providing that public water systems may reduce their frequency of monitoring based upon a demonstrated absence of a contaminant from the water supply.

In conclusion, ACC urges EPA to interpret the provisions of the SDWA that outline the Agency's EDSP authority by defining the key terms discussed above and evaluating its own accepted regulatory provisions for identifying regulated and unregulated contaminants that may pose risks in source waters based on actual data. ACC believes EPA must do this before it can identify substances for Phase 2 screening and before it implements Phase 2 of its EDSP. EPA has had 14 years to consider how it would interpret the EDSP provisions of the SDWA. For the last decade, ACC has asked EPA to define "may be found in sources of drinking water" and "that a substantial population may be exposed" so that the industry could understand EPA's interpretation of its authority under the SDWA and, therefore, the potential scope of the EDSP. Now we ask EPA to clearly outline its authority under the EDSP provisions of the SDWA and its broader regulatory provisions of the SDWA to ensure the Agency does not act arbitrarily when listing chemicals and implementing Phase 2 of the EDSP.

II. EPA Should Issue Phase 2 EDSP Orders Only To Current Manufacturers and Importers of Listed Chemicals

EPA states that it will rely on the authority granted the Agency by Federal Food, Drug and Cosmetic Act (FFDCA) section 408(p)(5)(A) to issue test orders requiring screening of substances identified in Phase 2 of the EDSP. The Act states:

> The Administrator shall issue an order to a registrant of a substance for which testing is required under this subsection, or to **a person who manufactures or imports a substance for which testing is required under this subsection**, to conduct testing in accordance with the screening program . . . .

FFDCA §408(p) (5) (a) (emphasis added). By its terms, FFDCA §408(p)(5)(a) refers to current registrants, manufacturers and importers ("manufacturers" for purposes of this comment). The Act uses the present tense when referring to potential order recipients, and does not explicitly or implicitly grant EPA authority to issue testing orders to those who are no longer manufacturers of a chemical.

EPA recognized the limit of its authority to current manufacturers when it issued testing orders for the first phase of its EDSP. At that time, it issued orders to current manufacturers of pesticide chemicals. Those who could demonstrate they no longer manufactured a chemical were exempt from the Phase 1 orders. Further, those who agreed to discontinue sale of the chemical into the pesticide market were also exempt from the Phase 1 orders. In sum, EPA limited its order authority to current, continuing manufacturers of Phase 1 pesticide chemicals.

In its Draft Phase 2 Policies and Procedures, EPA generally continues to

limit its order authority to current manufacturers of substances on the Phase 2 list. This is consistent with its policies and procedures issued for Phase 1 screening.[5] In its Draft Phase 2 Policies and Procedures, EPA acknowledges "the Agency generally intends FFDCA section 408(p) as giving the Agency authority to issue orders to **current** registrants, manufacturers, and importers of a chemical." Draft Phase 2 Policies and Procedures at 70567, col. 2 (emphasis added). Specifically, it proposes to exempt from Phase 2 screening those manufacturers who do not currently manufacture the chemical identified for testing (Test Order response option 4). See, Draft Phase 2 Policies and Procedures at 70564. ACC agrees with EPA's proposed approach for a number of legal and equitable reasons:

- First, EPA's proposed approach is consistent with the operative provisions of the FFDCA that limit the Agency's authority to issue test orders to current manufacturers and importers. This provides a strong legal basis for limiting testing to current manufacturers.

- Second, as EPA concluded, only manufacturers who continue to manufacture a chemical will receive economic benefit from the sale of the chemical with which to defray the cost of testing. This provides a very strong equitable basis for limiting testing to current manufacturers.

- Third, EPA's proposed approach is consistent with EPA's past implementation of its EDSP. Only current manufacturers were subject to the first phase of the EDSP. Again, from an equitable perspective, there is no basis for EPA to create different duties and burdens for different phases of the EDSP.

- Fourth, the proposed approach will make EDSP implementation easier and more equitable. If EPA extends its EDSP beyond current manufacturers, the Agency should explain the legal basis for that decision, how it will identify past manufacturers and how it will provide for cost sharing. EPA should publish those policies and procedures and provide an opportunity for public comment.

- Finally, extending its order authority to past manufacturers makes meaningless EPA's currently proposed option to exempt manufacturers who agree to discontinue manufacturing of the chemical. Little would be gained by a current manufacturer who agrees to cease manufacturing in order to be exempted from a test order if EPA could later require EDSP screening of that former manufacturer.

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5 EPA. Endocrine Disruptor Screening Program; Policies and Procedures for Initial Screening: Notice. 72 Fed. Reg. 17560, April 15, 2009 ("Phase 1 Policies and Procedures").

A. EPA Should Allow Order Recipients to Comply With Its Order by Ceasing Manufacturing

EPA proposes to exempt from Phase 2 screening those manufacturers who agree to discontinue manufacture of the chemical (Test Order response option 5). See, Draft Phase 2 Policies and Procedures at 70564. This proposal is consistent with the first phase of the EDSP in which EPA allowed order recipients to comply with testing orders by agreeing to cease sale of the listed chemical to the pesticide market. ACC agrees with EPA's proposal to allow a Phase 2 order recipient to comply with a testing order by ceasing all manufacturing of the listed chemical. This opt-out option is justified primarily because an order recipient who agrees to discontinue manufacture after receiving an EDSP order, like a former manufacturer, will receive no economic benefit from the sale of the chemical with which to defray the cost of testing.

EPA, nonetheless, requests comment on "whether it is generally inappropriate to allow companies to comply with an order by agreeing to cease manufacture or import of a SDWA chemical." Draft Phase 2 Policies and Procedures at 70567. In ACC's opinion, order recipients who opt to cease manufacture after receiving an order are, to any meaningful extent, similar to manufacturers who ceased manufacture at some point prior to receiving an order (i.e., non-current manufacturers). Both should be exempt from EDSP testing. Therefore, current manufacturers should be allowed to comply with an order by agreeing to cease manufacturing of the chemical. Whether an order recipient must conduct EDSP testing should not turn solely on when a manufacturer ceased manufacturing, it should turn on whether that manufacturer will continue manufacturing so that future sales may defray the cost of testing.

In support of its request for comment on the appropriateness of the option to cease manufacture, EPA argues that "[t]he chemical's current presence in sources of drinking water and the corresponding potential for public exposure is not altered by the fact that a particular company may subsequently choose to no longer manufacture or import the chemical in response to the order. The potential for continued exposure to the chemical exists despite any potential decrease that might be caused by the exit of one or more test order recipients." Draft Phase 2 Policies and Procedures at 70567. In ACC's opinion, this is not a valid reason for not offering order recipients the option to cease manufacturing. There is very little basis for distinguishing (in respect to whether chemicals are found in drinking water) manufacturers who ceased manufacture in the past and those who cease manufacture when they receive an EDSP order. Consider, for example, what the basis would be for distinguishing an order recipient who ceased manufacturing one day before receiving an EDSP order from one who ceased manufacturing one day after receiving an EDSP order. Beyond mere semantics, why would one be exempt from EDSP testing while the other would not? For the reasons discussed above, both should be exempt.

ACC also believes it is improper for EPA to suggest that a reason for offering the option to cease manufacturing is to manage "[t]he chemical's current presence in sources of drinking water and the corresponding potential for public exposure." EPA states that it believes that encouraging a test order recipient to stop manufacturing and importing will lead to less exposure to the chemical in sources of drinking water. See, Draft Phase 2 Policies and Procedures at 70567. In sum, EPA appears to propose to use the EDSP to manage chemicals and exposures. The EDSP provisions of the SDWA and FFDCA, however, are for information collection only. FFDCA Section 408(p) makes it clear that EPA must use other statutory authority to manage endocrine risks, once these risks are established. If EPA's goal is to use the EDSP to manage drinking water contaminants, EPA is acting well outside its FFDCA 408(p) authority.

Even if EPA had the authority to use the EDSP to manage exposures and chemicals in drinking water, EPA's approach likely would not be effective. As discussed above, whether a substance ends up in sources of drinking water often has more to do with use, disposal and environmental releases than with the level of manufacturing or importing. Further, to the extent a party ceases manufacture or import of a chemical, other parties could increase manufacture or import of the substance to fill a need. While decreasing the number of manufacturers or importers might improve chemical management or decrease production volumes, use and disposal of a chemical likely has the greatest impact on whether a chemical will be found in sources of drinking water.

EPA also states that requiring a company to provide EDSP data even if it ceases manufacture and import, "removes a major incentive for companies to stop producing chemicals for which test orders are issued." Draft Phase 2 Policies and Procedures at 70567. While this is clearly true, EPA's implication that merely ceasing production by a manufacturer will decrease amounts of a chemical in drinking water may not be correct for the reasons discussed above. Also, as discussed above, EPA does not have the authority to use testing orders to manage chemicals.

In support of its proposal to offer order recipients the option to cease manufacture, EPA reasoned correctly "an order recipient who ceases to manufacture or import a chemical that is subject to EDSP screening will no longer receive any economic benefit from the sale of the chemical with which to defray the cost of testing." Draft Phase 2 Policies and Procedures at 70567. ACC believes this is strong, equitable and sufficient reason for requiring EDSP screening by only current manufacturers and for allowing manufacturers to comply with a testing order by agreeing to cease manufacture of a chemical.

B. EPA Should Not Consider Persistence When Implementing the EDSP

EPA also requested comment on whether and how to factor a chemical's persistence in the environment into EDSP policies and procedures. It is ACC's opinion that EPA need not consider persistence when listing chemicals for EDSP Phase 2. It is not clear how EPA would incorporate persistence in determining whether a chemical may be found in sources of drinking water and whether a substantial population is exposed. Those findings should be based on actual data concerning the presence of a chemicals and a determination of what constitutes a substantial population. A chemical that meets those limitations will do so regardless of persistence. Trying to incorporate persistence is unnecessary and will likely confuse the listing process. Instead, as discussed above in Section I, ACC urges EPA to focus on interpreting the terms of the SDWA that directly influence which chemicals may be included in the EDSP Phase 2 list.

Further, EPA's persistence question is more relevant to the scope of EPA's authority with respect to limiting testing to current manufacturers and offering order recipients to comply with test orders by ceasing manufacturing of a chemical. Specifically, EPA appears to be asking whether it should require former manufacturers (those who are not current manufacturers) to test persistent chemicals, i.e., not limit orders to current manufacturers. With its persistence question, EPA is also asking whether it should withdraw the option to comply with a test order by ceasing manufacturing, since requiring former manufacturers to test makes the option to comply with a test order by offering to cease manufacturing meaningless. ACC believes persistence should not influence either consideration for all of the reasons discussed above.

To summarize, the legal and equitable reasons for limiting testing orders to current manufacturers of listed chemicals and for allowing an order recipient to cease manufacture/import of a chemical include: (1) the FFDCA limits EPA order authority to current manufacturers/importers; (2) it provides for the easiest and most equitable implementation of the EDSP; (3) an order recipient who ceases manufacture will no longer receive any economic benefit from the sale of the chemical with which to defray the cost of testing; and (4) it would allow consistency among phases of the EDSP.

C. EPA Should Consider Its Rationale for Testing to Determine Which Current Manufacturers Should Be Subject to EDSP Testing

Once EPA defines terms that outline its authority to identify SDWA chemicals for EDSP testing, the next question EPA must address is who will be subject to the EDSP test orders for those chemicals. EPA's goal should be to assure equitable resolution of who should either conduct the testing or contribute to the cost of testing (See also Section VII below.) ACC suggests that EPA's

experience with determining who should be required to test under Toxic Substance Control Act (TSCA) test rules should also be considered here, for two reasons. First, "manufacturers and importers" is the operative term in the EDSP statutory authorities and it's also a defined term under TSCA and its implementing regulations. Second, TSCA penalties apply for failure to test substances (non-pesticide chemicals) under the EDSP.

EPA has developed procedures for TSCA test rules aimed at determining the nature of the activities of manufacturers and importers with respect to specific test rules to determine which persons should be initially subject to a test rule (Tier 1 persons) and which persons (Tier 2 persons) should be required to test only as a secondary matter, (e.g., if no Tier 1 persons can be identified) or required to provide reimbursement to those persons who actually do the testing. In comments on previous TSCA test rules, ACC has asserted that EPA should retain flexibility in future test rules to identify considerations that would justify imposing testing responsibilities on those generally considered Tier 2 producers.[6] Importantly, however, ACC has also urged EPA to explain those considerations so the regulated community understands the rationale for EPA's approach in that particular circumstance in each specific rule.

While EPA is not choosing to use TSCA test rules in the EDSP, these two principles (equity and transparency) are important, particularly in Phase 2 of the EDSP where EPA is addressing substances in drinking water to which a substantial population may be exposed.

For certain chemicals on the Draft EDSP List 2, occurrence in drinking water sources can result from natural sources, from manufacturing, processing and importing of a specific chemical, and from uses of other products and from other activities. EPA should give due consideration to what manufacturing, importing, or other activities contribute to the occurrence of chemicals in drinking water to which a substantial population may be exposed in order to identify who should be subject to EDSP testing under the SDWA. These policies might address, for example, chemicals which may be found as contaminants in drinking water for which the major sources are from current commercial activities, but not from the current manufacture or import of the specific chemical per se. EPA should make its rationales clear in its final policies and procedures.

III. EPA Should Continue to Ensure Accurate, Complete and Consistent Communications Concerning the EDSP

Generally speaking, EPA has clearly and accurately communicated important aspects of its EDSP to the public. On occasion, however, Agency communications across EPA offices and programs have been unclear, inconsistent

[6] Comments of the Chemical Manufacturers Association on EPA's Proposed Test Rule for Dermal Absorption, at p.5,

and inaccurate. ACC urges EPA to maintain its efforts to accurately inform the public concerning the EDSP and to take steps to improve communications by all Agency offices and programs.

A. EPA Should Consistently and Clearly Describe the Purpose of the EDSP Tier 1 and Tier 2 Batteries

EPA clearly describes the purpose and structure of the EDSP in its Draft Phase 2 Policies and Procedures. EPA states: "In general, EPA intends to use the data collected under the EDSP, along with other information to determine if a pesticide chemical, or other substances, may pose a risk to human health or the environment due to disruption of the endocrine system." Draft Phase 2 Policies and Procedures at 70,560. Specifically, EPA accurately describes the EDSP as a two-tiered testing program. The purpose of Tier 1 screening is to determine whether a substance has the potential to interact with the estrogen, androgen or thyroid (EAT) systems. Substances that have the potential to interact with EAT systems will proceed on to Tier 2, which is designed to "identify any adverse endocrine-related effects caused by the substance, and establish a quantitative relationship between the dose and that endocrine effect." Draft Phase 2 Policies and Procedures at 70,560. ACC believes EPA's description of the EDSP in the Draft Phase 2 Policies and Procedures is clear and accurate, and should be consistently used by all EPA offices and programs.

It is important to understand how EPA's description of the EDSP, as stated above, is consistent with Agency authority. Congress expected EPA would use the EDSP to generate data enabling it to "take action under such statutory authority as is available to the Administrator . . . to ensure the protection of public health." FFDCA §408(p)(6). For these reasons, it is significant that EPA describes the purpose of EDSP as generating data that will determine adverse effects and risks. It is also significant that EPA clearly describes the EDSP and a two-tiered program in which the ultimate goal is not to simply generate Tier 1 data. Indeed, the purpose of the EDSP is not to merely determine whether a substance may interact with the endocrine system (the objective of Tier 1 screening). Rather, the purpose of the EDSP is to determine whether substances cause adverse effects through an endocrine mechanism. This understanding should underpin all Agency communications concerning the EDSP.

Although the Agency accurately describes the EDSP in its Draft Phase 2 Policies and Procedures, EPA's description has not been consistently applied across the Agency. Specifically, ACC is concerned that the description of Tier 1 screening has drifted. Assuming Tier 1 could accurately predict whether a substance interacts with the endocrine system[7], the mere interaction of a substance

[7] As the Agency knows, the Tier 1 screens were designed to be sensitive and have low false negative rates, and thus corresponding high false positive rates. Therefore, it may not be possible to determine with an adequate degree of scientific certainty whether a particular substance that is positive in some Tier 1 screens interacts with the endocrine system. Rather, as

with the endocrine system may be of no practical concern and certainly may not be the basis for Agency risk management action. The practical use or utility of Tier 1 is to generate data that will determine which substances should undergo Tier 2 testing. Tier 2 will generate data concerning risk and hazard that may be used by the Agency to manage risks. Indeed, ACC believes EPA would not have had the authority to develop an EDSP that consisted of only Tier 1 screens and, therefore, only determined whether a substance interacted with the endocrine system. That would have been a research program and would not meet the requirements of practical utility consistent with the Paperwork Reduction Act for a regulatory program.

Even within other recent EDSP notices generated by the Office of Pollution Prevention and Toxics (OPPT) there are inconsistent descriptions of the program. Unlike the Draft Phase 2 Policies and Procedures, the Phase 2 ICR[8] seems to confuse the well-established purposes of the EDSP Tiers. The Phase 2 ICR states that the purpose of Tier 2 is merely to "establish a dose-response relationship for any adverse effects that might result from the interactions identified through the Tier 1 assays." Unfortunately, here the Agency fails to clearly state that Tier 2 will also determine adverse effects. Some might get the incorrect impression from the Phase 2 ICR that Tier 1, which determines interaction with the EAT system, determines adverse effects. Further, they might infer from EPA's description that the Agency believes interaction with the EAT systems is an adverse effect. This would not be an unreasonable inference for someone unfamiliar with endocrinology and the history of the EDSP development.

Similarly, in its Phase 2 Listing Document, EPA again describes Tier 1 as "assays used to screen the chemicals for interaction with the [EAT] hormonal systems." Phase 2 Listing Document at 70,250. Concerning Tier 2, EPA simply states "Tier II test assays are intended to test for more specific chemical effects on the endocrine system . . ." *Id.* From this description, which doesn't mention adverse effects or dose-response, a reader might incorrectly conclude Tier I determines adverse effects. According to this description, the main difference between Tier I and Tier II is merely the specificity of the chemical effects detected in each tier. Again, EPA should have simply repeated the description of the EDSP it used for the Draft Phase 2 Policies and Procedures when describing the EDSP in the Phase 2 Listing Document.

Generally, ACC is concerned that if EPA can be inconsistent in describing

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EPA states, Tier 1 is designed to determine whether a substance "has the potential" to interact with the endocrine system.

[8] EPA, Agency Information Collection Activities; Proposed Collection; Addendum for the Second List of Chemicals; Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP: EPA ICR No. 2249.02, OMB Control No. 2070-0176. 75 Fed. Reg. 70,568, Nov. 17, 2010 ("Phase 2 ICR").

the EDSP in three related EDSP documents issued at the same time, it is unlikely EPA is consistently and accurately describing the EDSP across other EPA offices and programs. EPA – and in particular its Office of Chemical Safety and Pollution Prevention (OCSPP) and OPPT which manage the EDSP -- must be more diligent in ensuring consistent and accurate descriptions of the EDSP.

B. EPA Should Consistently and Accurately Define "Endocrine Disruptor"

ACC urges EPA to accurately and consistently communicate the definition of "endocrine disruptor" across the Agency. It is clear from EPA's long-standing policy statements that "endocrine disruptors" are substances that adversely affect organ systems by interacting with the endocrine system. EPA correctly states in its EDSP Policy Statement:

> 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. [9]

EPA's description of endocrine disruption has two important implications. First, a mere interaction with the endocrine system is not "endocrine disruption." Almost everything and anything can interact with the endocrine system. In many cases, depending on dose, there may be an endocrine response – most often a homeostatic response. Those responses are rarely adverse. Second, 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 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."

EPA's use and definition of the term "endocrine disruptor" has been inconsistent across EPA programs. On occasion, EPA's definition of "endocrine disruptor" has been inaccurate and has been inconsistent with EPA's descriptions of Tier 1 and Tier 2 testing in its policy statement on the EDSP. For example, EPA's Office of Research and Development (ORD) has described "endocrine

[9] EPA, Endocrine Disruptor Screening Program, Proposed Statement of Policy, 75 Fed. Reg. 71541, 71564, Dec. 28, 1998 ("EDSP Policy Statement").

disruptors" (at http://epa.gov/ncer/science/endocrine/#eds) in various ways:

- 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.

- EDCs can include man-made chemicals such as pesticides and plasticizers, natural chemicals found in plants (phytoestrogens), pharmaceuticals, or hormones that are excreted in animal or human waste.

ORD's description of "endocrine disruptors" states, contrary to the EDSP Policy Statement, that endocrine disruptors simply interfere with the endocrine system, rather than defining endocrine disruptors as substances that cause adverse effects. Any definition of endocrine disruption that does not include both the direct interaction with the endocrine system and adverse effects is inconsistent with Agency EDSP policy.

Another example of EPA's use of an incorrect definition of "endocrine disruptor" and its inappropriate use of the EDSP can be found in the Agency's Design for Environment (DfE) program. In that program EPA states:

> An **endocrine disruptor** is an external agent that interferes in some way with the role of natural hormones in the body. An agent might disrupt the endocrine system by affecting any of the various stages of hormone production and activity, such as by preventing the synthesis of hormones, by directly binding to hormone receptors, or by interfering with the natural breakdown of hormones.[10]

According to this Agency definition, a substance that is positive in an EDSP Tier 1 *in vitro* receptor binding assay would be termed an "endocrine disruptor" if it bound to a hormone receptor. This definition is irrational.

Recently, DfE again ignored the EDSP when it improperly proposed to use results of EDSP Tier 1 screening for product risk management actions. The DfE proposed standard, which is being circulated for review and comment, proposes action based solely on "interaction" or "perturbation" of the endocrine system states:

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[10] EPA, OPPT, Design for the Environment Program, Master Criteria for Safer Ingredients. July 2010, at 4. http://www.epa.gov/dfeprojects/gfcp/dfe_master_criteria_safer_ingredients.pdf

> Chemicals that are candidates for endocrine screening will be part of the review. **Chemicals found to interact with or perturb the endocrine system**—potentially leading to reproductive, developmental, carcinogenic, systemic, hormonal or other effects—will not be allowed based on the toxicological hazards they pose. (emphasis added) [11]

The proposed DfE risk management action is inappropriate and inconsistent with EPA's EDSP Policy Statement. In EPA's two-tiered EDSP, Tier 1 is specifically designed to maximize the sensitivity to detect any interaction with components of the estrogen, androgen and thyroid systems. The EDSP Tier 2 is designed to identify adverse effects and dose response and it is the Tier 2 results that are to be used for risk assessment and risk management. The EDSP Tier 1 assays, which determine the potential of a chemical to interact with components of the endocrine system, are not intended to signal a concern for health risks that would lead to bans or substitutions. EPA has been very clear on this point:

> EPA developed a two-tiered approach to implement the statutory testing requirements. 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 through the Tier 1 assays. (emphasis added). [12]

The description and proposed actions regarding endocrine disruption in the draft DfE Standard, as currently written, would base action on Tier 1 EDSP screening results, and would promote regulation based merely on the potential of interactions rather than on adverse effects and risk, thus shifting the Agency's well established, scientifically grounded, risk-based chemical management paradigm. This is inappropriate. Indeed, the NRC panel, which used the term "perturbation," clearly states it did not envision that regulatory actions would be triggered by any finding of a perturbation. The National Research Council's (NRC) experts stated in "Toxicity Testing in the 21st Century: A Vision and a

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[11] Proposed Enhancements to the Design for the Environment (DfE) Standard for Safer Products http://www.epa.gov/dfe/proposed_enhancements_to_dfe_standard_for_safer_products.html

[12] http://www.epa.gov/endo/pubs/revised_pandp_frn_041509.pdf

Strategy":

> Biological responses viewed as the result of an intersection of exposures with biological functions. The intersection leads to perturbations of biological pathways. **When perturbations are sufficiently large or when host is unable to adapt** because of underlying nutritional, genetic, disease or life-stage status, biological function is compromised (emphasis added).[13]

In sum, an adverse effect (or an effect that warrants use as an endpoint for risk assessment and the basis for determining product stewardship or risk management actions or consideration for possible substitution of a chemical in a product) is not merely any known biochemical or chemical change, or even any known or measureable precursor along the pathway that could lead to some degree of perturbation. The NRC Committee clearly indicated that consideration of adversity occurs when perturbations are sufficiently large or when a host is unable to adapt.

These are just a couple of examples of EPA's inappropriate and inconsistent description of endocrine disruptors and use of its EDSP. EPA Offices and programs should follow the Agency's policies in describing what EDSP Tier 1 screening results are and are not, properly define "endocrine disruption" and ensure the appropriate use of information generated in the Tier 1 EDSP. In sum, EPA should improve its communications concerning endocrine disruption and the EDSP.

C. EPA Should Continue its Accurate Depiction of the EDSP Phase 2 List

EPA accurately communicated the significance of draft Second List of Chemicals for Tier 1 Screening. 75 Fed. Reg. 70248, Nov. 17, 2010 ("Draft Listing Notice"). EPA correctly stated in the Draft Listing Notice that "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." Draft Listing Notice at 70250. The Agency must continue to communicate accurate and complete information about the substances on the EDSP Phase 2 list, especially

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[13] Toxicity Testing in the 21st Century: A Vision and a Strategy (2007). The National Academies Press, Washington, DC, 20001. Page 49.

after EPA finalizes the list. For example, in addition to the caveat quoted above, EPA should clarify that the current lack of endocrine mechanistic information for any particular substance does not mean that the substance poses significant risks to human health, even at environmentally relevant levels of exposure.

D. EPA Should Communicate that a Majority of the Commodity Chemicals on the Draft Phase 2 List Have Already Been Evaluated for Potential Health Hazards that Could Arise from the Endocrine Mode of Action

Further, while it is appropriate for EPA to base EDSP prioritization on exposure potential, it should emphasize in all of its EDSP communications that, for many if not all of the EDSP Phase 2 substances, the Agency already has data and information on relevant apical tests that are used for risk assessment purposes, including tests for reproduction and developmental toxicity (potential effects which can be mediated by endocrine pathways). This is especially true of all pesticide chemicals, which are data-rich by virtue of stringent FIFRA testing requirements. Furthermore, many of the commodity chemicals identified on the draft EDSP List 2 also have extensive toxicity testing databases. Even if specific endocrine screening has not yet been conducted on certain compounds, hazard identification based on observable outcomes from apical toxicity tests (e.g., outcomes such as pathologic states indicative of disease conditions) covers <u>all</u> modes of action, including endocrine pathways.

As EPA is well aware, endocrine activity, as determined by Tier 1 screening, is not a distinct toxicological hazard per se, but rather a measure of a compound's ability to interact with components of the endocrine system. Interaction with or modulation of endocrine processes may or may not give rise to adverse effects. It is the apical tests, the EDSP Tier 2 tests or similar toxicology tests that determine adverse effects and dose response that are to be used for hazard identification and risk assessment. Beyond merely determining endocrine activity, the toxicity information developed by many chemical manufacturers as part of product stewardship and regulatory programs is directly relevant to evaluating risks (including potential effects mediated by endocrine pathways) and to evaluating the health of individuals, including children. Such data typically includes: 1) identification and definition of possible hazards upon all major organ systems from both acute and repeated exposures; 2) detection of potential hazards arising from *in utero* exposures; 3) evaluation of potential of a substance to affect reproduction; and 4) evaluation of the potential of a substance to damage DNA. While the acute toxicity studies are not directly relevant for determining endocrine disruption, the developmental and reproductive toxicity studies are relevant because they assess risks that could affect normal prenatal and postnatal growth, development and maturation.

Of the commodity chemicals included in the Draft EDSP List 2, for every

substance that is a regulated drinking water contaminant, EPA has conducted a hazard evaluation based on apical toxicity data to set a Maximum Contaminant Level Goal (MCLG). The MCLG is "the maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on the health of persons would occur, and which allows an adequate margin of safety."[14] In addition, approximately 70% are included in the OECD HPV chemical list,[15] and available hazard information for these substances can be accessed on the e-ChemPortal.[16] What's more, greater than 75% of these chemicals have been assessed by EPA and included in the Agency's Integrated Risk Information System (IRIS http://www.epa.gov/IRIS/). IRIS assessments include evaluation of apical toxicity tests, and, IRIS establishes Oral Reference Doses which are an "estimate of a daily oral exposure for a given duration to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime."[17] For chemicals with potential carcinogenic activity, IRIS establishes Oral Slope Factors for use in deriving estimates of upper bound lifetime cancer risks. The Agency relies on IRIS assessments in a number of programs, including the Drinking Water Office, for assessing and for determining risk management options.[18] Therefore, because Agency decisions on these substances are based on adverse effects in the toxicology studies that cover all modes of action, and the Agency already has the results of such studies in hand for a majority of the commodity chemicals included in the draft EDSP List 2, there should be little concern that potential significant risks have not been accounted for.

ACC believes that it is important for the public to understand the extent of toxicity data that is relevant to endocrine disruption that is already available for the commodity chemicals included in the EDSP. By not referencing existing, publicly available sources of hazard and risk information, such as Drinking Water Standards and Health Advisories, IRIS and the e-ChemPortal, the Agency has missed an opportunity to inform the public and policy makers of the extent of existing toxicity information already in the public domain concerning the EDSP Draft List 2 candidates. This oversight should be corrected when the Agency publishes the final EDSP List 2, by including references and links to relevant Agency hazard and risk information data sources.

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http://water.epa.gov/lawsregs/rulesregs/regulatingcontaminants/basicinformation.cfm

15 OECD (2004). The 2004 OECD List of High Production Volume Chemicals. http://www.oecd.org/dataoecd/55/38/33883530.pdf

16 http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en

17 http://www.epa.gov/IRIS/

18 http://water.epa.gov/action/advisories/drinking/upload/dwstandards2009.pdf

IV. EPA Must Develop Meaningful Weight of Evidence Guidance Before it Implements EDSP Phase 2

Tier 1 of the EDSP will generate large amounts of data that must be assessed to determine whether a substance interacts with the endocrine system and whether those data trigger further Tier 2 testing. It is critical that EPA develop meaningful weight of evidence (WoE) guidelines. Without a meaningful WoE process and guidelines to direct the Agency, not only will EPA be unable to properly assess Tier 1 data, actions it takes in response to Tier 1 findings may be arbitrary. Further, the availability of clear, meaningful WoE guidance may help order recipients conduct Tier 1 assays: knowing how the Agency will evaluate the Tier 1 screens may inform study deigns to ensure scientifically robust and reliable results are obtained. For these reasons, industry has for a number of years urged the Agency to develop a WoE process for assessing EDSP data and has offered its assistance in that regard.

EPA committed to developing a WoE process and publishing WoE guidance. In its Phase 2 Policies and Procedures, EPA states it will use a WoE process to (1) assess whether existing data are sufficient to satisfy an EDSP order; (2) assess Tier 1 data and other information to determine if a chemical has the potential to interact with the EAT systems; and (3) determine which Tier 2 tests might be required. In its Phase 1 Policies and Procedures, EPA also committed to developing WoE guidance for evaluating Tier 1 screens and the Tier 1 battery.

OMB, in its Terms of Clearance for Phase 1 of the EDSP, directed EPA to develop a WoE process for assessing Tier 1 EDSP data before it revised its ICR (EPA's Draft Phase 2 ICR is a proposed revision to its ICR). OMB stated:

> [I]n 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.[19]

Congress, in the House Appropriations Committee report for EPA's FY 2010, also directed EPA to develop and publish criteria for evaluating the results of Tier I screening and determining whether a chemical should undergo Tier II analysis.

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[19] Office of Information and Regulatory Affairs, Office of Management and Budget, *Approval of EPA's Information Collection Request: Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP)*, OMB Control No: 2070-0176, ICR Reference No: 200904-2070-001, Oct. 2, 2009, ("OMB Terms of Clearance").

EPA was to have done that within one year of enactment of the appropriations bill and was to allow for public input.[20]

On November 3, 2010, EPA issued what it termed Draft WoE Guidance Document for evaluating EDSP Tier 1 screening and to identify chemicals for Tier 2 testing.[21] This draft WoE Guidance is in large part, however, merely a brief review of the existing EDSP. Only slightly more than two pages of the Guidance actually discuss the assessment of Tier 1 data, and that discussion offers only general considerations that EPA might make in its WoE determinations. EPA's Draft WoE Guidance provides only introductory material that might precede an actual guidance document for conducting WoE evaluations on results of the Tier 1 Endocrine Screening Battery (ESB). Although the Agency claims that the Draft WoE Guidance will provide transparency and consistency to ESB evaluations, the lack of substantive information and detail contained in the Draft WoE Guidance is of considerable concern. It is difficult to envision how this guidance would assure transparency and consistency, and prevent arbitrary Agency determinations.

In sum, the draft WoE document does not provide useful or meaningful WoE guidance. Further, in contrast to EPA's expectations, the Draft WoE Guidance does not comply with the OMB and Congressional directives for the first list of chemicals to be screened under the EDSP. Draft WoE Guidance at 2. EPA has not yet developed a sufficiently thorough and transparent WoE process nor has it issued clear and comprehensive WoE guidance that indicates how EPA will or should assess Tier 1 data. EPA should draft meaningful guidance to comply with those directives, and fulfill its stated commitments to develop and publish WoE guidance.

In ACC's opinion, EPA is obligated to develop and publish a thorough guidance document for conducting WoE evaluations of the Tier 1 Endocrine Screening Battery that includes a clear delineation of guiding principles, clear criteria for evaluating studies, and a methodology for weighting evidence and reaching conclusions. When it develops its WoE guidance, EPA should leverage and apply the work of other scientists who have published on the topic and

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[20] Congress's House Appropriations Committee report for EPA's FY 2010 appropriations (H.R. 2996, H. Rept. 111-180), June 23, 2009.

[21] EPA, Weight of Evidence Guidance: Evaluating Results of EDSP Tier 1 Screening to Identify Candidate Chemicals for Tier 2 Testing; Draft for Public Comment, Nov. 3, 2010 ("Draft WoE Guidance"). See, EPA's notice announcing the availability of its Draft WoE Guidance. 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. 67963, Nov. 3, 2010.

consider available advice for building a robust and transparent WoE framework.[22] EPA might also reach out to the scientific community to help it develop a scientifically sound and meaningful WoE framework and guidance. EPA should do this before Tier 1 data are generated in Phase 1 of the EDSP and certainly before the Agency issues new Phase 2 orders. Furthermore, the Agency's EDSP WoE guidance should also undergo scientific peer review, in accordance with the requirements of EPA's Peer Review Handbook (and Peer Review Policy) and Information Quality Guidelines.

ACC urges EPA to develop useful, meaningful WoE Guidance and to publish that guidance as soon as possible - certainly before it implements Phase 2 of its EDSP. ACC will be submitting specific comments on EPA's draft WoE Guidance and calls EPA's attention to those.

V. EPA Should Provide a Meaningful Opportunity for Order Recipients to Rely on OSRI

EPA provided order recipients the opportunity to submit Other Scientifically Relevant Information (OSRI) in lieu of some or all of Tier 1 screening. This was consistent with: Congress' directive in the Food Quality Protection Act to limit unnecessary testing; OMB's directive to promote and encourage the use of OSRI[23]; sound science-based policy; and with the concerns

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[22] EPA's Draft WoE Guidance fails to consider the discussion of WoE methods in the scientific literature. Indeed, EPA provided no references to the peer-reviewed literature regarding WoE evaluations.

[23] OMB, in its Terms of Clearance, 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. 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 responses to the Tier I 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 time of submission of revision of this information collection to cover additional chemicals."

Office of Information and Regulatory Affairs, Office of Management and Budget, *Approval of EPA's Information Collection Request: Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP)*, OMB Control No: 2070-0176, ICR Reference No: 200904-2070-001, Oct. 2, 2009, ("OMB Terms of Clearance").

of the animal welfare community. EPA's offer to order recipients to submit OSRI is especially justified given that many of the substances on EPA's EDSP Phase 1 and 2 lists of chemicals for EDSP screening are data rich chemicals for which relevant testing data exist including, in many cases, high quality reproductive and developmental toxicity data.

EPA has not, however, clearly articulated its basis for evaluating the OSRI submissions and has not clearly outlined its policy goals concerning OSRI. Until it does that, its OSRI determinations may be inconsistent and misunderstood, and it will not be clear what information should be submitted to the Agency. For that reason, EPA should outline its basis for evaluating the OSRI and its policy goals concerning OSRI in order to provide a meaningful opportunity for order recipients to rely on OSRI. EPA should publish clear guidance stating how it will evaluate OSRI before it issues new EDSP Phase 2 orders.

A number of EDSP Phase 1 order recipients have collected OSRI and have submitted those data to EPA. EPA is in the process of responding to those submissions. Yet, to date, EPA has not published clear guidance that explains how EPA intends to assess OSRI nor has it fully explained the bases for the OSRI decisions made to date. Indeed, based on the EPA responses to date, it is difficult to discern EPA's method for assessing OSRI. In some instances, it appears EPA has summarily dismissed some OSRI submissions. There is no way for order recipients to know whether EPA acted justifiably in dismissing OSRI submissions. In any event, it is not reasonable for EPA to expect the regulated community to try to decipher EPA's intent and requirements by having to analyze the emerging series of Agency OSRI actions. For these reasons, EPA must articulate its basis for evaluating OSRI submissions and clearly outline its policy goals concerning OSRI.

Because EPA has not issued clear, publically available, peer reviewed OSRI assessment criteria, ACC is also concerned that the public could misinterpret EPA's OSRI rejections as an overall assessment of the quality of existing data. Order recipients have undertaken (often in response to an EPA directive) extensive, costly product stewardship programs designed to ensure products can be used safely for their intended purposes. Data from those programs have been and will be submitted as OSRI. Because EPA has not explained how it assesses OSRI, its rejection of OSRI submissions may, in the public eye, undermine the value of good quality data, in many cases, apical toxicity test results identical, or very similar to, EDSP Tier 2 tests. Again, much of the problem arises from EPA's failure to adequately articulate its criteria for evaluating OSRI. Therefore, ACC urges EPA to clearly articulate its basis for assessing OSRI and to outline its policy objectives concerning the use of OSRI in the EDSP. EPA should do this before it issues additional EDSP testing orders.

VI. EPA Should Provide for CBI Protection Specific to the EDSP

Congress explicitly stated that EPA should, in collecting information pursuant the EDSP, develop procedures for handling confidential business information (CBI) to the extent practicable. FFDCA §408(p)(5)(B). In the Draft Phase 2 Policies and Procedures, EPA chose not to develop CBI procedures. The Agency interpreted the statutory language as not granting EPA authority "to create new rights or to modify existing rights to confidentiality," but rather as directing EPA to act within existing statutory authority. Draft Phase 2 Policies and Procedures at 70566. For non-pesticide chemicals, existing authority according to EPA is limited to CBI protections granted by the Trade Secrets Act and the Freedom of Information Act (FOIA). ACC disagrees with EPA's narrow reading of FFDCA §408(p) and believes EPA should, as Congress directed, develop CBI procedures specific to the EDSP since this program is being conducted under FFDCA and SDWA authorities, but impacts TSCA manufacturers and importers. If Congress had intended EPA to do nothing and simply rely on existing CBI procedures, it would not have explicitly directed EPA to develop CBI procedures.

ACC believes that protecting CBI from disclosure to competitors is critical to protecting industry's legitimate intellectual property interests. ACC believes everything exempt from disclosure under the FOIA should be deemed eligible for CBI protection, provided it can be substantiated against well-established criteria. ACC supports the current health and safety study exception to CBI under TSCA. Finally, ACC believes that it is important to protect information that alone may not be particularly sensitive, but when combined with one or more other pieces of information, may reveal confidential information.

VII. EPA Should Provide for Meaningful and Enforceable Data Compensation Provisions Specific to the EDSP

Congress explicitly stated that EPA should, in collecting information pursuant the EDSP, develop to the extent practicable procedures for fair and equitable sharing of test costs. FFDCA §408(p)(5)(B). EPA narrowly interprets this congressional directive as "merely establish[ing] a qualified direction" that does not create new authority, but merely directs the Agency to create procedures that operate within the confines of existing statutory authorities. Draft Phase 2 Policies and Procedures, at 70565.

Generally, ACC disagrees with EPA's narrow reading of FFDCA §408(p) and believes EPA should, as Congress directed, develop new procedures to ensure fair and equitable sharing of test costs. If Congress had intended EPA to do nothing and rely on existing data compensation procedures, it would not have explicitly directed EPA to develop data compensation procedures. ACC believes, therefore, EPA should provide EDSP data submitters explicit, legally enforceable

data compensation rights. ACC would be happy to work with EPA to develop a fair and workable data compensation program for non-pesticide chemicals.

Although EPA hasn't created new procedures for ensuring cost sharing and the need for a legally enforceable program, ACC compliments the Agency for its development of a workable cost sharing plan that utilizes EPA's FFDCA order authority to determine compliance. ACC also agrees with EPA's plan to issue catch up orders to require cost sharing by manufacturers and importers who enter the market after initial orders are issued and EDSP testing is complete. Future market entrants should have an obligation to compensate EDSP data generators if they rely on the EDSP data. ACC believes, however, catch up orders should be issued for 10 years rather than 5 years. While we acknowledge that this may create an additional burden for EPA, given the significant expense of generating EDSP Tier 1 and Tier 2 data, 10 years is clearly justified.

Further, while EPA's proposed approach appears to offer data compensation protection, actual protection will depend on EPA's desire to enforce the provisions. EPA offers its cost sharing approach in non-binding policies and procedures. EPA makes it very clear that it is not bound to these policies and procedures. Therefore, the usefulness of EPA's cost sharing approach depends on the Agency's ability to enforce the outlined provisions and to diligently issue catch up orders. ACC is concerned that EPA expressly determined not to bind itself to its EDSP policies and procedures, and therefore, to its cost sharing approach. As discussed in Section X. below, ACC continues to believe that EPA needs to promulgate a broad EDSP rule, establishing all of EPA's procedures for the EDSP so that the Agency is bound to follow those procedures. Data compensation should be part of such a rulemaking to legally bind the Agency to those duties and procedures to ensure equitable treatment of data generators.

VIII. EPA Should Not Implement EDSP Phase 2 Until it Has Completed the EDSP Phase 1

EPA has wisely adopted a phased approach for implementing its EDSP. Pursuant to the current EPA approach, the Agency ordered Tier 1 Screening for 67 pesticide active and inert chemical ingredients. According to its EDSP Phase 1 policies and procedures, after receiving results from the first phase of EDSP screening, EPA intended to review and revise as necessary its Tier 1 battery prior to issuing new testing orders. EPA does not indicate in its Draft Phase 2 Policies and Procedures when it intends to issue Phase 2 orders. ACC strongly urges EPA to abide by its current plan to issue new orders after it receives the results of Phase 1 screening, assesses those results and, if necessary, modifies its Tier 1 battery and policies and procedures.

ACC believes the tiered implementation of the EDSP is scientifically

justified and necessary. Although EPA has worked to validate individual Tier 1 screening assays, the Agency has not yet validated the full Tier 1 battery as a whole. Information from the initial screening phase should be useful for validating the battery. Further, concerns remain as to the usefulness, accuracy and repeatability of some of the individual assays, and thus the Tier 1 battery and individual assay protocols will likely need to be modified. Indeed, EPA will learn of battery, assay and compliance problems only after it assesses the results of the first phase of screening.

EPA's phased approach is consistent with the recommendation of the Agency's Scientific Advisory Board/Science Advisory Panel (SAB/SAP) to initially screen 50 to 100 substances.[24] The SAB/SAP recommended that, once EPA collects data from these 50 to 100 substances, the Agency should review all endocrine screening battery phase one screening data and test methods to revise the program "with an eye towards revising the process and eliminating those methods that don't work."[25] Likewise, the Office of Management and Budget approved EPA's Information Request for the initial 67 chemicals and stated in its Terms of Clearance: "This information collection is approved for the 67 chemicals published by EPA at 74 Fed. Reg. 17579 (April 15, 2009). OMB appreciates the continuing dialog with respect to the practical utility of the Tier I 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."[26] It is clear OMB also envisioned that EPA would not order additional endocrine screening until the first phase of EDSP screening was completed, EPA assessed the performance of its screening assays and battery, and the Agency made necessary changes to the assays and battery.

EPA bases its authority to list potential drinking water contaminants for EDSP screening on FFDCA, SDWA and the House Appropriations Committee report for EPA's FY 2010 appropriations. The FFDCA and the SDWA do not require EPA to list or order the testing of potential drinking water contaminants. While the House Appropriations Committee report directs EPA to list potential drinking water contaminants and to issue orders for those substances, it is not a

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[24] EPA, *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 ("SAB EDSP Report").

[25] SAB EDSP Report at 2.

[26] Office of Information and Regulatory Affairs, Office of Management and Budget, *Approval of EPA's Information Collection Request: Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP)*, OMB Control No: 2070-0176, ICR Reference No: 200904-2070-001, Oct. 2, 2009, ("OMB Terms of Clearance").

statutory requirement. Therefore, EPA's decision to undertake a phased EDSP implementation and issue EDSP Phase 2 testing orders after it completes EDSP Phase 1 and after it completes the SAB/SAP recommended review is not contrary to law. In fact, such an approach is consistent with SDWA Section 1412(b)((3)(A) that requires EPA to "use the best available peer reviewed science and studies conducted in accordance with sound and objective scientific practices."

For the reasons discussed above, the scientifically supportable approach is for EPA to await completion of its first phase of EDSP screening and to make necessary modifications to its Tier 1 battery and assays before ordering additional EDSP screening. Premature issuance of Phase 2 EDSP testing orders could result in unnecessary screening, and unnecessary use of assays and protocols that may be unable to determine with adequate scientific certainty whether a substance interacts with the endocrine system. Again, after completion of the first phase of EDSP screening EPA could learn of significant assay, battery and compliance problems. Requiring new EDSP testing before EPA has an opportunity to learn of and correct problems with its existing assays and battery would likely result in unnecessary testing costs and the unnecessary use of laboratory animals. Indeed, assays may need to be repeated and new assays may need to be included in the screening battery. Conceivably, significant resources could be unnecessarily directed to using unreliable or non-specific Tier 1screening assays if EPA departs from its originally planned phased implementation plan and disregards the SAB/SAP recommended review and adjustment.

A phased approach would also give EPA time to accelerate the determination of the relevance, reliability, sensitivity and specificity of available high throughput and high-content endocrine screening techniques. Once these assays meet the requisite degree of scientific rigor, they may be useful in the EDSP to replace some of the existing Tier 1 screening assays. The methods hold great promise for increasing the efficiency of EDSP Tier 1 screening, providing greater sensitivity and specificity at a lower cost, and allowing for the use of fewer lab animals. Indeed, EPA's ToxCast™ and the Tox21 NIH Chemical Genomics Center molecular/cellular screening tests were used by EPA, in lieu of the Agency's own EDSP Tier 1 battery, to compare the dispersant's available for use in the Deepwater Horizon oil spill for the potential for endocrine activity and relative toxicity to living cells. The power of those methods is exemplified by the Agency's full reliance on those test results to conclude the dispersants did not display biologically significant endocrine disrupting activity.[27]

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27 http://www.epa.gov/ncct/download_files/factsheets/Technical%20Fact%20Sheet%20EST%20paper%20In%20Vitro

IX. EPA Should Provide Greater Guidance for the Reporting of Adverse Effects

EPA briefly discusses the general provisions of TSCA §8(e) and FIFRA §6(a)(2) in its Draft Phase 2 Policies and Procedures. EPA, however, does not provide clear guidance as to what positive EDSP Tier 1 data must be reported pursuant to those provisions. EPA should discuss the significance, for purposes of reporting, of the fact that it is not clear that the results of individual EDSP Tier 1 assays will demonstrate adverse effects. The Tier 1 assays are designed to have a low false negative rate (and thus may have a high false positive rate) and, in any event, do not determine adverse effects (which is the purpose of Tier 2). At best, they will determine whether a substance may interact with the endocrine system. Given that almost everything (sunlight, for example) interacts with the endocrine system, it would not make sense for the standard of reporting to be interaction with, or perturbation of, components of the endocrine system. Thus an argument might be made that no Tier 1 results would need to be reported as required under TSCA §8(e) and FIFRA §6(a)(2). Further, it may be necessary to view the Tier 1 battery as a whole (or at least a number of assays together) to determine whether a substance is "positive" in an assay or the Tier 1 battery. This last issue is complicated because EPA has not yet developed meaningful weight of evidence guidance that would allow an assessment of the overall Tier 1 data. (See Section IV above.) It is important to note that the issue here is not whether Tier 1 data will be reported – they will be pursuant to the requirements of EDSP testing orders. The issue is when those data must be reported – as they are generated or when they are best understood.

Throughout development and implementation of its EDSP, EPA has remained relatively silent concerning TSCA adverse effects reporting requirements, despite industry requests for information. One exception is EPA's 1998 EDSP Proposed Statement of Policy in which EPA stated that it would not require TSCA 8(e) or FIFRA 6(a)(2) reporting of EDSP Tier 1 *in vitro* results. EPA stated:

> 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. Therefore, based on the current state of the knowledge, EPA will not, at this time, require submission of TSCA section 8(e) or FIFRA section 6(a)(2) reports containing only the results of these in vitro assays.[28]

EPA should reiterate in its EDSP Tier 2 Policies and Procedures that it believes EDSP Tier 1 *in vitro* results are not reportable pursuant to TSCA §8(e) and FIFRA §6(a)(2). EPA should also consider exempting EDSP Tier 1 *in vivo*

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[28] EPA, Endocrine Disruptor Screening Program, Proposed Statement of Policy, 75 Fed. Reg. 71541, 71564, Dec. 28, 1008.

results since under EPA's definition in the EDSP, Tier 1 assays do not demonstrate adverse effects. To the extent it believes EDSP Tier 1 *in vivo* results should be reported pursuant to TSCA §8(e) and FIFRA §6(a)(2), however, it should clearly state its reasoning in light of the above discussion.

X. EPA Should Promulgate a Broad Procedural Rule for the EDSP

FFDCA §408(p)(5)(d) states that non-pesticide registrants who fail to comply with an EDSP testing order are subject to the stiff penalties of TSCA §16. FFDCA fails, however, to explicitly provide the due process protections of TSCA §4, which would require EPA to promulgate test rules. EPA has attempted to avoid the legal problem of denying order recipients due process protections by interpreting TSCA in such a manner that EDSP test orders would be judicially challengeable, final agency actions.

In ACC's opinion, EPA's interpretation would appear to avoid due process concerns for non-registrant order recipients. However, order recipients are dependent on EPA following its interpretation and plan. EPA offers its interpretation and plan in non-binding policies and procedures. EPA makes it very clear that it is not bound to these policies and procedures. ACC is concerned because EPA expressly determined not to bind itself to its EDSP policies and procedures, and therefore, to its TSCA interpretation and approach for ensuring due process.

In several sections of our comments above, ACC has called on EPA to interpret its FFDCA and SDWA authority to implement the EDSP (particularly with respect to testing of substances by manufacturers and importers as opposed to registrants) and has called on EPA to establish procedures that are specific to the EDSP, for example, to address CBI protections and data compensation. Taken together, these recommendations strongly suggest the need for EPA in the near future to promulgate an EDSP procedural rule that establishes EPA's duties and its policies and procedures, and legally binds the Agency to those duties and policies and procedures.

XI. Conclusion

ACC appreciates this opportunity to provide comments on EPA's Draft Phase 2 Policies and Procedures. Please contact Rick Becker at 202-249-6405 or Rick_Becker@americanchemistry.com if you have questions about these comments.

Comments of the American Chemistry Council
On EPA's Endocrine Disruptor Screening Program
Filed on January 18, 2011

3. ACC Comments on EPA Information Collection Activities; Proposed Collection; Addendum for the Second List of Chemicals; Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP); EPA ICR No. 2249.02, OMB Control No. 2070-0176

January 18, 2011

OPPT Document Control Office (DCO)
EPA East Building, Room 6428
1201 Constitution Avenue, N.W.
Washington, DC. 20460
Attention: Docket ID Number EPA-HQ-OPPT-2007-1081
Submitted via Federal eRulemaking Portal: http://www.regulations.gov

Re: Comments on "Agency Information Collection Activities; Proposed Collection; Addendum for the Second List of Chemicals; Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP); EPA ICR No. 2249.02, OMB Control No. 2070-0176"

Dear Sir or Madam:

The American Chemistry Council (ACC)[1] appreciates the opportunity to submit comments on the *Agency Information Collection Activities; Proposed Collection for the Second List of Chemicals; Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP); EPA ICR No. 2249.02, OMB Control No. 2070-0176* (the "Draft ICR Addendum").

The American Chemistry Council (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. 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 also has sponsored technical studies to supply needed data for endocrine test development and validation, and has participated with the broader scientific and stakeholder

[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 $674 billion enterprise and a key element of the nation's economy. It is one of the nation's largest exporters, accounting for ten cents out of every dollar in 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.

communities on EPA's standardization and validation advisory committees. Additionally, ACC has 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 we do concerns about all potential chemical risks.

ACC, in a joint submission with other trade associations, provided detailed comments on the deficiencies of the original EDSP ICR.[2] Our organizations concluded that the EPA's April 15, 2009 EDSP ICR was inaccurate and that the actual burdens associated with the EDSP Tier 1 were at least two to three times larger than what EPA estimated. The major deficiencies identified in EPA's April 15, 2009 EDSP ICR were technical flaws in the Agency's burden estimates, Paperwork Reduction Act compliance, and an inadequate demonstration of practical utility, as EPA could not demonstrate that certain Tier 1 assays adequately distinguish substances that have endocrine activity from those that do not. Although EPA appears to have made corrections that address some of these deficiencies, they were not significantly responsive to our comments.

Subsequently, OMB approved the information collection activity of the Agency for EDSP List 1. However, OMB issued Terms of Clearance which included very specific conditions the Agency would need to meet prior to the Agency expanding the list of EDSP substances. The OMB Terms of Clearance[3] state:

> This information collection is approved for the 67 chemicals published by EPA at 74 Fed. Reg. 17579 (April 15, 2009). OMB appreciates the continuing dialog with respect to the practical utility of the Tier I 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 I 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

[2] Comments from ACC, CPDA, CSPA and CLA (May 22, 2009). EPA Information Collection Submission To OMB for Review and Approval; Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP); EPA ICR No. 2249.01, OMB Control No. 2070-New Docket ID Number EPA-HO-OPPT-2007-1081http://www.regulations.gov/contentStreamer?objectId=09000064809c90ed&disposition=attachment&contentType=pdf [accessed January 10, 2011]

[3] Office of Management and Budget (2009). Notice of Office of Management and Budget Action, ICR Reference Number 200904-2070-001; New ICR 2070-0176.
http://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=200904-2070-001# [accessed January 10, 2011]

> the burden of this information collection based on responses to the Tier I 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 time of submission of revision of this information collection to cover additional chemicals. In addition, 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.[4]

With respect to the current 2010 Draft ICR Addendum, the Agency has not adequately addressed the shortcomings of the initial 2009 EDSP ICR, and it has not satisfied OMB's Terms of Clearance. As Crop Life America and the Chemical Producers and Distributors Association have noted in their comments, EPA has ignored significant burden components (such as the burdens of establishing, managing, and participating in testing consortia), with the result that EPA has incorrectly excluded 65% of the burden of generating test data. Furthermore, the Agency has yet to demonstrate that certain Tier 1 assays can adequately distinguish substances that have endocrine activity from those that do not. In short, the discussion on practical utility is far from resolved.

In addition, EPA has not complied with OMB's Terms of Clearance in the following areas:

- EPA has not provided a report to OMB concerning burden based on data collected from actual respondents dealing with EDSP List 1 test orders.

- EPA has not provided a report on cost-sharing and data compensation pertaining to compliance with EDSP List 1 test orders.

- EPA has to date not developed or adopted, through public comment and independent

[4] ibid

scientific peer review, scientific guidance for evaluation of OSRI. Nevertheless, the Agency has partially responded by rejecting a majority of OSRI submissions based on what seems to be very narrow interpretation of what are "functionally equivalent" scientific data and "other scientifically relevant information."

- EPA has not yet developed Standard Evaluation Procedures (SEPs) for reviewing each of the 11 EDSP Tier 1 tests, has not yet made SEPs available for public comment and has not yet subjected such SEPs to independent scientific peer review.

- Although EPA has released for public review and comment "Draft Weight-of-Evidence Guidance" for the EDSP, the draft guidance falls short of what stakeholders expected. In this nine-page document, the material instructs the analyst to conduct a weight of evidence evaluation, but beyond some general considerations, provides no substantive guidance on how to do so. The Agency's guidance is far from a detailed protocol that a qualified scientist could follow to arrive at an overall decision regarding whether the results of the Tier 1 EDSP Battery indicate significant potential of an agent to interact with the components of the estrogen, androgen and thyroid systems. Furthermore, the "Draft Weight-of-Evidence Guidance" has not been subjected to independent scientific peer review.

When final and integrated into EDSP test orders, the EDSP List 2 will create new duties and obligations for members of the regulated community. EPA's statement in the List 2 Federal Register notice[5] that "the Agency does not plan to respond formally to information or comments that may be submitted…" is based on a flawed rationale, inconsistent with EPA's actions under EDSP Phase 1, and is inconsistent with open and transparent regulatory practices. ACC urges EPA to respond to comments on the Draft List 2.

Furthermore, ACC believes that the Agency's criteria for evaluating substances for initial inclusion on the Draft EDSP List 2 and for subsequent exclusion from the Draft EDSP List 2 (due to such scientific criteria as " not likely to be biologically active" or "incompatible with testing assays for various reasons due to one or more of their physiochemical properties"), and the final EDSP List 2 itself, should undergo scientific peer review, in accordance with the requirements of EPA's Peer Review Handbook, Peer Review Policy and the Agency's Information Quality Guidelines.

[5] EPA (2010). Endocrine Disruptor Screening Program: Second List of Chemicals for Tier 1 Screening. 75 FR 70248; 11/17/2010; EPA-HQ-OPPT-2009-0477. [accessed January 10, 2011]

While ACC does not object to EPA's prioritizing additional substances for EDSP Tier 1 screening, ACC believes that EPA should not issue screening orders for these new substances before the Agency has collected and analyzed data from the initial set of EDSP substances. The

EDSP Tier 1 screening is still an ambitious testing program that is being implemented under new policies and procedures. It utilizes a suite of newly validated test methods with which the Agency and industry have little experience. Tier 1 screening costs alone may run as high as $500,000 to $1,000,000 per substance and utilize a significant number of lab animals. Tier 2 testing costs could reach several million dollars per substance.

Given the expense of endocrine screening and testing, and the lack of experience with the EDSP screening and testing assays and the Tier 1 battery, it is imperative that the Agency proceed to collect and analyze data from the initial set of EDSP substances before proceeding to additional substances. That approach would allow EPA to examine and revise its Tier 1 assays, the Tier 1 battery and EDSP procedures, such as "functional equivalence" and "other scientifically relevant information" before undertaking additional testing that could result in the unnecessary use of resources and test animals.

ACC believes this approach is in line with the Science Advisory Board (SAB) and Science Advisory Panel (SAP) recommendation, set forth in the July 1999 SAB/SAP Review[6] of the EPA's Proposed Environmental Endocrine Disruptor Screening Program, that EPA convene an external panel of independent scientists to review the initial screening data of 50 to 100 chemicals for the purpose of evaluating whether the Tier 1 screening program could be improved or optimized. EPA's reference to this SAB/SAP recommendation is contained in the Agency's description of the EDSP in both the "Response to Comments on the DRAFT Endocrine Disruptor Screening Program (EDSP): Policies & Procedures for Initial Screening and Testing"[7] and the Final "Policies and Procedures for Initial Screening"[8] published in 2009. We have interpreted EPA's reference to the SAB/SAP recommendation as an indication of EPA's intent to follow this recommendation as it proceeds with the EDSP.

[6] EPA (1999). Review of the Endocrine Disruptor Screening Program by a Joint Subcommittee of the Science Advisory Board and Scientific Advisory Panel. http://www.epa.gov/scipoly/sap/meetings/1999/finalrpt.pdf. [accessed January 10, 2011] "There was broad support among the Subcommittee for the concept that the Agency should convene a panel of independent scientists to review all the screening data for 50-100 compounds, with an eye towards revising the process and eliminating those methods that don't work."

[7] EPA (2009). Docket ID #: EPA-HQ-OPPT-2007-1080 Response to Comments on the DRAFT Endocrine Disruptor Screening Program (EDSP): Policies & Procedures for Initial Screening and Testing. Page 2. http://www.epa.gov/endo/pubs/pandp_r2c_041509.pdf [accessed January 10, 2011]

[8] EPA (2009). Endocrine Disruptor Screening Program; Policies and Procedures for Initial Screening. Federal Register, Volume 74 Number 71 (Wednesday, April 15, 2009) Page 17561

ACC believes EPA should follow the SAB/SAP advice and await completion of the EDSP Phase 1 and conduct the SAB/SAP-recommended review prior to requiring screening for additional substances. A staged implementation of EDSP screening (in which new screening orders would be issued only after completion of the first phase of screening) would allow the Agency to modify and/or replace Tier 1 assays as necessary based on the Agency's Phase 1 experience.

In conclusion, there are a number of clear deficiencies in the Draft EDSP ICR Addendum that need to be addressed prior to the Agency moving forward. The American Chemistry Council appreciates the opportunity to comment on EPA's Draft EDSP ICR Addendum. If you have questions regarding these comments, please contact me at 202-249-6405 or by e-mail at Rick_Becker@americachemistry.com.

Sincerely,

Richard A. Becker, Ph.D., DABT
Senior Toxicologist and Senior Director
Regulatory and Technical Affairs Department
American Chemistry Council

Comments of the American Chemistry Council
On EPA's Endocrine Disruptor Screening Program
Filed on January 18, 2011

4. ACC Comments on EPA's EDSP Draft Weight-of-Evidence Guidance Document, 75 Fed. Reg. 67963 (Nov. 4, 2010) (Docket ID: EPA-HQ-OPPT-2010-0877)

January 18, 2011

OPPT Document Control Office (DCO)
EPA East Building, Room 6428
1201 Constitution Avenue, N.W.
Washington, DC. 20460
Attention: Docket ID Number EPA–HQ–OPPT–2010–0877
Submitted via Federal eRulemaking Portal: http://www.regulations.gov

RE: Endocrine Disruptor Screening Program (EDSP) Draft Weight-of-Evidence Guidance Document, 75 Fed. Reg. 67963 (Nov. 4, 2010) (Docket ID: EPA-HQ-OPPT-2010-0877)

Dear Sir or Madam:

The American Chemistry Council (ACC)[1] welcomes this opportunity to submit comments on the Environmental Protection Agency's (EPA) Draft Document regarding the Weight of Evidence (WOE) for evaluating the results of Endocrine Disruptor Screening Program (EDSP) Tier 1 screening to identify chemicals for Tier 2 testing. In general, ACC considers the draft WOE guidance helpful document, but significant additional guidance is necessary to make this a complete, useful document. With respect to this EPA draft WOE guidance document, ACC fully supports the substantive comments of Crop Life America / Endocrine Policy Forum.

The American Chemistry Council (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. 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 also 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 has sponsored scientific research on the endocrine hypothesis through its Long-Range Research Initiative. As these actions

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 $674 billion enterprise and a key element of the nation's economy. It is one of the nation's largest exporters, accounting for ten cents out of every dollar in 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.

demonstrate, ACC members take concerns about endocrine disruption seriously, as we do concerns about all potential chemical risks.

For a number of years now ACC has been very explicit in communicating the importance of clear and comprehensive guidance for determining the WOE of results from each of the EDSP Tier 1 assays and the overall EDSP Tier 1 Battery. While publication of the Agency's Draft EDSP Weight of Evidence Document is a step in the right direction, it leaves much to be desired. Since 1998, with its publication of the EDSP Policy Statement,[2] the Agency has stated time and again that a WOE evaluation will be employed in interpreting the EDSP Tier 1 assays and in evaluating the EDSP Tier 1 Battery to make decisions regarding whether to proceed to Tier 2 testing. The brief, non-specific guidance in the current draft is thus somewhat puzzling. ACC is disappointed that the draft WOE guidance falls short of what stakeholders expected. In this nine-page document, less than one-third of it addresses WOE. The material instructs the analyst to conduct a WOE evaluation, but beyond some general considerations, provides no substantive guidance on how to do so. If the EDSP Tier 1 Battery yields a significantly large number of false positives[3], this could trigger extensive unnecessary Tier 2 testing at considerable cost, time and use of lab animals. Thus it is imperative that the Agency's WOE approach fully consider the sensitivity and specificity of each of the EDSP Tier 1 assays.

The Agency's overall WOE approach must be science-based, transparent, and lead to reproducible outcomes across labs and chemicals. ACC emphasizes that the Agency must develop and publish 1) clear evaluative procedures for reviewing results for each EDSP Tier 1 assay, and 2) a structured evaluative framework for conducting a weight of evidence assessment of the results of the EDSP Tier 1 battery, which would include integrating results from both the EDSP Tier 1 assays and other scientifically relevant studies. Detailed guidance for each of these elements is needed to provide the necessary consistency and transparency in EPA's EDSP determinations. Without detailed descriptions of how results of each of study are to be evaluated, and integrated into an overall evaluation, and how the Agency intends to weight various considerations, there is no assurance of scientific accuracy, consistency or transparency in EDSP WOE determinations.

The EDSP WOE evaluation should allow for the possibility of non-endocrine modes of action arising from those EDSP Tier 1 assays that rely on apical endpoints, which are influenced by both non-endocrine and endocrine modes of action. In addition, when evaluating WOE using results from the Tier 1 EDSP assays and other scientifically relevant data, it is entirely appropriate for greater weight to be given to studies that have employed standardized and validated test methods and have been conducted in accordance with Good Laboratory Practices (GLP). Relatively less weight should be

[2] Federal Register / Vol. 63, No. 248 / Monday, December 28, 1998, Pages 71542- 71568.
[3] In accordance with EDSTAC recommendations and consistent with EPA's EDSP Policy Statement, the Tier 1 screens were designed to be sensitive and have low false negative rates. Thus, the EDSP Tier 1 battery may have a correspondingly high false positive rate.

afforded studies that use novel, non-validated methods, and/or have not conformed to GLP requirements (Becker et al. (2009)).[4]

ACC is concerned that in developing its draft WOE guidance, EPA apparently neglected to examine WOE approaches that have been developed and successfully used to assess a variety of toxicological responses, including endocrine-mediated toxicities. This shortcoming needs to be rectified. There is considerable merit in EPA reviewing published mode of action WOE frameworks, such as that of Boobis et al. (2008)[5], Seed et al. (2005)[6], Rhomberg (2008)[7] , ECETOC (2009)[8], and Borgert et al. (2010)[9] to examine the applicability of these, in whole or in part, to the EDSP.

ACC believes that the Agency's EDSP WOE guidance must undergo scientific peer review, in accordance with the requirements of EPA's Peer Review Handbook (and Peer Review Policy)[10] and Information Quality Guidelines.[11] The Agency's policies and guidance on scientific peer review are clear: 1) Agency guidance, such as the EDSP WOE, is included in the suite of Agency actions that meet the definition of dissemination of information to the public; 2) EPA's Policy states, "[p]eer review of all scientific and technical information that is intended to inform or support Agency decisions is encouraged and expected;" 3) EPA's Handbook states, "all influential scientific and technical work products used in decision making will be peer reviewed;" and 4) the EPA EDSP WOE guidance meets the definition of "influential scientific information" in that it will have a clear and substantial impact on important public policies or private sector decisions, since its application will result in determinations that could trigger EDSP Tier 2 testing.

In conclusion, ACC believes the draft EDSP WOE guidance in its present form does not serve the Agency's technical experts, EPA's program managers, the regulated community or the public very well. The Agency's EDSP WOE guidance should be constructed in a manner which provides a detailed protocol that a qualified scientist could follow. The guidance must enable EPA to arrive at an overall decision regarding whether the results of the Tier 1 EDSP Battery indicate significant potential of an agent to interact with the components of the estrogen, androgen and thyroid systems. The guidance must ensure scientific accuracy, consistency and transparency in EPA EDSP WOE

[4] Becker, R.A., et al. 2009. Good laboratory practices and safety assessments. Environ. Health Perspect. 117, A482–A483.
[5] Boobis, A.R., et al., 2008. IPCS framework for analyzing the relevance of a noncancer mode of action for humans. Crit. Rev. Toxicol. 38 (2), 87-96
[6] Seed, J., et al., 2005. Overview: Using mode of action and life stage information to evaluate the human relevance of animal toxicity data. Critical reviews in toxicology. 35 (8-9), 664-672.
[7] Rhomberg, L., 2008. A framework for weight of evidence: application to endocrine effects and the low-dose hypotheses. ISRTP Workshop: Conducting and Assessing the Results of Endocrine Screening, February 19 and 20, 2008. Available from: http://www.isrtp.org/endocrine_workshop_02-08/RHOMBERG%20SLIDES.pdf.
[8] ECETOC, 2009. European Centre for Ecotoxicology and Toxicology of Chemicals TR 106 - Guidance on Identifying Endocrine Disrupting Effects.
[9] Borgert, C.J., Mihaich, E.M., Ortego, L.S., Bentley, K., Holmes, C., Levine, S.L., and Becker, R.A. 2010. The development of a weight of evidence approach for the evaluation of endocrine activity. SETAC North America, 31st Annual Meeting, November 7-11, 2010, Portland, OR.
[10] http://www.epa.gov/peerreview/pdfs/peer_review_handbook_2006.pdf
[11] http://www.epa.gov/quality/informationguidelines/documents/EPA_InfoQualityGuidelines.pdf

determinations. There must be criteria for determining data quality, study reliability, and a structured evaluative framework to provide a systematic and consistent approach for assessing the overall weight of the evidence for observed effects. ACC requests that the Agency devote the time and effort necessary to revise the draft WOE guidance to achieve these objectives. In proceeding along this path, ACC encourages EPA to 1) explore greater opportunities to build upon existing WOE frameworks; and 2) increase peer involvement by organizing and/or participating in venues that encourage the open exchange of data, insights, and ideas on EDSP WOE from scientific experts across the academic, public and private sectors. Since such a revision will yield a substantially more detailed WOE guidance document, we believe stakeholders should be provided an opportunity for additional public review and comment on the revised EDSP WOE document. Finally, in accordance with EPA's policies on peer review and information quality, the EDSP WOE guidance should undergo independent scientific peer review before it is adopted by the Agency.

Thank you in advance for consideration of our views. Should you or your staff have questions about ACC's comments, please contact me Rick_Becker@americanchemistry.com at or by phone at 202-249-6405.

Sincerely,

Richard A. Becker, Ph.D., DABT
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