

CropLife America/Endocrine Policy Forum Comments on  
Second List of Chemicals for Tier I Screening.  
Docket ID: EPA-HQ-OPPT-2009-0477

CropLife America<sup>1</sup> and the Endocrine Policy Forum (EPF)<sup>2</sup> are pleased to have this opportunity to submit comments on EPA's Endocrine Disruptor Screening Program; Second List of Chemicals for Tier I Screening, 75 Fed. Reg. 70248, Nov. 17, 2010. These comments do not address specific substances the Agency has chosen as candidates for the initial list. Rather our comments are focused on the general approach outlined and implementation of the Endocrine Disruptor Screening Program (EDSP).

**Background**

The 1996 Food Quality Protection Act (FQPA) directed EPA to develop a screening program, using appropriately validated test systems and other scientifically relevant information, to determine whether certain substances may have hormonal effects in humans. FQPA instructed EPA to determine the endocrine-disrupting potential of pesticide chemicals and other substances, and based on those findings, to take action to protect the public health and the environment. EPA developed the EDSP in response. The determination that a chemical may or may not have the potential to interact with the endocrine system will be made on a weight of evidence basis taking into account data from the Tier I assays and/or other scientifically relevant information. Chemicals that go through Tier I screening and are found to have the potential to interact with the estrogen, androgen, or thyroid hormone systems will proceed to the next stage of EDSP where EPA will determine which, if any, of the Tier II tests are necessary. Tier I is intended by the Agency to serve as a screening battery. Tier II testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a quantitative dose-response relationship. The approval of EDSP mandated that EPA base its findings on appropriately validated test systems and other scientifically relevant information (OSRI) and to minimize duplicative testing.<sup>3</sup>

The status of the initial phase of EDSP Tier I test orders that EPA has already issued is available online.<sup>4</sup> October 2011 is the current first deadline for complying with these test

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<sup>1</sup> CropLife America (CLA) is a not-for-profit trade organization representing the nation's developers, manufacturers, formulators and distributors of plant science solutions for agriculture and pest management in the United States. Our member companies produce, sell and distribute virtually all the crop protection technology products used by American farmers and other consumers. We are committed to the safe and responsible use of the industry's products in order to provide safe and abundant food, as well as for the control of insect and plant disease vectors for the protection of human health, all providing valuable benefits back to the consumer.

<sup>2</sup> The Endocrine Policy Forum is a consortium of CLA members and non-member stakeholders formed to address the aggregate needs of the group with respect to technical guidance and regulatory policy in response to the implementation of the EPA Endocrine Disruptor Screening Program.

<sup>3</sup> [http://www.reginfo.gov/public/do/PRAViewICR?ref\\_nbr=200904-2070-001](http://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=200904-2070-001)

<sup>4</sup> [http://www.epa.gov/scipoly/oscpendo/pubs/edsp\\_orders\\_status.pdf](http://www.epa.gov/scipoly/oscpendo/pubs/edsp_orders_status.pdf)

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orders. Some OSRI applications, and EPA's responses to them, are available online.<sup>5</sup> The test order recipients submitted timely OSRI applications (within the mandated 90 days for a single company or within 150 days for a consortium). However, with only a few remaining months until the first deadline for complying with the test orders, several CLA/EPF members do not know yet whether they will have to perform all or any of the Tier I tests.

In November 2010, EPA released in the Federal Register a series of draft documents relating to the expansion of the EDSP. The new list of chemicals<sup>6</sup>, the amended information collection request<sup>7</sup> and the amended Draft Policies and Procedures<sup>8</sup> all refer to EPA's second phase of the EDSP. Presently CLA/EPF are providing public comment on EPA's draft second list of chemicals for Tier I 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").

#### **Sharing the common goal of safety:**

The EPA, state regulatory agencies and the crop protection industry all share the common goal of creating effective products that are environmentally safe and sustainable. When the process of development and registration for crop protection products is fully understood by the general public, their importance and safety are readily apparent. Crop protection technologies provide modern agriculture some of the tools necessary to feed the growing world population. An understanding of the current regulatory process and requirements under FIFRA provides an appreciation for the amount of data that exists on any given crop protection product that allows one to answer the question: "Does this product have the potential to interact with certain hormonal systems?" [the ultimate goal of EDSP Tier I screening].

#### **EPA should respond to comments on List 2 chemicals:**

We note that the Agency does not intend to respond to these public comments, however, we urge the Agency to reconsider and provide responses. The decision by the Agency to include a chemical on List 2 is the de facto prelude to the Agency's issuance of binding EDSP test orders. The EDSP program is a significant and important undertaking for both EPA and industry. The program requires tremendous resources both by the regulated industry and by the Agency, and we believe that public dialogue is key to the successful implementation of the EDSP. As members of the EPF know first hand, Tier I

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<sup>5</sup> [http://www.epa.gov/scipoly/ospendo/pubs/EDSP\\_OSRI\\_Response\\_Table.pdf](http://www.epa.gov/scipoly/ospendo/pubs/EDSP_OSRI_Response_Table.pdf)

<sup>6</sup> EPA, *Endocrine Disruptor Screening Program; Second List of Chemicals for Tier 1 Screening* 75 Fed. Reg. 70248, Nov. 17, 2010 ("Draft List 2")

<sup>7</sup> EPA, *Agency Information Collection Activities; Proposed Collection; Comment Request; 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. 2070-017675*. Fed. Reg. 70568, Nov. 17, 2010 ("Draft ICR")

<sup>8</sup> 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").

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screening costs range between 500,000 and 1,000,000 US dollars per chemical. Additional costs are associated with the administrative efforts to comply with the test order and to develop and submit Other Scientifically Relevant Information (OSRI)<sup>9</sup>.

When finalized, List 2 will create new testing obligations for specific members of the regulated community. (The finalization of List 2 is one component to Phase 2 of EDSP by EPA.) Thus, EPA has specific legal obligations. CLA/EPF believes EPA should adhere to the requisite notice and comment provisions of the Administrative Procedure Act (APA), and formally respond to comments received on Draft List 2. By responding to the comments, EPA can avoid the appearance of acting in an arbitrary and capricious manner and promote an open and transparent process with the regulated industry and other stakeholders. The fact that EPA needs to process another Information Collection Request (ICR) indicates the significance of the publication of this list.

**List 2 is not a list of endocrine disrupting chemicals:**

We encourage the Agency's continued use of qualifying language that highlights chemicals subject to listing (either under List 1 or List 2) as not being endocrine disrupting chemicals. Specifically, we congratulate the Agency in clearly stating that the public should not presume the listing of a chemical or substance indicates it interferes with the endocrine systems of humans or other species simply because it has been listed. As the Agency further notes, selection of chemical candidates for screening under Tier I reflect only their pesticide registration status or population exposure potential. As the Agency is well aware, the purpose of Tier I is screening. The screening selection process for the proposed substances on List 2 is based on potential exposure (SDWA chemicals) or registration review status (most pesticide active ingredients) and not based on suspected endocrine activity.

**Description of EDSP Tier I and Tier II:**

EPA should clarify and be consistent as to the purpose of Tier I screening and what the results of Tier I screening mean and do not mean. As EPA<sup>10</sup> noted in 1998, the purpose of Tier I is to identify substances that have the potential to interact with the estrogen, androgen, or thyroid hormone systems and the purpose of Tier II is to identify and establish a dose-response relationship for any adverse effects that might result from the interactions identified through the Tier I assays. Only after completion of Tier II testing will EPA be able to determine whether a particular chemical may have an effect in humans that is similar to an effect produced by naturally occurring estrogen, androgen, or thyroid hormones.

Within the various documents associated with Phase 2 of the EDSP, EPA is not consistent in how Tier I and Tier II are described. EPA clearly describes the purpose and structure of the EDSP with the Draft Phase 2 Policies and Procedures. The Draft Phase 2 Policies and Procedures states the EPA intends to use the data collected under the EDSP,

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<sup>9</sup> <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2007-1081-0037.2>

<sup>10</sup> EPA, *Endocrine Disruptor Screening Program; Proposed Statement of Policy*. 63 Fed. Reg. 71545 December 28, 1998.

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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.

In the Draft Phase 2 Policies and Procedures, EPA describes the EDSP as a two-tiered testing program. “The purpose of Tier I 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 II, 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.” 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.

Within the FR Notice for Draft List 2, EPA describes Tier I as “assays used to screen the chemicals for interaction with the [EAT] hormonal system.” And for Tier II, EPA simply states “Tier II test assays are intended to test for more specific chemical effects on the endocrine system”. This description of Tier II does not mention adverse effects or dose-response. Within the second list of chemicals FR Notice, the difference between Tier I and Tier II is described as merely the specificity of the chemical effects detected in each tier. A naïve reader might incorrectly conclude Tier I determines adverse effects. EPA should have simply repeated the description of the EDSP it used for the Draft Phase 2 Policies and Procedures when describing the EDSP. CLA/EPF is concerned that if EPA can be inconsistent in describing the EDSP in three related EDSP documents issued at the same time, it is unlikely EPA is consistently and accurately describing the EDSP across EPA offices and programs. CLA/EPF suggests that the specific language in the Draft Phase 2 Policies and Procedures document be used within all Phase 2 EDSP documents.

Why does the exact description of the EDSP matter so much? The wording defining Tier I and Tier II within EPA documents must be consistent with Agency authority. As mandated by the Paperwork Reduction Act, EPA may not use the EDSP as a research program designed to gather information that has no practical use or utility. Rather, the purpose of the EDSP should be to collect data concerning endocrine risks posed by chemical substances. That data must be useful for managing risks to human health. In sum, the purpose of the EDSP should be to determine adverse effects and risk, not simply to determine whether substances may interact with the endocrine system, which does not determine risk or adverse effects. It is also important that EPA clearly describes the EDSP as a two-tiered program. Indeed, the purpose of the EDSP is not to merely determine whether a substance may interact with the endocrine system. Rather, the purpose is to determine whether substances cause adverse effects through an endocrine mechanism. This understanding should underpin all Agency communications concerning the EDSP. It is critically important that EPA describe the purpose of EDSP as generating data that will determine adverse effects and risks.

**Defining endocrine disruptors to include adverse impacts on whole organisms:**

We encourage the EPA to harmonize with the World Health Organization’s definition of an endocrine disruptor: “An endocrine disruptor is an exogenous substance or mixture

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that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations." Broader definitions only serve to unnecessarily alarm the public and perpetuate the waste of animals and resources extensively evaluating compounds that do not pose any real risk.

The WHO definition is consistent with the scientific community's recognition that while substances may interact with the endocrine system, they may not adversely affect health or the ecosystem. Within the WHO definition, endocrine disruption is not considered a toxicological end point per se but a functional change that may lead to adverse effects. An adoption of an unnecessarily broad definition that suggests that any molecular or cellular response observed in animal or in vitro experiments is endocrine disruption provides no use or clarity.

The endocrine system is complex and seeks to maintain homeostasis in a continually variable and fluctuating natural environment. Evidence that a substance interacts with a component of the endocrine system does not provide any information on whether that substance causes other biological changes, which may, in turn, cause adverse health effects. Within endocrine systems, natural variations in hormone levels and reversible or transient changes that are not considered adverse have been well documented. Endocrine interactions also must be looked at in the context of dose and timing of exposures. Importantly, studies must determine whether endocrine interactions are within the normal range of biological fluctuations or whether they are of such a magnitude as to overcome natural defense mechanisms and exert adverse effects. The interaction of a chemical with a component of the endocrine system may be insufficient to result in adverse health effects at environmentally relevant levels of exposure. Endocrine disruption should be defined more carefully as interactions with the endocrine system that result in adverse effects.

**Inclusion of pesticides in List 2:**

EPA issued the first list of 67 chemicals to be evaluated in Tier I assays under the EDSP on April 15, 2009. This list included 58 pesticides and 9 high production volume chemicals and/or inert ingredients of pesticide products. The test screens are estimated to cost in the range of \$500,000 to \$1,000,000/chemical. List 2 contains 50 additional pesticide active ingredients (and several discontinued pesticide products). Pesticide active ingredients are approved for use under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). As mandated under FIFRA, the process of developing and registering crop protection products for commercial use is methodical and demanding. Collectively, sub-chronic and chronic toxicity studies in rats, mice and dogs, developmental toxicity studies in rats and rabbits, as well as reproduction studies in rats evaluate a wide array of estrogen-, androgen- and/or thyroid-sensitive tissues. Data are obtained on potential endocrine-mediated responses such as reproductive parameters (e.g. mating, fertility, and gestational indices), estrous cyclicity, sperm parameters, and histological alterations in a variety of endocrine controlled tissues, (e.g. epididymides, testes, ovaries, uteri, thyroid, adrenals, pituitary). The development of fetuses and offspring is also assessed by measuring endpoints related to growth, survival, and sexual development. Often additional endpoints such as hormone levels are included in study

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designs to better understand the toxicity profile of a compound. Data on endpoints pertaining to endocrine-mediated effects are also available from the studies performed on representative wildlife species, including fish and birds. Metabolism studies in rats, poultry, ruminant animals and fish demonstrate the extent of absorption and excretion of the pesticide over time as an indication of potential exposure and can help to identify any metabolites of concern. The extensive toxicity profile available on a pesticide across its FIFRA dataset provides an appreciable amount of information about patterns of effects and downstream outcomes all of which are relevant in the assessment of a compound's potential to interact with the endocrine system.

The Office of Pesticide Programs has indicated that, subsequent to the first list of substances to be evaluated in the Tier I screening battery, the EDSP for pesticide active ingredients will be implemented in conjunction with the Registration Review process. Given this decision, it is unnecessary to continue to list pesticides for screening. In fact, because the pesticides on the draft List 2 are from the 2007 and 2008 registration review schedule, the listing comes very late in the Registration Review process for these products. To include them on a screening list at this late date has the potential to disrupt the Registration Review process for the pesticides listed. We would suggest that it is, therefore, unnecessary to include pesticides on List 2 and that EPA evaluate the appropriate timing and procedure for EDSP screening of pesticides within the existing pesticide registration review process.

Additionally, we urge EPA to refrain from listing or issuing new test orders for pesticide active ingredients, or any other chemical, until the Agency has had an opportunity to properly evaluate the performance of the Tier I screening battery based on the results of the first 67 chemicals on EPA's List 1. This recommendation is consistent with the SAP/SAB recommendation to collect and analyze data from List 1 before proceeding to the evaluation of additional substances in the EDSP.<sup>11</sup>

Given that the focus of List 2 is potential presence of a chemical in drinking water and potential substantial exposure to the human population, we recommend that pesticides which do not fulfill both criteria as outlined in Table 1 of the Federal Register Notice (FR 75, No 221, Wednesday, November 17, 2010) be removed from List 2. In describing the method for inclusion of chemicals on List 2, an emphasis is placed on potential contamination of drinking water. This is clearly not the case because 29 pesticides are not identified as a concern regarding the SDWA. They were listed solely due to the Registration Review schedule. To include these pesticides on List 2 erroneously suggests to the public that the active ingredients are of concern in drinking water. Despite EPA's best efforts to accurately describe the listing criteria, we know from experiences with List 1 and the perception that the list was an endocrine disruptor list such misinterpretations do occur.

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<sup>11</sup> 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").

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**Inclusion of legacy chemicals in List 2:**

Like EPA, member companies and organizations of CLA and EPF share the common goal of protecting the environment. Given the importance of this goal, we question the Agency's inclusion of legacy chemicals in List 2. In our opinion the inclusion of legacy chemicals does not appear to be aligned with safeguarding the public. The EDSP is a resource and time-intensive program. Priority should be given to those chemicals in current use with the potential for substantial or potentially increasing environmental exposure. As the Agency is well aware there are several chemicals on the draft List 2 that are no longer in commercial use (either in general or for pesticide use). We would suggest that the Agency does not spend its limited resources on legacy chemicals. The Agency has in-house *in vitro* rapid screening programs, such as those used for the oil dispersants, that are better suited to activities with legacy chemical concerns.<sup>12</sup>

**Defining "sources of drinking water":**

We ask EPA to define what is meant by "sources of drinking water." A chemical listed on the National Primary Drinking Water Regulation (NPDWR) or the third Candidate Contaminant List (CCL3) does not *a priori* meet the EDSP SDWA requirement that the chemical is found within drinking water.

SDWA specifies that the Candidate Contaminant List (CCL) must include contaminants that are not subject to any proposed or promulgated NPDWRs, are known or *anticipated* to occur in public water systems (PWSs), and *may* require regulation under SDWA<sup>13</sup> [*emphasis added*]. With a stated scope for CCL3 that includes 'anticipated' presence in public water systems, such a listing cannot be considered an appropriate selection for prioritization of draft list 2 for the EDSP program, which clearly specifies that the administrator needs to determine that a '*substantial population may be exposed to such a substance*'. This implies that deriving the EDSP Draft List 2 from such a list cannot produce a definitive, scientifically rigorous list of chemicals with a high potential for human exposure via drinking water. Chemicals listed on CCL3 do not *a priori* meet the SDWA requirement for testing under EDSP as a determination of regulation under SDWA may not actually have occurred.

For certain substances on List 2, environmental releases may occur from natural sources, from manufacturing and processing, and from such products as fuels. For such materials, EPA should first consider the relative contributions of potential water-borne exposures of each activity and then direct EDSP test orders to manufacturers and importers in a manner consistent with the exposure.

Before EPA can move forward with selecting substances for Phase 2, the Agency must interpret the SDWA consistent with procedures provided by the Administrative Procedures Act and subject to judicial review. CLA/EPF notes that the Agency should

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<sup>12</sup>[http://www.epa.gov/ncct/download\\_files/factsheets/Technical%20Fact%20Sheet%20EST%20aper%20In%20Vitro%20Tests%208%20Oil%20Dispersants%207-6-2010.pdf](http://www.epa.gov/ncct/download_files/factsheets/Technical%20Fact%20Sheet%20EST%20aper%20In%20Vitro%20Tests%208%20Oil%20Dispersants%207-6-2010.pdf)

<sup>13</sup> EPA, *Drinking Water Contaminant Candidate List 3- Draft*. 73 Fed. Reg. 9629, February 21, 2008.

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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.”

**Defining “substantial population” which may be exposed:**

We ask EPA to define what is meant by “substantial population may be exposed.” A chemical listed on the NPDWR or CCL3 does not a priori mean the EDSP SDWA requirement that a “substantial population” has been exposed to the chemical has been met.

Before EPA can move forward with selecting substances for Phase 2, the Agency must interpret the SDWA consistent with procedures provided by the Administrative Procedures Act and subject to judicial review. CLA/EPF notes that the Agency should 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.”

**Recommendation to apply lessons learned from initial Tier I testing prior to issuance of any further EDSP test orders:**

Final data submissions for the first 67 chemicals undergoing EDSP Tier I screening are not due until beginning in October 2011 with deadlines continuing into 2012. However, this timeline is expected to be extended due to delays in receiving EPA responses to waiver requests based on OSRI. Given the above, EPA is not likely to complete its evaluation of these Tier I data until sometime in 2013. Also, CLA/EPF members have encountered a number of issues in the required EPA screens with List 1. It does not make sound scientific sense to begin testing a new group of chemicals (List 2) until these issues have been resolved. Therefore, consistent with the SAB/SAP recommendations (in the SAB EDSP Report) to initially screen 50-100 substances and to evaluate the performance of the individual assays and the battery as a whole, CLA/EPF encourages EPA to not issue test orders for List 2 chemicals or any other substances, until this assessment has been completed and issues with the initial Tier 1 screens are resolved.

CLA/EPF is providing these comments to encourage EPA to proceed in a considered step-wise manner before issuing test orders on this new list of chemicals and initiate Phase 2 of the EDSP. We would like to note that under the first list of chemicals under the EDSP (in Phase 1), the test order recipients are still seeking the following information to best help with compliance by industry and implementation by the Agency:

- Agency criteria used for evaluating ORSI submitted by Phase 1 test order recipients,
- Resolution of errors within the 890 Series Test Guidelines,
- Standard Evaluation Protocols for the 890 Series assay reports,

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- Further clarity on the procedures the agency will use to consider the overall weight of evidence.

CLA/EPF echoes the sentiment from Executive Branch's Office of Management and Budget (OMB) Terms of Clearance<sup>14</sup> by encouraging EPA to implement OMB's specified terms. We believe that an initial focus on resolving many of the pending issues with the EDSP implementation under the first list of chemicals will ultimately enhance the integrity of the EDSP program.

Thank you for the opportunity to provide these comments. Please contact Dr. Wendelyn Jones at [wjones@croplifeamerica.org](mailto:wjones@croplifeamerica.org) or at 202-872-3885 if you have any questions.

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<sup>14</sup> [http://www.reginfo.gov/public/do/PRAViewICR?ref\\_nbr=200904-2070-001](http://www.reginfo.gov/public/do/PRAViewICR?ref_nbr=200904-2070-001)